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ABSTRACTS

# Abstracts of the 53 Annual Conference of the Italian Society of Neurology

## CEREBROVASCULAR DISEASES

### THE PROGNOSTIC ROLE OF ACUTE STROKE LESION CHARACTERISTICS IN A SAMPLE OF MECHANICAL THROMBECTOMY ELIGIBLE PATIENT

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Objective: Mechanical thrombectomy is an effective treatment for large vessel occlusion causing ischemic stroke. Several clinical and radiological factors guide outcome prediction and treatment eligibility. The Alberta Stroke Program Early CT score (ASPECTS), a 10-point quantitative score assessing early ischemic changes, and stroke volumetric variables (penumbra and lesion volumes) are the most common metrics that drive hyperacute stroke management [1]. We investigated the prognostic role of these outcomes, compared to clinical and stroke-induced brain dysconnectivity patterns, new metrics showing promising results in predicting post stroke impairment [2].

Methods: We retrospectively included patients who underwent acute mechanical thrombectomy (Clinica Neurologica, Hospital of Padova). The following metrics were collected: ASPECTS scores, (hyperacute) core and penumbra volumes, post mechanical thrombectomy lesion volumes. The latter were used to compute structural disconnection maps [2]. Functional outcome was represented by the modified rankin scale (mRS) at admission (pre-mRS), discharge (post-mRS) and after 90-days (mRS-90) [3]. National Institutes of Health Stroke Scale (NIHSS) at presentation was also evaluated. A multiple linear regression analysis compared four models including mRS-90 as the dependent variable. In the first model (M1) regressors included age, pre-mRS, and NIHSS; in the second model (M2) ASPECTS, core, and penumbra volume were added; in the third model (M3) structural disconnection information was included. The fourth model (M4) included age, pre-mRS, post-mRS, and NIHSS. Models were compared using a modified jackknife procedure. Finally, we investigated the voxel-wise relationship between mRS and structural disconnections.

Results: Fifty patients were included (thrombectomy performed from 2018 to 2021; mean mRS-90 = 2.2±1.8). M4 provided the highest adjusted r-squared in predicting mRS-90 (adjusted r2=0.614). The variance explained by the other models was: M1: r2=0.517; M2: r2=0.504; M3 r2=0.549. We then compared models r2 from the jackknife procedure, showing that M4 was significantly higher than the other models, while M3 (including structural disconnections) was higher compared to M2. Finally, a significant relationship ($p<0.05$) was observed between mRS-90 and damage to the corticospinal tract extending to the cingulum and the corpus callosum.

Discussion: We reported that clinical status is the most valuable prognostic factor after three months from the event. The ASPECTS and volumetric information showed the lowest prediction. On the contrary, structural disconnection was more informative for functional outcome. Conclusions: While clinical characteristics showed the highest prognostic prediction, brain dysconnectivity patterns may be helpful for post stroke prognosis.

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### THE ROLE OF NOX-2 AND ET-1 IN PERIHEMATOMAL HYPOPERFUSION, ISCHEMIC LESIONS AND HEMATOMA EXPANSION IN PATIENTS WITH INTRAPARENCHYMAL CEREBRAL HEMORRHAGE

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Objectives: Perihematomal hypoperfusion may lead to the development of ischemic damage during intraparenchymal cerebral hemorrhage (ICH), resulting in worse prognosis. We aimed [1] to investigate the relationship between serum biomarkers related to vasoactive substances and the occurrence of hypoperfusion and ischemic perihematomal lesions in ICH [2] to evaluate their correlation with volumetric evolution of the hematoma and perihematomal edema.

Materials and methods: We included patients with ICH admitted to our Stroke Unit from January 2019 to July 2021. Blood samples were collected at three different timepoints (T0: admission to Emergency Room, T1: 12-24hs from symptoms onset, T2: 48-72hs from symptoms onset) to measure Endothelin-1 (ET-1), nitrites/nitrates (end products of nitric oxide, NO), NADPH oxidase-2 (NOX-2), metalloproteinase-12 (MMP12), asymmetric dimethylarginine (ADMA), and cortisol. Patients underwent brain MRI with perfusion study at T1 and MRI without perfusion at T2.

Results: Of 28 patients included in the study, 12 had ischemic perihematomal lesions at T1. We observed a borderline statistically significant difference in the NOX-2 concentration at T0 with higher levels in patients with ischemic perihematomal lesions compared to those without (34.9ppmv vs 22.4ppmv, p=0.051). NOX-2 values were significantly associated with hematoma-ipsilateral

hemispheric hypoperfusion at T1 (p=0.034) and the development of severe edema at T2 (p=0.011). ET-1 values at T1 inversely correlated with hemorrhage volume at T2 (ρ=-0.717, p=0.030). The development of ischemic perihematomal lesions was significantly associated with an increased volume of hematoma (p=0.005), perilesional edema (p=0.046), greater midline shift (p=0.036), and had a borderline statistically significant association with hemispheric hypoperfusion (p=0.055).

Discussion and conclusions: We found that oxidative stress-related biomarkers were associated with perihematomal hypoperfusion, severe edema and ischemic perihematomal lesions, although we cannot conclude on a causal relationship. The association between the lower ET-1 values with a larger hemorrhage volume is probably related to a decrease in the vasoconstriction of the ruptured vessel wall. Our study provides a starting point for the understanding of the physiopathological mechanisms of ICH.

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## MULTIPLE CEREBRAL INFARCTS AND ENCEPHALOPATHY AS THE FIRST CLINICAL MANIFESTATIONS OF HYPEREOSINOPHILIC SYNDROME

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Background and aims: Hypereosinophilic syndrome (HES) is characterized by a peripheral blood eosinophil count >1.5 x 10^3/uL on two separate examinations at least one month apart and/or a bone marrow eosinophil percentage of 20% or higher, along with organ damage. Neurological involvement rarely occurs during the progression of this disease, particularly in its early stages. We present a case study of a 73-year-old patient with hypertension, dyslipidemia and mild obesity, who suddenly exhibited weakness in all limbs

Materials: Neurological examination revealed impaired consciousness and a deficit in the left lower cranial nerve VII. Additionally, the patient showed mild weakness in the right upper limb, severe weakness in the left upper limb, and moderate weakness in the lower limbs.

Methods: Brain CT-scan, brain-MRI, magnetic resonance angiography of the head, transthoracic echocardiography, cardiac magnetic resonance (CMR) EEG and osteomedullary biopsy were performed.

Results: Neuroimaging exams revealed multiple bilateral ischemic lesions. Laboratory tests indicated hypereosinophilia. Parasitological examination of the stool was negative, no allergies were reported, cytogenetic examination of the bone marrow aspirate and osteomedullary biopsy excluded a lymphoproliferative process. Echocardiography showed thickening of the mid-apical lateral wall of the left ventricle and subendocardial hyperdensity, confirmed by CMR, which also revealed hyperintensity due to late gadolinium enhancement and a thrombus within the mid-apical lateral wall of the left ventricle. These findings strongly suggested a diagnosis of Loeffler's endocarditis. During hospitalization, the patient experienced disorientation, aggression, and anosognosia, with EEG showing Generalized Rhythmic Delta Activity sequences preceded by point-wave-like graphoelements. Anticoagulant and steroid therapy were administered. The patient showed gradual clinical improvement, encephalopathy remitted and follow-up CMR indicated resolution of thrombus.

Discussion: A comprehensive diagnostic workup confirmed idiopathic HES. The increased blood viscosity induced by hypereosinophilia itself, along with cardioembolism related to intracardiac thrombus formation, are believed to be the primary mechanisms underlying ischemic strokes. Consequently, all lesions are typically found in watershed areas where the clearance of in situ-microthrombi or emboli from the heart is impaired. Finally, the encephalopathy results both from multiple cerebral infarctions and the neurotoxicity induced by hypereosinophilia.

Conclusions: According to the literature, most cases of HES, particularly those with Loeffler's endocarditis, show cardiorespiratory symptoms upon admission. Neurological findings as the first clinical manifestations make this case-report intriguing. Through this clinical case, we aim to raise awareness among clinicians about hypereosinophilia as a rare cause of stroke and encephalopathy, even in the absence of other symptoms.

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## POSSIBLE MRI PREDICTORS OF HEMORRHAGIC TRANSFORMATION IN ACUTE STROKE PATIENTS UNDERGOING DAPT: A CLINICAL STUDY

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Aims: DAPT is a stroke secondary prevention therapy for different clinical scenarios. DAPT safety and hemorrhagic transformation (HT) predictors in acute ischemic stroke aren't well known. The aim of this study was to identify HT predictors to early detect patients at higher risk of bleeding on DAPT.

Material and Methods: We enrolled consecutive acute ischemic stroke patients, admitted to Stroke Unit between 2020-2022, undergoing DAPT (ASA + Clopidogrel) according to current guidelines, within 96 hours from onset. We collected clinical data. We evaluated the number of acute lesions, lesion volume using ABC/2 method and SVD markers on MRI performed when DAPT was started. The primary outcome was safety, defined as the absence of HT at control CT, 7 days after DAPT beginning.

Results: We enrolled 194 patients [median age 70, 66,5% men]. 28(14,4%) patients presented HT, among these, 4(2%) were PH. 87 patients (44,8%) underwent DAPT for acute carotid stent placement, 61(31,4%) for minor stroke and 46(23,7%) for symptomatic intracranial stenosis. Patients undergoing stenting procedures had higher HT rates (p<0,01). Treatment with Clopidogrel and dual antiplatelet loading dose had more HT (p=0,04, p=0,03). Higher NIHSS relate to HT. We defined a cut-off of 4, over which HT risk increases [AUC 0.799(95% CI 0.753-0.881), p<0.001]. No association between intravenous thrombolysis and HT was found. SVD radiological markers associated in CSVD and individually didn't rely with HT, except for lacunae, determining lower risk of HT (p=0,03). Larger lesion volume on MRI was the best predictor of HT risk (p<0.01). We identified a cut-off volume of 8.2 ml (AUC 0.82, 95% Sensibility 0,79, Specificity 0,8,

CI 0.745-0.9, p<0.001). Lesion volume>8.2 ml resulted in a 10-fold increased HT risk (95% CI 3.69-28.37, p<0.001).

Discussion: MRI volume cut-off is the best HT predictor in acute ischemic stroke patients undergoing DAPT. For patients with stroke volume >8.2 ml, at higher risk, a strict clinical-radiological monitoring could be warranted. Because of higher HT risk, management of Clopidogrel and dual antiplatelet loading dose should be evaluated, particularly, in moderate stroke and after stent positioning. Intravenous thrombolysis isn't associated with HT, so, in patients with minor stroke undergoing this treatment, DAPT for 21 days should be deepened and discussed.

Conclusions: Symptomatic HT during DAPT isn't very frequent, so DAPT may be considered safe in its various indications. However, minor HT events aren't negligible, because they may impair DAPT duration and expose to early ischemic risk, thus, it is useful to identify predictors.

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## ROLE OF ENDOTHELIN-1 AND NITRIC OXIDE IN ACUTE ISCHEMIC STROKE LEPTOMENINGEAL COLLATERALS ACTIVATION


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Background and aims: Good leptomeningeal collaterals (LMC) after large vessel occlusion (LVO) extend time window for endovascular therapy (EVT). Mechanisms regulating the LMC activation are not completely known. Aim of this study was to investigate the role of Endothelin-1 (ET1) and nitric oxide (NO) in post-stroke LMC regulation.

Methods: Ischemic stroke patients within 6 hours from LVO were included. Collateral status was evaluated on a Computed Tomography Angiography scan using the Menon scoring system. Patients were accordingly divided into three groups: poor, intermediate and good LMC. Recanalization was evaluated using Thrombolysis in cerebral infarction (TICI) score. Serum ET1 and NO were evaluated at three different time points from stroke onset: T0 (< 6h), T1 (24h), T2 (48h).

Results: We enrolled 102 patients (mean age was 76 ± 12.35): 45 with good (44.5%), 35 with intermediate (34.3%) and 22 with poor LMC (21.6%). Serum ET1 levels increased whereas NO levels decreased from T0 to T1 regardless of the collateral status. However, in patients with poor recanalization and poor LMC, serum ET1 values were higher at each time point (p 0.005). A significant association was also found between higher ET1 levels at T1 and poor outcome despite a good recanalization (p 0.030).

Conclusion: Although we found no significant association between the extent of LCM and ET1 and NO serum concentrations, present data show that the highest ET1 serum levels at 24 hours predict a poor outcome despite a good recanalization. A sustained ETA receptor mediated vasoconstriction could be hypothesized in these patients.

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## THE OPACIFICATION TIME OF ASCENDING AORTA DURING CT ANGIOGRAPHY AS A PREDICTOR OF HEART FAILURE


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Objective: Heart failure (HF) represent the second most frequent cause of cardioembolic (CE) stroke. Brain CT angiography is routinely performed in the suspect of a large vessel occlusion. Placing a region of interest (ROI) at the level of the ascending aorta during the initiation of CT angiography, the opacification of the vessel is monitored until a threshold value of Hounsfield Unit (HU) is reached, automatically starting images acquisition. The opacification time of the ascending aorta (OTAA) may be affected by heart ejection fraction (EF) and inform on the occurrence of HF already during the emergency management of a stroke patient. We evaluated the existence of a correlation between the OTAA and the EF and tried to identify a cut-off value of this time, able to predict a diagnosis of heart failure and cardioembolic stroke.

Materials and Methods: We screened all patients discharged from the Policlinico Gemelli in Rome during an 18-month period, with a CT angiography of cerebral vessel and an echocardiographic evaluation of the EF performed during hospitalization. The opacification time of the ascending aorta was calculated as the time needed to reach a threshold of 40 Hounsfield Unit (T40HU) in the ROI. This threshold was chosen arbitrary as the one to which the machine (Meditech, GE-Optima TC 660) automatically starts arterial phase imaging acquisition. The Spearman correlation test was used to evaluate the existence of a correlation between the EF and the T40HU. We used a receiver operating characteristic (ROC) curve analysis to identify a cut-off value of the T40HU able to diagnose with good sensitivity and specificity the presence of HF and cardioembolic stroke.

Results: We enrolled 382 patients and found an inverse correlation between the EF and the T40HU, indicating longer time for aorta opalization as the EF decreases (Spearman Rho= -0.46, p<0.001). The ROC curve analysis identified a cut-off value of 16,8 seconds for the T40HU as able to predict with good sensitivity (90%) and specificity (63%) a diagnosis of heart failure with EF <40% (AUC = 0.84, CI=0.78-0.89) and acceptable sensitivity (67%) and a specificity of (66%) a diagnosis of cardioembolic stroke (AUC = 0.68, CI=0.61-0.74). Through the multivariate logistic regression, we confirmed this cut-off as an independent predictor of HF (EF<40%), and cardioembolic stroke.

Conclusions: The T40HU is a reliable indicator of HF with reduced EF, allowing to esteem heart function already in the emergency department even in the setting of an acute stroke.

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## CAROTID WEB AND ISCHEMIC STROKE, AN UNEXPECTED CASE

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Background: One third of all ischemic strokes is still defined as cryptogenic. The underlying mechanism upon most of them is considered to be the embolism from an undetermined source (ESUS). The Carotid Web is an intraluminal projection of hyperplastic intima arising from the carotid artery bulb which causes blood stagnation with the potential for distal embolization. Recent studies enlight the role of Carotid Web as an under diagnosed cause of stroke, especially in young healthy patients.

Case Presentation: A 66-year-old man came to Policlinico Umberto I ER because of appearance of pain and paresthesias, began in the right arm and extended in 20 days to the omolateral leg. A Cerebral MRI was performed, showing a thrombus inside the intra-cranial left Internal Carotid Artery and a left parietal-occipital and frontal acute ischaemic lesions. A Cerebral CT scan with angio sequences was performed next, detecting a plus image in the left Carotid Bulb, compatible with Carotid Web. The patient underwent a series of exams aimed to detect other plausible causes of the ischaemic stroke (auto-anticorpal screening, trans-toracic echocardiogram, long term ecg monitoring, cardiological examination, …), with negative outcome. Due to the absence of other causes of the stroke, after a brainstorming between Neurologists and Interventistic Neuroradiologists, it was decided to perform a left carotid stenting in order to exclude the Carotid Web, site of blood stasis.

Discussion: Our case underlines how Carotid Web has to be researched as a cause of stroke not only in young and healthy patients. Our patient is an over-sixtyfive but, due to the absence of other relevant causes of stroke, we assumed the carotid web as the responsible of the cerebral infarct. Literature data suggest endovascular treatment in symptomatic Carotid Webs as the best secondary prevention strategy, but there are not trial there to prove it. The rarity of CW hinders randomized clinical trials, so the creation of a unique database grouping all the observed and treated Carotid Webs from international stroke-units would be desirable in order to analyse and confront the results from various treatments (medical treatment vs endovascular treatment).

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## MULTICENTRE TRANSLATIONAL TRIAL OF REMOTE ISCHAEMIC CONDITIONING IN ACUTE ISCHAEMIC STROKE (TRICS BASIC): A MULTICENTRE, RANDOMIZED, PRECLINICAL TRIAL IN FEMALE AND MALE RATS AND MICE. ON BEHALF OF THE TRICS BASIC STUDY GROUP

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Previous results from single laboratories support the efficacy and safety of remote ischemic conditioning (RIC), but phase 2-3 clinical trials have provided conflicting results. TRICS BASIC is a preclinical trial performed within a consortium of 7 Italian research laboratories. The TRICS BASIC trial investigated efficacy and safety of RIC in experimental acute ischemic stroke, using a robust, translationally oriented, randomized preclinical trial design, which included two animal species (rats and mice) of both sexes. The transient endovascular occlusion (60 min in mice; 100 min in rats) of the middle cerebral artery was chosen as the stroke model to be used for the trial. RIC treatment was applied by transient surgical clamping of the femoral artery after reperfusion (10 min in mice; 20 min in rats). Blinded outcomes assessment was performed for functional neuroscore (primary outcome) and infarct volume (secondary outcome) at 48 hours. A dedicated harmonization phase, which included all the participating laboratories, was performed before starting enrollment, to reduce the assessment bias for the neurobehavioral evaluation. The experimental cohort consisted in 206 animals (n=110 mice and n=96 rats). RIC treatment increased the proportion of good functional outcome (composite + 19%; OR 2.15; 95% CI 1.12 to 4.13; $p = 0.021$) and reduced the infarct volume (composite -38%; 95% CI -5% to -71%; $p = 0.013$) in both species, without safety concerns, compared to sham surgery. This study showed a moderate beneficial effect of surgically-delivered RIC treatment applied early after reperfusion in acute ischemic stroke models from multiple species and both sexes.

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## LARGE-SCALE NETWORK TOPOLOGY OF ACUTE ISCHEMIC STROKE PREDICTS FUNCTIONAL OUTCOME AFTER ENDOVASCULAR TREATMENT

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Objective: Mechanical thrombectomy restores blood flow after the acute occlusion of a brain vessel causing ischemic stroke. Volumetric data and vascular atlases guide acute stroke management entirely. [1] Recent literature recognizes the additional predictive value of remote disconnection data reflecting a large-scale network functional organization of the brain. [2] In this study, we test the prognostic ability of lesion topography embedded in different parcellations of

the brain. We compare a vascular atlas with a functional (i.e. grey matter) and structural (i.e. white matter) atlas to test which provides the best outcome prediction.

Materials and methods: We enrolled patients suffering from stroke who underwent EVT at the Stroke Unit of the Padua University Hospital from January 2018 to June 2022. On admission, we collected NIHSS scores, pre-event mRS and post EVT CT/MRI scans. At discharge and after three months we collected the NIHSS and mRS. [3] Lesions following EVT were manually segmented and embedded in a vascular atlas, a functional grey matter atlas and a structural white matter atlas. We performed a ridge regression model with a bagging procedure to assess outcome prediction. In addition, BCB toolkit indirectly estimated the structural disconnection caused by the lesion and whole-brain temporal correlation maps were calculated. We investigated the relationship between functional outcome and brain features at a voxel-wise level implementing a linear correlation including disconnectivity maps for each patient.

Results: A total of n=66 patients met inclusion criteria. The prediction of the mRS using lesion topography was the most robust for the functional and structural atlas (R2=0.382), followed by Figley's structural atlas (R2=0.338), while the vascular atlas provided the lowest prediction (R2=0.146). The voxel-wise functional dysconnectivity map showed areas significantly correlated with the mRS overlapped with the visual, sensorimotor and dorsal attention networks. The structural disconnection analysis showed the corticospinal tract, corpus callosum, corona radiata, thalamic radiation, left inferior and superior longitudinal fasciculus significantly correlated with the mRS ($p<0.05$).

Discussion: Considering lesion topography in a functional/structural atlas framework provided a better estimation of functional outcome in comparison to a vascular framework. In addition, we described post-stroke disconnectome patterns as applicable prognostic measures.

Conclusion: These results suggest these measures could be used in clinical practice, at present driven by neuroimaging features including solely volumetric and vascular scores.

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## SUCCESSFUL DELAYED THROMBECTOMY IN A 12-YEAR-OLD PATIENT WITH ACUTE ISCHEMIC STROKE: A CASE REPORT

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Aims: To describe a case of pediatric acute ischemic stroke (AIS) due to middle cerebral artery dissection and treated with delayed endovascular treatment (EVT).

Materials and Methods: A patient with an ischemic stroke underwent a neurological examination, brain computerized tomography (CT) scan, brain magnetic resonance imaging (MRI) with angiography and perfusion studies, and EVT.

Results: A 12-year-old girl with no previous medical history was driven to the pediatric emergency department for sudden onset of aphasia associated with paresthesias and weakness in the right upper limb that occurred after minor facial trauma (dip in the pool). Upon arrival, the symptoms had already regressed. She was discharged after a normal brain CT scan. The following day, she returned to hospital after waking up with recurrence of symptoms. Her National Institutes of Health Stroke Scale (NIHSS) score at admission was 9. Brain CT scan showed a left lenticular hypodensity [Alberta Stroke Program Early CT Score (ASPECTS) of 8] and in supraortic CT angiography a left middle cerebral artery occlusion was found, with good collateral flow. MRI with perfusion imaging underlined a significant Diffusion Weighted Imaging – Perfusion Weighted Imaging mismatch in the left middle cerebral artery territory. She was treated with EVT with a final extended thrombolysis in cerebral infarction (eTICI) score of 2c. The patient experienced a full neurological recovery and was discharged home in excellent conditions one week after AIS.

Discussion: In the pediatric setting, EVT still remains an off-label procedure, especially for patients presenting outside the 6-hour time window. Emerging evidence suggests that patient selection should be more imaging-based than time-based and that the therapeutic window for EVT in children may extend beyond the established window for adult patients, with several reports of successful EVT even after 48h from AIS onset [1,2].

Conclusions: In pediatric strokes, advanced neuroimaging techniques could ameliorate the selection of patients who may benefit from reperfusion therapy. However, whether it is correct to apply the same criteria used in adults is still uncertain.

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## A CASE OF EARLY CT-SCAN FALSE NEGATIVE TYPE-A AORTIC DISSECTION PRESENTING WITH SYNCOPE AND ISCHAEMIC MYELITIS: A CASE REPORT

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Introduction: Aortic dissection is defined as disruption of the medial layer caused by intramural bleeding, followed by the separation of the aortic wall layers and formation of a false and a true lumen. Ischaemic spinal cord damage due to type A aortic dissection is rare, having an incidence of 1.0% [1]. Sensitivity and specificity of Computed Tomography Angiography (CTA) for aortic dissection are > 95%, with an accuracy reaching 99.5% [2]: CTA and Magnetic Resonance Imaging (MRI) are highly accurate, although false negatives and positives could occur.

Case Presentation: A 77-year-old man who had been suffering from hypertension, hypercolesterolemia and bradicinetic syndrome was admitted to the Emergency Department for a sudden loss of consciousness. Blood exams showed high levels of cardiac troponins. ECG revealed an episode of bradicardic atrial fibrillation associated with alteration of the ST segment in the inferior precordial derivations. Cardiac echography showed no pathologic changes of the aortic shape and normal kynesis of the left ventricule. CT scan was negative for acute aortic pathology. After a few hours, the patient appeared aware and collaborant, but he developed palsy and anesthesia of both legs, which did not improve during hospitalization. As MRI showed a case

of transverse myelitis, a chest CTA scan was performed, which was negative. After having ruled out other aetiologies, we prescribed an oral anticoagulant therapy to avoid cardioembolic events. However, since the strong clinical suspect, we performed a third CTA scan after a week, which revealed an aortic dissection of the sino-tubular junction associated with an intramural heamatoma expanding to the abdominal aorta. The patient underwent a surgical operation.

Discussion: This case is a rare example of a false negative result of a CT scan in the context of a type A aortic dissection. Aziz and others [3] described a case series in which four patients had a type-A aortic dissection which was not recognised by CT scan, pointing out the existence of the chance of failing of this technique, although the high accuracy.

Conclusion: We believe it is important to highlight false-negative cases of this acute and high mortality-related pathology in order to improve the diagnostic process and even to consider an ideal timing in which it could be useful to repeat the CT scan. This could avoid missing the chance to offer a correct surgical treatment and the possibility to recover from the ischaemic process.

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## STURGE WEBER SYNDROME TYPE III IN ADULT PATIENT: A CASE REPORT

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Clinical presentation: A 50y old woman, without a previous relevant medical record, presented to emergency room (ER) reporting a first acute episode of left hemianopsia lasting 30 minutes followed shortly by the appearance of left hemisoma weakness and hypoesthesia with a marching course lasting 30 minutes. Neurological examination showed no focal signs. CT brain showed right cortical frontal-parietal-occipital hyperdensity similar to subarachnoid bleeding but with normal CT angiography. Brain RMN showed an enhancing right cortical fronto-parietal hyperintensity and thickening and a lesser extent also in the right occipital side and in left cingulate gyrus with possible post-critical significance but not excluding inflammatory disease like FLAMES or meningitic causes. We started anticonvulsant therapy and patient was admitted in the Neurological Unit Care. Laboratory test including autoimmunity, infectivological and thrombophilia screening were normal. Cervical spine MRI, EEG and full body CT were negative. CSF analysis showed 33 mg/dL protein, 9 white blood cells/mm3, intrathecal oligoclonal bands synthesis, virological and culture grew negative and malignant cells absent. In the hypothesis of inflammatory disease started Methylprednisolone ev therapy. The brain RMN check was found to be unchanged to previous one and anti MOG antibodies were negative. We decided to perform an angiographical study that showed a slightly prominent capillary-venous reticulum with early opacification of adjacent cortical outflow veins suggested the hypothesis of right hemisphere angiomatosis.

Discussion: Sturge-Weber syndrome (SWS) is a rare pediatric neurocutaneous syndrome defined, in the complete form, by the association of a facial capillary malformation with choroidal angioma, and/or leptomeningeal angiomatosis. Clinical presentation in late adulthood is possible but rarely reported and all the described cases are without facial port-wine stain but with specific typical characteristic neuroradiological findings (type III) [1]. Seizure is the most common neurological manifestation and stroke-like episodes, paroxysmal paralysis, transient hemiparesis and migraine are other neurological manifestations [1,2]. MRI features are in the form of T2W hyperintense signal in the subcortical white matter beneath the region of leptomeningeal angiomatosis. Cerebral angiography demonstrates aberrant pattern of both the arterial and venous cerebral circulation such as arterial thrombosis, abnormal venous drainage, paucity of superficial draining veins [2,3].

Conclusions: We report a rare case of adulthood variant of SWS in the fifth decade of life with no cutaneous and ophthalmological abnormalities. Diagnosing isolated leptomeningeal angiomatosis in late adulthood is challenging. Characteristics find of brain MRI different modalities and cerebral angiography can aid in establishing the diagnosis of SWS III after excluding infection, granulomatous inflammation and meningeal carcinomatosis.

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## UNDERSTANDING THE PHYSIOPATHOLOGY OF CAROTID ARTERY DISSECTIONS AND PREDICTING THE EVOLUTION. A REAL CASE FLUID DYNAMIC AND MECHANICAL SIMULATION

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Purpose: In this study, we performed a computer simulation to investigate the mechanical and rheological properties of symptomatic carotid artery dissection. The flow and vessel wall of a right internal carotid artery dissection in a patient with ischemic stroke were simulated. The aim was to evaluate the ability of the simulation to predict the clinical and physiopathological course of the dissection [1] in terms of the risk of thrombosis (by analyzing the shear strain rate, which evaluates the risk of thrombosis and its pathogenesis [2], cerebral hypoperfusion, deformation of the vessel wall, and extension of the dissection.

Methods: A two-way fluid-structure interaction (FSI) approach was adopted for simulation using Ansys multiphysics software [3]. The simulation considered three different arterial pressure conditions (hypotension, normotension, and hypertension) and two wall elasticity

conditions (normal and atherosclerotic) to analyse the factors influencing dissection evolution. The study results were analysed in terms of vascular wall shear strain rate, wall shear stress, flow velocity, intraluminal pressure, and wall deformation. Results were then compared with the clinical course and CT-angiography data obtained during the 6-month follow-up visit of the patients.

Results: Maximum shear rate was observed at the initial portion of the true lumen, while minimum shear rate was found at the terminal portion of the false lumen. The highest pressure occurred just prior to the dissection, coinciding with the greatest wall deformation. Maximum wall shear stress was identified at initial part of the true lumen.
Discussion: Analysis of shear rate demonstrated a low thrombotic risk, consistent with the absence of ischemic recurrence in the patient after 6 months. Wall shear stress analysis indicated a low risk of dissection extension, in line with the radiological stability observed during the same period. The simulation revealed high shear stress in the medial wall of the patient's C2 carotid segments, which correlated with aneurysmal dilation in those areas at the 6-month follow-up. Arterial pressure emerged as the primary determinant of thrombotic risk and wall deformation.

Conclusions: Computational simulation successfully predicted the clinical and pathophysiological evolution of a carotid artery dissection in a real case. The findings highlight the importance of studying rheomechanical parameters in determining the risk of complications and the course of dissection. This approach holds promise for personalized study and treatment of arterial dissections, leading to improved clinical management of patients.
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## RISK FACTORS FOR POST-STROKE SEIZURES FOLLOWING REVASCULARIZATION THERAPIES: DATA FROM THE POPULATION OF MODENA, NORTHERN ITALY

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Introduction: Cerebrovascular diseases represent the most frequent cause of acquired epilepsy in adult patients. However, the incidence and risk factors for post-stroke seizures in patients receiving reperfusion therapies have not yet been completely assessed.
Materials and Methods: Retrospective monocentric study of adult patients who received reperfusion therapies (e.g. intravenous thrombolysis [IVT] and endovascular thrombectomy [ET]) for a first ever acute ischemic stroke at the OCB Hospital in Baggiovara (Modena), Italy. Data collection occurred from January 2014 to December 2020. Early (ES) and late (LS) post-stroke seizures were classified according to the last ILAE definitions. The incidence of LS was assessed through a survival analysis, while a Cox regression model was used to identify outcome predictors.

Results: 974 patients were included, 607 (62%) and 139 (14%) of whom were treated with IVT or ET, respectively. In 228 cases, both treatments were performed. Overall, 25 patients (3%) developed ES, whereas LS occurred in 59 patients (6%). The highest incidence of LS was observed within 12 months from stroke (3.5%), whereas the cumulative rate of LS was 5.5% and 6.2% at 3 years and 5 years, respectively (mean follow-up: 48 months). Cortical involvement (HR 6.9 95% CI 2.3 – 20.4; $p = 0.04$) and stroke severity (e.g. NIHSS $\geq 11$) (HR 4.4, 95% CI 1.02 – 18.6; $p < 0.001$) were the main variables independently associated to the development of LS.

Conclusion: In our cohort the cumulative incidence of post-stroke seizure was low. Stroke severity and cortical involvement were independently associated to the risk of LS.
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## UNILATERAL RELAPSING PRIMARY ANGIITIS OF THE CNS IN ISOLATED HEMIHYPERPLASIA: A RARE CASE REPORT

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Introduction and Aims: Primary angiitis of the central nervous system is a well-known clinical entity, characterized by inflammation of the arteries of the brain, spinal cord and leptomeninges. Strictly unilateral findings, involving only one cerebral hemisphere, have been reported very rarely: in such cases, hemispheric differences in immune response mechanisms have been postulated [1].

Materials: We present the case of an 18-year-old man previously diagnosed with isolated hemihyperplasia (OMIM:235000), a rare congenital condition implying mild overgrowth of the right side of the body. The patient, whose medical history was negative for cerebrovascular risk factors, presented at the Emergency Department with right-sided hemiparesis starting abruptly one day prior.
Methods: An urgent contrast-enhanced brain MRI revealed an acute ischemic lesion in the left middle cerebral artery territory, just adjacent to the lateral ventricle, in the context of widespread unilateral white matter disease. Antiplatelet therapy was started as secondary prevention. The supra-aortic trunks and the circle of Willis were extensively examinated; however, the combination of Doppler ultrasound, CTA, black blood MRI, FDG PET-MRI and cerebral angiography displayed no sign of lumen or vessel wall alterations, with normal cerebral hemodynamics. A cardiac work-up, including both a transthoracic and a transesophageal echocardiography as well as a 24-hour Holter ECG monitoring gave negative results. Transcranial Doppler with bubble test found no evidence of intracardiac or intrapulmonary right to left shunts and toxicology, thrombophilia and immunological screenings were unremarkable except for positive serum anti-nuclear antibodies. Genetic testing for hereditary cerebral microangiopathies came back negative. The patient underwent a lumbar puncture and CSF analysis resulted within the normal range; however, oligoclonal bands were

detected. At this point, the hypothesis of small-vessel cerebral vasculitis was formulated and infectious causes were ruled out. As the diagnostic work-up was approaching its end, our patient experienced a recurrent acute ischemic stroke involving the left nucleocapsular region, as demonstrated by a control brain MRI.
Results: A diagnosis of primary angiitis of the CNS with strictly unilateral presentation was made and the patient was started on intravenous Cyclophosphamide. After a 6-month neurological follow-up, no signs of relapse were found.
Discussion and Conclusions: To the best of our knowledge this is the first literature report describing a case of unilateral relapsing primary angiitis of the CNS in the context of isolated hemihyperplasia. We believe this association supports the intriguing hypothesis of lateralized immune reactivity between the right and left brain.
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## NEUROEMOTICONS: MOTOR APHASIA ASSOCIATED WITH AGRAPHIA AND ASYMBOLIA FOR NON-LINGUISTIC PICTURES REVEALED BY A WHATSAPP MESSAGE

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Objective: To describe the case of a patient with sudden onset of motor aphasia associated with agraphia and asymbolia for non-linguistic pictures revealed by a WhatsApp message.
Methods: Case report.
Results: A 76-year-old woman affected by diabetes mellitus, Hashimoto thyroiditis and stomach neuroendocrine tumor underwent a thromboendarterectomy for a severe asymptomatic left-sided carotid artery stenosis. A few hours after the surgical procedure, she developed a motor aphasia with retained comprehension and mild right-sided facial-brachial paresis. She attempted to write a WhatsApp message to her daughter (later, she recalled that she aimed to inform the daughter about her status, asking if she was able to come to visit). The WhatsApp message that she sent revealed a severe impairment of written language, with incongruous use of emoticons that were inappropriate to the context and the intended meaning. The head CT and angio-CT did not reveal any acute cerebrovascular lesion or new vessel occlusion. Symptoms disappeared completely in a couple of hours. A subsequent brain MRI did not reveal any recent ischemic lesion.

Discussion: Patients with aphasia are generally able to represent objects, events and states using concrete and abstract graphic symbols [1]. Alexia and agraphia can be interpreted as manifestations of visual asymbolia (also called cortical visual aphasia) caused by a lesion or functional disruption of the left angular and supramarginal gyrus, involved in language processing. In 1870 Carl Finkelnburg (1832-1896) challenged the view that aphasia was a language disorder, by proposing that it should be regarded as a disruption in the correct understanding of the symbolic meaning (asymbolia) [2]. Our patient was affected by motor aphasia with agraphia; her neurological deficit entailed an impairment in the choice of emoticons used to graphically accompany the meaning of a written text providing emotional nuances to it. During the acute phase only motor aphasia and motor impairment were identified and adequately tested; it was not established whether she could accurately perceive and describe but not recognize the emoticons (visual agnosia).

Conclusions: This case is intriguing as it reproposes the ancient question of whether and to what extent aphasia and agraphia should be interpreted as the result of an impaired ability to understand and intentionally use concepts by means of acquired symbols (linguistic or graphic).
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## PULSATILITY INDEX AS A PROGNOSTIC MARKER OF COGNITIVE AND CLINICAL OUTCOME IN A COHORT OF PATIENTS WITH ACUTE NON-DISABLING STROKE AND TIA WITH DIFFERENT ETIOPATHOGENESIS

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Background and aims: An impaired vasomotor reactivity (VMR) represents a negative prognostic factor for vascular and degenerative cognitive deterioration [1,2]. An elevated Pulsatility index (PI) might be related to impairment in several cognitive domains in patients with lacunar infarcts [3]. Currently, no prognostic markers are available in acute phase to assess the clinical/cognitive outcome of patients with acute non-disabling stroke or TIA. We aimed to assess if cerebral hemodynamics, evaluated by VMR and PI, represented a prognostic marker of clinical/cognitive outcome in acute Stroke/TIA patients.

Methods: Patients with TIA/non disabling stroke of anterior circulation were enrolled. Stroke etiopathogenesis was defined according to clinical guidelines. The observation period of 12 months included 4 assessments: T1 (48-72h from onset), T2 (1 month follow up [FU]), T3 (6 months FU) and T4 (12 months FU). Clinical scales and cognitive tests were performed every time (T1-T4), whereas VMR and PI of MCA and PCA were registered at T1 and T3.
Results: 124 patients with acute non disabling stroke/TIA and a median age of 66 (54.75-74.25) years were enrolled. 71% were men and 69,4% had a stroke. At T1, we found an inverse correlation between MCA PI and MMSE ($p<0.0001$) and MOCA ($p=0.001$) and between PCA PI and MMSE ($p=0.004$) and MOCA ($p=0.003$). A positive correlation was found between age and MCA PI ($p<0.0001$) and PCA PI ($p<0.0001$), while an inverse correlation was registered between age and MMSE ($p<0.0001$) and MOCA ($p<0.0001$). The same results were confirmed at T3. An inverse correlation was found between MCA PI at baseline and MOCA at T2 ($p=0.001$), MMSE ($p=0.014$) and MOCA ($p=0.001$) at T3, MMSE ($p=0.005$) and MOCA ($p=0.003$) at T4. An inverse correlation was registered between baseline PCA PI and MMSE ($p=0.003$) and MOCA ($p=0.004$) at T2, MMSE ($p=0.027$) and MOCA ($p=0.003$) at T3, MOCA at T4 ($p=0.020$). A positive correlation was observed between baseline MCA PI and mRS at T2 ($p=0.025$), T3 ($p=0.003$) and T4 ($p=0.001$). We also performed a multi-regression

analysis to explore the effect of all the vascular risk factors on PI at baseline. We found that age and diabetes were the main risk factors influencing MCA PI at T1 ($p<0.0001$) and that age was the only factor influencing PCA PI at T1 ($p<0.0001$).
Conclusion: A higher MCA/PCA PI in acute phase is a prognostic marker of worst cognitive/clinical outcome in patients with ischemic non disabling stroke/TIA.
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## SPORADIC CEREBRAL AMYLOID ANGIOPATHY IN LATE-ONSET EPILEPSY: A CASE-CONTROL STUDY

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Aim of the study: Sporadic cerebral amyloid angiopathy (CAA) is characterized by progressive amyloid deposition in the walls of leptomeningeal and small cortical arteries of the central nervous system [1]. Epilepsy is a common manifestation during the course of CAA [2]. Given the high frequency of CAA in elderly population and the epileptogenic role of cortical hemorrhagic lesions, it may be hypothesized that CAA can explain a proportion of late-onset epilepsies of unknown etiology. This study aims to assess the prevalence of CAA in patients with late-onset (>50 years) epilepsy of undetermined or vascular etiology and in age-matched non-epileptic controls.

Materials: We included subjects with late-onset epilepsy and controls affected by other neurological conditions.
Methods: All subjects underwent MRI (1.5 Tesla) including blood-sensitive sequences. In the epilepsy group, MRI had to be performed within 60 days from epilepsy onset. The diagnosis of probable CAA was posed according to Boston criteria 2.0 [3]. To evaluate differences between groups, a Chi-squared test was performed. We also calculated odds ratio (OR).

Results: We included 76 patients with late-onset epilepsy (39 males, mean age 71.01±8.93 years) and 134 age-matched controls (82 males, mean age 71.04±8.95 years). A diagnosis of probable CAA was done in 15.8% (12/76) of patients with late-onset epilepsy and in 2.9% (4/134) of the control group. This difference was statistically significant ($p=0.0008$). OR for seizures in CAA versus non-CAA was 6.09 (95% CI:1.89-19.64).
Discussion and Conclusion: In the present study, the prevalence of CAA was significatively higher in patients with late-onset epilepsy, suggesting a significant association between probable CAA and late-onset epilepsy. We suggest to perform MRI with blood-sensitive sequences in patients with late-onset epilepsy of undetermined or vascular etiology.

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## WHICH CAME FIRST VERTIGO OR BASILAR ARTERY STROKE? [A CHICKEN AND EGG SITUATION]

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Introduction: Vertigo is considered one of the most insidious diagnoses in the emergency setting. A study evidenced that almost one-fourth of patients with acute vestibular syndrome had stroke [1]. Moreover, 19% of patients with basilary artery occlusion had a prodromal transient ischemic attack, with vertigo and headache being the most common prodromal symptoms (BASICS registry) [2,3].

Case Presentation: A 57-year-old woman with no relevant medical history except for occasional episodes of vertigo came to the emergency department (ED) because of objective dizziness and faintings. The neurological evaluation (NE) suggested a relapse of peripheral vestibular syndrome. As the brain CT showed no relevant features, the patient was discharged home with symptomatic therapy. Over the next three days, she experienced intense episodes of vomiting and remained bedridden. On the fourth day, after waking up healthy, new fluctuating symptoms occurred namely transient speech disturbances and weakness of the right hemisoma followed by contralateral weakness and headache. Therefore, she returned to the spoke center ED where she underwent a new NE which this time was consistent with an acute stroke (NIHSS = 9). A basilar artery occlusion was confirmed by CT angiogram. Because of the unclear onset of symptoms, she was centralized to the Hub Center in order to proceed to mechanical thrombectomy (MT). Upon arrival in Parma, the patient's clinical condition had worsened: she presented with decreased consciousness, speech absence, oculomotor abnormalities (right conjugate gaze deficit and nystagmus in leftward gaze), quadriparesis, more severe on the left side (NIHSS = 18). The endovascular procedure was effective and the patient had a gradual and complete recovery. As a brain MRI performed a few days later excluded recent ischemic lesions, it was unlikely to date the stroke onset back to the first episodes of dizziness. Further diagnostic investigations were performed and a patent foramen ovale with a large shunt and deep vein thrombosis were found out. Rheumatologic and thrombophilic screenings added no relevant elements. Thus, we postulated an etiology of paradoxical embolism, probably caused by episodes of vomiting (Valsalva maneuver) caused by peripheral dizziness. At this time has not yet undergone PFO closure surgery.

Conclusions: Dizziness remains one of the most insidious symptoms in neurology, making the differential diagnosis between posterior circulation stroke and otolaryngologic disorders complex. In this case, we assume that vertigo of peripheral origin was responsible (together with the patient's comorbidities) for a posterior circulation stroke.
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## CONTROVERSIAL ENDOVASCULAR THERAPY IN CHILDHOOD ARTERIAL ISCHEMIC STROKE: A CASE REPORT

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Introduction: Childhood arterial ischemic stroke (ch-AIS) poses a challenge in terms of treatment options due to limited data and different etiology from AIS in adults.
Materials and Methods: We report a case of a 15-year-old basketball player with AIS who underwent rescue therapy with intracranial stenting.

Results: He was admitted to the emergency department of pediatric hospital for acute onset, during a basketball game, of motor aphasia and right hemiplegia (NIHSS score 14) lasting two hours. Brain magnetic resonance imaging (MRI) showed left intracranial carotid apex (ICA) near-occlusion and globus pallidus ischemic lesion. The day after he experienced motor aphasia lasting 40 minutes so he was transferred to our Stroke Unit and cerebral angiography (CA) was done, confirming left ICA subocclusion involving the origin of the medial lenticulostriate vessels, probably due to dissection. Despite medical therapy with dual antiplatelet therapy (ASA plus clopidogrel then ASA plus ticagrelor) and appropriate hemodynamic control, neurological deterioration after 48 hours due to new ischemic lesions in left basal ganglia involving internal capsule occurred. The new CA revealed left ICA occlusion involving also the middle cerebral artery origin. Triple angioplasty with self-expandable stent was performed with ICA recanalization (mTICI 2c) and suspecting an inflammatory etiology, we did not proceed to ICA stenting (ICAS), but nimodipine and high-dose methylprednisolone were started. At 12-hours follow-up, the NIHSS score increased from 1 to 14, and transcranial doppler showed left ICA severe restenosis. ICAS was proposed but the parents declined, referring to another hospital. Meanwhile, a single bolus of cyclophosphamide was infused. In the other hospital, due to ongoing focal deficits, the patient underwent ICAS after 36 hours, but moderate right hemiplegia persisted.

Discussion: Identifying the cause of stroke can be challenging during the acute phase, making timely decisions about acute therapies difficult. Fluctuation of symptoms may provide clues but is not pathognomonic of different ch-AIS etiologies. The potential short and long-term sequelae of mechanical vessel manipulation, particularly in perforator-bearing segments and suspected diseased arterial walls, were additional concerns. The timing of ICAS in this case remains debatable, and we cannot exclude that earlier intervention may have yielded a better neurological outcome.

Conclusion: Endovascular therapies in childhood ischemic stroke remain a subject of controversy. This case report highlights challenges in managing ch-AIS and the potential role of ICAS as a rescue therapy. Future studies should aim to elucidate the safety and effectiveness of ICAS, also depending on stroke etiology.

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## PREDICTING PROGNOSIS OF ACUTE ISCHEMIC STROKE THROUGH ARTIFICIAL INTELLIGENCE: A NOVEL APPROACH BASED ON REAL WORLD DATA

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Background and aims: Making a reliable prognosis when acute ischemic stroke patients are admitted to the emergency department is challenging. Our aim is to assess whether machine learning methods that collect and analyse clinical, demographic and radiological data of patients who are admitted to acute stroke care can predict the individualized clinical outcome at discharge.

Methods: We tested different artificial intelligence (AI) approaches (XGBoost, random forest, and support vector machine regressors) in 715 patients randomly divided into a training cohort (537) and a testing cohort (178). We tested the ability of AI to predict the variation of NIHSS at discharge compared to NIHSS at admission in each patient. We accepted a difference of $\leq$3 points between the predicted and the observed NIHSS variation when the initial NIHSS score was<5 and a difference of $\leq$4 points when the initial NIHSS was $\geq$ 5. For each model, we evaluated the prediction accuracy through the number of patients correctly predicted. Moreover, we calculated the median absolute error and mean absolute error of the regression.

Results: XGBoost emerged as the best machine learning model with an accuracy of 0.61, mean absolute error of 4.35 and a median absolute error of 3.0 in the testing cohort. The results show that NIHSS at admission, evident ischemic lesion at the first brain CT, age and M1 occlusion are the most significant predictors of the NIHSS variation.
Discussion: Our findings can potentially have important clinical implications if we consider that we have no predicting tool that can describe, in the very acute phase, the evolution of severity for each stroke patient. Moreover, we argue that integrating the model with variables acquired in different subsequent phases of the stroke pathway, we can improve the personalized prediction and further extend the prediction of outcome at 3 months or more.

Conclusions: In conclusion, the XGBoost regression model applied to the data available at admission shows promising results in predicting personalized NIHSS variation at discharge.

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## REPERFUSION THERAPIES IN PATIENTS WITH ACUTE ISCHAEMIC STROKE AND ATRIAL FIBRILLATION: DATA ON SAFETY AND EFFICACY FROM A MULTI-CENTER COHORT STUDY

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Background and Aim: Intravenous thrombolysis (IVT) and/or mechanical thrombectomy (MT) are considered best practice in the acute management of ischaemic stroke, improving functional outcome and reducing both mortality, as well as long-term disability. Currently, data regarding the efficacy and safety of reperfusion therapies in patients with atrial fibrillation (AF) reports conflicting rates of hemorrhagic transformation, mortality, and functional outcome. [1] Our study aimed to evaluate the efficacy and safety of reperfusion therapies in patients with acute ischaemic stroke and AF.

Materials and Methods: We pooled individual data from two multicenter prospective cohort studies (RAF and RAF-NOACs) [2,3] which had enrolled consecutive patients with acute ischemic stroke and AF. Demographic, clinical, and treatment data were collected. We compared the baseline characteristics of patients treated and untreated with acute reperfusion therapies (IVT and/or MT) using the $\chi 2$ test for categorical variables or the Mann-Whitney U test for continuous variables. Multivariable logistic regression analysis was performed with the aim of identifying independent predictors for outcome events: 90-day favourable outcome (mRS 0-2) and mortality.

Results: Overall, 1,736 patients were included, 441 (25.4%) in the reperfusion-treated group and 1,295 (74.6%) in the untreated group. Treated and non-treated patients differed in age (mean 73.5±9.9 years versus 76.8±9.7, respectively), NIHSS score (mean 11.7±6.2 versus 7.2±6.7), presence of paroxysmal AF (48% versus 39.9%), and history of stroke or TIA (18.8% versus 28.7%). At 90 days, 120 patients were deceased (18 in the treated group and 102 in the untreated group) and 1,032 patients had favourable outcome (270 in the treated group and 762 in the untreated group). The results of the multivariable analysis evidenced that reperfusion therapies were significantly associated with a favourable outcome, but not with mortality (OR:2.28, 95% IC:1.65-3.17 versus OR:0.61, 95% IC:0.33-1.11, respectively). Regarding other risk factors, age and the NIHSS score were inversely correlated with favourable outcome (OR:0.97, 95% IC:0.96-0.99 and OR:0.84, 95% IC:0.81-0.86, respectively). These variables were also associated with a higher rate of mortality (OR:1.04, 95% IC:1.01-1.07 and OR:1.09, 95% IC 1.06-1.12 for age and NIHSS score, respectively).

Discussion and Conclusions: Patients with AF treated with reperfusion therapies had a significantly higher rate of favourable outcome compared to those patients with AF who had undergone conservative treatment. Mortality tended to be higher in patients with AF who had not been treated with reperfusion therapies.

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## ISCHEMIC STROKE DESPITE ORAL ANTICOAGULANT: RETROSPECTIVE ANALYSIS OF INTRA-HOSPITAL COURSE

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Objectives: Oral anticoagulants (VKA and DOACs) are well-established therapies for the prevention of embolic stroke in patients with atrial fibrillation. Although anticoagulants are associated with a substantial reduction in risk, a limited group of patients (about 1.2% per year) suffer ischaemic stroke despite anticoagulation therapy. The objective of this study is to define the epidemiological characteristics, acute therapeutic management, and intra-hospital course of patients who suffer ischaemic stroke while undergoing anticoagulant therapy.
Materials: Medical records of all patients admitted to the Stroke Centre of the "Policlinico San Martino" Hospital in Genoa from 01/01/2021 to 31/12/2022.

Methods: Selection of all patients suffering ischaemic stroke while undergoing oral anticoagulant therapy. Detection of patients' weight, age, CHA2DS2-VASC, HAS-BLED, ongoing anticoagulant therapy, reason for said treatment, biohumoral parameters, ASPECT, NIHSS, mRS.

Results: Of the 1351 patients admitted to the Stroke Centre between 01/01/2021 and 31/12/2022, 149 (11%) had an ischaemic stroke during oral anticoagulant therapy. Of those, fifty-five patients (36%) were female, mean age 81 years. The mean CHA2DS2-VASC score was 4.6. One hundred and nine patients (71%) were taking DOAC, 40 patients (26%) were taking AVK. The mean value at NIHSS was 11 at admission, 8 at 24 hours and 7 at discharge from the Stroke Centre. The mRS at admission was 1, at discharge 3.7, with thirty-three patients passing away at the hospital. Eighty-five patients (55%) had LVO, fifty-nine (38%) underwent mechanical thrombectomy and twenty-one (13%) were treated with rTPA. In fifty-four (35%) patients the cause was due to inappropriate underdosing or poor compliance. In fifty (33%) patients no clear reason was identified, in twenty-one (14%) there was congruous stenosis of an intra/extracranial vessel. In the remaining cases, rarer aetiologies, multiple causes (including underdosing and malabsorption) or alternative diagnoses were identified.

Discussion: In the majority of the examined patients, the occurrence of stroke seems to be explained by inappropriate subtherapeutic dosing, by poor adherence to treatment or a non-cardioembolic aetiology. These observations are consistent with what is currently reported in the literature.

Conclusions: The problem under review is as topical and pressing as ever, and many related questions still lack an unanimous response. In particular, which is the best therapeutic strategy for secondary

prevention. For this reason, this analysis represents a starting point for the generation of subsequent prospective studies.

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## HYPOGLOSSAL NERVE PALSY DUE TO CAROTID ARTERY DISSECTION: REPORT OF TWO CASES

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Introduction: Unilateral hypoglossal nerve palsy may result from several different pathologies. It is important to define the underlying pathology to manage the condition wisely. Among the vascular causes of isolated HN palsy ICA dissection is the most common. We present two cases of hypoglossal nerve palsy due to internal carotid artery dissection (ICAD) and discuss the potential mechanisms of acute hemi lingual atrophy.

Case Report: The first patient was admitted to the Department of Neurology due to swallowing difficulties, hypomobility of the tongue, ptosis and miosis of the left eye and neck pain. The tongue deviated to the left when protruded with left hemiatrophy. Magnetic resonance angiography (MRA) of the head and neck visualized a lack of opacification of the left internal carotid artery starting from the bulb, where it appeared markedly thinned, a finding compatible with occlusion due to dissection. The patient was discharged with antiplatelet therapy and extracranial vessel ultrasound (US) control, after one week, showed recanalization of the vessel. The second patient was referred to the Department of Neurology due to articulation disorders and swallowing difficulties associated to altered movements of the tongue. On admission, neurological examination revealed tongue deviation towards the left side with evidence of atrophy of the left half of the tongue. Computed tomography angiography (CTA) of the head and neck showed severe stenosis of both distal cervical and petrous part of left internal carotid artery. Epiaortic vessel US was normal. The patient was discharged with antiplatelet therapy. In both patients the atrophy of the tongue began acutely and resolved after a few weeks. Furthermore, the two patients didn't present cerebral ischemic events.

Discussion: Malignancy and surgery are the most common causes of isolated HN palsy. Vascular causes are rare, but they should be suspected when risk factors are present and symptom onset is acute. In our two patients the atrophy of the tongue had an acute onset and gradually improved during the hospitalization. Likely it was consequent to the local mass effect by which the dissection might acutely impair the function of the HN.

Conclusion: ICAD must be considered in differential diagnosis for young and middle-aged patients when an acute XII nerve palsy is found, isolated, or associated with other focal neurological symptoms. Vascular etiologies are rare and generally cause compressive HN neuropathy that could be identified with meticulous imaging.

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## ADVANCED STROKE EVALUATION IN EMERGENCY DEPARTMENT

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Background: The ischemic stroke, one of the principle leading causes of death and disabling disease, can depend on various causes divided into 5-6 subtypes, including cryptogenic stroke (CIS). A common cardiac cause of CIS, especially in young patients, is the foetal persistence of the patent foramen ovale (PFO) which allows communication between the two atria and determines a right-to-left shunt with the consequent risk of passage of thrombi from the venous to arterial circulation system bypassing the pulmonary tree. The presence of PFO affects around a quarter of population, but it should be emphasized that it does not necessarily cause CIS.

Case Report: Man, 35 years old, arrived in emergency department (ED) for suspected CVA with symptoms that occurred few hours before. During the anamnesis, there were no noteworthy pathologies. Vital parameters, EKG and ABG were normal, while the neurological objective examination showed speech disorder, right facio-brachio-crural weakness with greater brachial involvement, for which it was performed a skull CT that was negative. Considering his young age and in the doubt of a possible malformation-aneurysmatic pathology of the intracranial arterial branches, an angio-CT was executed, which also was negative. Given the need to identify the cause of the ischemic event, a possible cardioembolic origin was investigated and a transthoracic echocardiogram (TTE) was performed which revealed a moderate tricuspid regurgitation with evidence of a jet directed towards the interatrial septum where there was an aneurysm without apparent shunt with color-Doppler. Therefore, the TTE was concluded by performing a Bubble test which highlighted a right-to-left shunt probably due to PFO and a transcranial Doppler (TCD) was executed to confirm the diagnostic suspect. The patient was directed in a cardiology department.

Conclusion: The increased diffusion of ultrasound practice in ED allows to diagnose easily the PFO-related stroke, recording a higher incidence than in the past. Nowadays, transesophageal echocardiography with contrast (c-TOE) is accepted as the gold standard for detecting right-to-left shunt through a PFO, but it is not a procedure to execute in ED. Moreover, other imaging modalities that use contrast agent such as TTE, TCD, CT and cardiac MRI have shown to have similar sensitivity and specificity in detecting a PFO, or making a differential diagnosis, when compared to TOE.

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## THE ROLE OF ATRIAL CARDIOPATHY AS POTENTIAL CAUSE OF EMBOLIC STROKE OF UNDETERMINED SOURCE

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Background: Atrial cardiopathy (AC) is increasingly considered a potential mechanism of embolic stroke of undetermined source (ESUS). [1,2] Preliminary data from the ARCADIA trial have shown that anticoagulation would not be beneficial for preventing strokes in patients with AC. Etiological misclassification may have limited our understanding of the link between AC and ESUS due to the heterogeneous ESUS construct. After application of a recently proposed ESUS update[3], we investigated the pathogenic role of AC in ESUS.

Methods: We retrospectively included consecutive ESUS patients admitted to our Stroke Unit from-2018-to-2022. ESUS was defined according to standard criteria, then we applied the recently proposed construct and excluded patients with (1) high-risk PFO, (2) high-risk characteristics of supracardiac non-stenosing atherosclerosis, (2) cancer-related hypercoagulability. AC was defined as left atrial enlargement (LAE) based on standard criteria: LAVI>34mL/m2. The entire cohort was divided per LAE presence/absence: AC+ESUS if LAVI>34mL/m2 and AC-ESUS if LAVI≤34mL/m2. We assessed (1) clinical and radiological features of ESUS with AC, (2) the association between AC and stroke severity/outcome, (3) the risk of stroke recurrence, (4) the association between LAVI and stroke risk.

Results: Among 414 consecutive ESUS patients with LAVI measurement, 116 (28%) did not meet the recently proposed ESUS construct, 298 patients were included in the final analysis. The overall AC prevalence was 42%. AC+ESUS patients are older, have more hypertension, coronary artery disease and supracardiac atherosclerosis compared to AC-ESUS, suffers from more cortico-subcortical infarcts and fewer small isolated cortical lesions. We found no association between AC and stroke severity (aOR 0.99, 95%CI 0.95-1.03) and good outcome at 3-months (aOR 1.43, 95%CI 0.78-2.63). Over a median of 20 months, recurrent ischemic stroke occurred in 17 patients (5.9%). Kaplan-Meier analysis showed no difference in stroke recurrence among patients stratified according to AC (log-rank test, p=0.149), even after adjusting for baseline risk factors (HR 1.40, 95%CI 0.47-4.18). LAVI as a continuous variable was associated with stroke recurrence in AC-ESUS (aOR 1.44, 95%CI 1.08.1.93, p=0.013).

Conclusion: The prevalence of AC is higher in ESUS defined according to the proposed update, but despite this, it still unclear the role of AC as potential cause of ESUS and whether AC is an indicator of stroke recurrence. Other biomarkers other than LAE may better discriminate AC or we may have applied the wrong LAVI threshold to define LAE. Our results could be useful in the design of future trials attempting to demonstrate the benefit of anticoagulation in ESUS patients with AC.

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## NEUROSONOLOGICAL VASCULAR EXAMINATION IN DIAGNOSIS AND FOLLOW-UP OF AN INTRACRANIAL ARTERIAL STENOSIS IN A PATIENT WITH DOUBLE-POSITIVE ANTIPHOSPHOLIPID SYNDROME: A CASE REPORT

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Objectives: A case report on a young patient with antiphospholipid syndrome (APS) who experienced an ischemic stroke due to focal stenosis of the right middle cerebral artery (MCA). The study emphasizes the significance of ultrasonographic diagnostics in diagnosing and monitoring cerebral arterial stenosis.

Materials: A 42-year-old female admitted to our ward in 2022 due to clinical suspicion of a minor stroke.

Methods: A multidisciplinary team conducted comprehensive clinical assessments, laboratory tests, neurosonological vascular examination and radiological diagnostics to evaluate the patient.

Results: The patient had a medical history of essential hypertension, oral contraceptive use, and pregnancy-related complications, including an early miscarriage. In 2012, she tested positive for Lupus Anticoagulant (LAC) but she underwent no further checks or therapies. She presented in Emergency Room with dizziness, visual disturbance and left facial weakness lasting for approximately 12 hours. Brain CT-scan revealed a right parieto-occipital hypodense lesion. We immediately performed a thorough neurosonological study of carotid (extra- and intracranial) and vertebro-basilar circulation. The most significant finding was a severe stenosis of the proximal M1 segment of the right MCA (peak systolic velocity = 300 cm/sec), with microembolic signals (MES) in the downstream tract during continuous monitoring for 15 minutes. Angio-MRI confirmed the stenosis, and brain-MRI showed subacute multifocal right-sided ischemia. Blood tests indicated double positivity for aPL antibodies (LAC activity and aβ2GPI IgG). With the APS diagnosis, the patient's treatment was changed to acetylsalicylic acid and warfarin. Subsequent neurosonological examinations showed no changes in the stenosis and, after 6 days, disappearance of MES.

Discussion: Combination of laboratory findings with clinical history and previous LAC positivity led to the diagnosis of APS, according to the revised Sapporo Criteria [1,2]. In APS, stroke and transient ischemic attack (TIA) are the most common manifestation of vascular occlusion [1]. The neurosonological findings in this case pointed towards artery-to-artery embolism as the likely cause of the multifocal

ischemia. The disappearance of MES in neurosonological monitoring during the follow-up, indicated stenosis stabilization and reduced embolic risk after combined therapy with acetylsalicylic acid and warfarin.

Conclusion: A neurosonological vascular examination focused on the concept of Neuro-POCUS (Point of Care Ultrasound) offers a rapid and well-tolerated diagnostic tool. In this case it facilitated immediate identification of both morphological and hemodynamic characteristics of the stenosis through B-mode imaging and various flow-velocity assessment modalities (Color-Doppler, Power-Doppler and Micro-V technology). Furthermore, as we described, it allowed rapid and real-time monitoring of therapeutic response.

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## PROPOSING A REPORTING METHOD FOR NEUROSONOLOGICAL ASSESSMENTS IN CASE OF CAROTID STENOSIS TO TRY TO CLEAR THE CLUTTER. THIS IS HOW WE DO… WHAT ABOUT YOU?

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Objective: Sharing research on establishing a standardized language for ultrasound (US) evaluation of carotid stenosis, based on examination reports, addressing the current heterogeneity in terminology and measurements.

Materials: Carotid US reports often mention stenosis percentages and severity adjectives. However, the variability in calculating stenosis range and lack of reproducibility with digital angiography pose challenges, resulting in ambiguous conclusions and interpretation-dependent outcomes.

Methods: We retrospectively collected carotid stenosis Doppler US reports from patients admitted to our Neurology department between January and December 2022. Definitions of stenosis degree, method used (NASCET or ECST), severity adjectives, and terms related to hemodynamic significance, near occlusion and collateral circulation were examined.

Results: A total of 104 carotid US reports were collected, with 54 also including transcranial color Doppler US for cerebral circulation evaluation. Neurologists conducted 48 examinations, while other specialists performed the rest. Precise percentage diagnoses were reported in 43 exams, while stenosis range was mentioned in 26 exams. NASCET and ECST methods were used in 41 and 23 exams, respectively. Severity adjectives like "moderate" and "critical" were present in 22 and 13 exams respectively. "Collateral circulation" and "near occlusion" were noted in 42 and 9 exams respectively.

Discussion: US has been used for detecting carotid plaques for decades, but discrepancies exist in how carotid stenosis is assessed and defined, not only because of the differences between angiography and US metrics but also because of the high heterogeneity of findings descriptions in the reports. In our opinion, in advanced settings with adequate expertise, it may be feasible to abandon the dichotomous description extracranial/intracranial findings and adopt a new definition: neurosonological study of carotid and vertebro-basilar circulation. Usage of NASCET stenosis range based on velocity criteria and consideration of "unstable plaque" characteristics would be beneficial. Also, different velocity cut-off in symptomatics and asymptomatics for < and > 50%, < and > 70% carotid stenosis should probably be considered.

Conclusions: Accurate carotid stenosis diagnosis with US requires integrating pathophysiological knowledge, clinical evaluation and multiparametric US measurements. Reports should not be limited to measurements but should represent a synthesis of information. In the case of stenosis, the report should encompass local findings as well as those from upstream and downstream circulation, following the pathophysiology of cerebral circulation rather than relying solely on topographical anatomy. Categorizing stenosis within a range helps establish treatment boundaries, although overall clinical and instrumental assessments remain crucial for decision-making both in symptomatics and asymptomatics.

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## ACUTE ISCHAEMIC STROKE DESPITE ANTICOAGULANT THERAPY WITH DOAC: AN UPDATE

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Objective: To investigate patients who developed acute ischemic stroke (AIS) despite appropriate prevention therapy of cardio-embolism with DOACs (Direct Oral Anti-Coagulants).

Materials and Methods: We retrospectively collected data from our single-centre stroke registry of patients admitted from 1st Jan 2020 to 30th Apr 2023. Our sample included patients > 18 yo, treated with DOACs and admitted for AIS. We considered "true DOACs failure" patients reporting optimal adherence, treated with an appropriate DOACs dosage according to currently available guidelines and showed no other determined aetiology according to TOAST classification1.

Results: We collected 52 patients taking DOACs at the time of their AIS (age = 77,5 ± 9,6 yo; NIHSS = 7,3 ± 6,4). 9/52 (17%) had a recurrent event. Only 1 patient was treated with intravenous thrombolysis, 12 with mechanical thrombectomy. 5 patients were excluded because of other emerging determined aetiologies of stroke: 3 had Small Vessel Disease (SVD), 1 had Large Artery Atherosclerosis (LAA) and 1 had two concurrent mechanisms of stroke (LAA + other determined aetiology). Finally, 47 strokes fulfilled criteria for "true DOAC failure": 29 (61,7%) were cardioembolic (CE) and 18 (38,3%) were undetermined because at least one cause other than CE coexisted (UND-a). DOACs plasmatic levels (anti-Xa activity, ng/ml) were determined, at the time of admission, in 22/47 (mean = 103,5 ng/ml ± 81,6): 14 in the group

with CE as unique cause of stroke (92,1 ng/ml ± 67,2) and 8 in the group with competing mechanisms of stroke (118,0 ng/ml ± 98,5). Plasma levels were non significantly different in the two groups (p = 0,44). 3 patients treated with Rivaroxaban 20mg, 1 with Dabigatran 110 BID and 1 with Apixaban 5 BID, had very low DOAC levels (i.e.: <20 ng/ml); in all but one patient the very low levels corresponded to measurements at trough.

Discussion: A residual stroke risk in patients with Atrial Fibrillation despite anticoagulation ranges from 0.7% to 2.3% annually in primary and secondary prevention, respectively. AIS related to DOAC's failure requires a more extensive diagnostic work-up, revealing alternative causes (e.g.: paraneoplastic thrombophilia, mild unstable epi-aortic atherosclerosis, paradoxical embolism, etc.). However, the investigation of DOACs' plasmatic levels reveals low anti-Xa activity at the time of stroke in several patients, who consequently seem not to be protected from cardio-embolism itself. Further assessment of those patients will help to trace the boundaries between "true" and "apparent" failure, and to improve secondary stroke prevention strategies.

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## PSEUDOTUMOR CEREBRI IN SYSTEMIC LUPUS ERYTHEMATOSUS: A CLINICAL CASE

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Introduction: Pseudotumor cerebri (PTC) is a clinical syndrome due to intracranial hypertension (IH), which can be idiopathic or secondary to specific conditions such as venous sinus thromboses, drugs and systemic illnesses. The underlying pathogenic mechanisms are uncertain, but proposed etiologies mainly include cerebral venous outflow abnormalities. In systemic lupus erythematosus (SLE), IH may be due to occult cerebral venous thrombosis (related to vessel inflammation or hypercoagulability) or to corticosteroid withdrawal. Here we describe a clinical case of PTC associated with SLE and cerebral venous thrombosis (CVT).

Materials: A 19-year-old woman presented to our ER with severe headache and vision loss. She has been diagnosed with SLE four years earlier and suffered from arthritis, butterfly rash, renal involvement (class VI nephritis), thrombocytopenia. Her blood exams were positive for ANA and anti-DNA antibodies, with low complement levels. Neurological examination showed bilateral lateral rectus muscle palsies and bilateral early papilledema. Brain CT scan and CT angiography were performed and resulted normal. A diagnosis of PTC was made and both prednisone and acetazolamide were started. After a week, ophthalmologic examination showed severe bilateral papilledema, therefore a lumbar puncture was performed showing an extremely high opening pressure (40 mmHg); subsequently the patient was referred for ventricular shunt surgery.

Results: Brain MRI revealed a right sigmoid sinus slowed down flow, suggestive for cerebral venous thrombosis, which was also confirmed on a repeated CT-angiography. After administration of anticoagulant therapy, the patient showed a progressive improvement of her symptoms.

Discussion: We described a clinical case of PTC presenting with headache, vision loss and bilateral nerve palsy in a patient with SLE. Several risk factors predispose SLE patients to develop PTC: anemia and hypertension, use of corticosteroids, and a hypercoagulable condition. In several reports dural sinus thrombosis was proposed to be the cause of PTC.

Conclusions: PTC should always be suspected in SLE patients presenting with headache, cranial nerve palsies and progressive visual loss, since it is a treatable condition, if rapidly recognized. We also suggest repeating brain imaging if the clinical suspicion remains high, even in presence of normal initial CT/MRI studies. Indeed, the sensitivity of angiography examinations may be limited in the early stages of CVT.

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## ISCHEMIC STROKE FROM MULTIPLE LARGE VESSEL OCCLUSIONS IN SICKLE CELL ANEMIA, A THERAPEUTICAL CHALLENGE

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Background: Acute Ischemic stroke (AIS) is one of the leading causes of disability worldwide. We here report a case of severe steno-occlusive disease affecting both intracranial and extracranial large arteries with an uncommon etiology.

Case report: A 46-year-old man was admitted to the emergency room complaining of the onset, more than 10 hours before, of headache, right-sided sensory disturbances (paresthesias), and visual complaints. The neurological exam with visual field analysis revealed right hemianopia. The patient immediately underwent a brain CT scan and Angio-CT studies of the neck and intracranial vessels. Bilateral occlusion of the Internal Carotid Arteries, and bilateral occlusion of the P1 tract of the Posterior Cerebral Arteries, were discovered. The presence of remarkable compensatory hypertrophy of the right Ophthalmic Artery and Anterior Communicating Artery suggested underlying chronic processes. Despite symptoms compatible with acute stroke, IVT could not be administered as he was late for that line of intervention. Notably, the patient also had Sickle cell disease (SCD), a condition that could be responsible for the acute occlusion of cerebral arteries. The laboratory exams confirmed a current severe anemia (Hb 8,4 g/dL) with hemoglobin S (HbS) levels of 50%. The patient was also dehydrated. IV hydration was started along with erythrocyte apheresis and antiplatelet therapy. The therapeutical targets were HbS <30% and total Hb>10g/dL. The patient successfully underwent these treatments, and the acute neurological deficits significantly improved.

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## LONG-TERM COGNITIVE OUTCOME IN PATIENTS UNDERGOING MECHANICAL THROMBECTOMY FOR MIDDLE CEREBRAL ARTERY OCCLUSION

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Objectives: We had initially investigated the neuropsychological profile of previously cognitively intact patients one week after a successful mechanical thrombectomy for middle cerebral artery occlusion presenting with basal ganglia infarction. The rate of cognitively impaired patients was significantly high. There is limited knowledge regarding the long-term cognitive outcome of these patients. Indeed, the primary objective of this study was to evaluate potential modifications in the severity of cognitive impairment during a stabilized phase following the acute event, with an additional aim to potentially characterize the associated neuropsychological profile.

Materials & Methods: 8 months after thrombectomy (SD = + 2.5) for middle cerebral artery occlusion (M1 tract), 30 patients (M/F = 13/17) underwent a general cognitive assessment using MoCA and an extensive neuropsychological battery evaluating memory, visual praxis, attention, executive functions, and language. Patients were classified as cognitively impaired (CImp) or not (noCImp) according to a MoCA score $< 18$ or $\geq 18$, respectively.

Results: CImp amounted to 53.3%. CImp and noCImp did not differ in NIH-Stroke Scale (NIHSS) at admittance, NIHSS at discharge, ASPECT score, mRS at admittance and discharge, but they did in age ($p = 0.019$). Compared to noCImp, CImp showed worse performances in ratings of executive and attention functions and noun naming. Compared to MoCA performed one week after stroke (mean 15.3), mean follow-up-MoCA was more than 2 points higher (17.73). However, only two patients changed their status from CImp to noCImp, and two others worsened from noCImp to CImp. In the whole sample, the MoCA score was predicted by the age at stroke, NIHSS at admission, NIHSS at discharge, pre-stroke mRS and post-stroke mRS, and by the middle temporal atrophy scale ($p = 0.021$).

Discussion and Conclusions: Patients considered in this longitudinal study showed a relative long-term improvement in cognitive functions. However, the prevalence of CImp remained the same. Patients' long-term cognitive outcome strictly depended on age at stroke, clinical severity of the stroke, and degree of disability (especially residual post-stroke). Their cognitive profile was similar to other conditions involving basal ganglia damage, such as Parkinson's disease and vascular dementia.

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## A RARE CAUSE OF CARDIOEMBOLIC STROKE: CASE REPORT

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Case presentation: A 78-year-old man, who had a medical history of arterial hypertension and dyslipidemia, came to the Emergency Room due to a sudden onset of difficulty in speech and left hemiparesis. He was undergoing treatment using ACE inhibitors. On neurological examination he appeared conscious, oriented and dysarthric. Expressive aphasia and left hemiparesis were observed. The brain CT showed a subacute fronto-temporal ischaemia in the left hemisphere of the brain. The CT-angiography demonstrated a 45% stenosis of the left proximal internal carotid artery, while no stenosis was observed in intracranial vessels. There was no indication for immediate revascularization treatments. The patient was admitted to the Neurology Department. The Brain MRI confirmed the presence of the previously identified ischemic area, without any sign of haemorrhagic infarction. Dual antiplatelet therapy was administered. The transthoracic echocardiogram showed a large mobile mass in the left atrium of the heart (MD 4,2 cm). During diastole, the mass protruded into the left ventricular chamber. There was no apparent impact on systolic function (ejection fraction of 60%) caused by the mass. The patient was referred to the cardiothoracic surgery team. He underwent urgent surgical removal of the mass. The surgical intervention was successful, resulting in complete removal of the mass without any complications. The definite diagnosis of high-grade myxofibrosarcoma was established through histopathological analysis. The Total body PET did not reveal any hypermetabolic focality at the left atrium or at a distance. Two months later, the patient developed dyspnoea on exertion. The cardiac MRI showed a new growth in the left atrium that required additional investigation using cardiac CT which showed a large irregular polylobed growth with implant base in the left auricle, characterized by a significant contrast enhancement. The patient died 2 weeks later.

Discussion: Nearly one-fourth of ischemic strokes are caused by a cardioembolic event. While atrial fibrillation is the leading cause of cardioembolic strokes, cardiac tumours can also be a rare cause. Primary cardiac myxofibrosarcoma is an uncommon and highly malignant tumour that affects the heart. It is characterized by a set of three complications, namely constitutional, obstructive, and embolic complications. Stroke can occur as the initial presentation of this condition [1].

Conclusion: When evaluating a patient with stroke symptoms, it is crucial for healthcare providers to consider a comprehensive range of potential causes, including rare conditions like primary cardiac tumours [2].

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## EARLY NEUROLOGICAL DETERIORATION IN PATIENTS WITH MINOR STROKE DUE TO ISOLATED M2 OCCLUSION UNDERGOING MEDICAL MANAGEMENT: A RETROSPECTIVE MULTICENTER STUDY

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Background: Patients with minor stroke and M2 occlusion undergoing best medical management (BMM) may face early neurological deterioration (END) that can lead to poor long-term outcome. In case of END, rescue mechanical thrombectomy (rMT) seems beneficial. Our study aimed to define factors relevant to clinical outcome in patients undergoing BMM with the possibility of rMT on END and find predictors of END.

Materials and Methods: Patients with M2 occlusion and a baseline National Institutes of Health Stroke Scale (NIHSS) score ≤5 that received either BMM only or rMT on END after BMM were extracted from the databases of 16 comprehensive stroke centers. Clinical outcome measures were a 90-day modified Rankin Scale (mRS) score of 0–1 or 0–2, and occurrence of END.

Results: Among 10169 consecutive patients with large vessel occlusion admitted between 2016 and 2021, 208 patients were available for analysis. END was reported in 87 patients that were therefore all subjected to rMT. In a logistic regression model, END (OR 3.386, 95% CI 1.428 to 8.032), baseline NIHSS score (OR 1.362, 95% CI 1.004 to 1.848) and a pre-event mRS score=1 (OR 3.226, 95% CI 1.229 to 8.465) were associated with unfavorable outcome. In patients with END, successful rMT was associated with favorable outcome (OR 4.549, 95% CI 1.098 to 18.851). Among baseline clinical and neuroradiological features, presence of atrial fibrillation was a predictor of END (OR 3.547, 95% CI 1.014 to 12.406).

Discussion: END is a frequent event in patients with a minor stroke due to involvement of the M2 segment of the middle cerebral artery and represents the most important predictor of long-term poor outcome in patients that are initially intended for medical therapy. Our study corroborates the evidence that rMT is indeed beneficial when END occurs. Clear-cut predictive factors of END are still missing. In our cohort, AF was associated with END, probably due to a series of mechanisms, including the cardiological comorbidities, the reduction of cerebral blood flow, in conjunction with less effective leptominengeal collaterals. Regardless of the underlying mechanism, the results of our study suggest that minor stroke patients with isolated M2 occlusion and concomitant AF should be closely monitored for possible worsening during BMM and promptly considered for rMT.

Conclusion: Patients with minor stroke due to M2 occlusion and atrial fibrillation should be closely monitored for possible worsening during BMM and, in this case, promptly considered for rMT.

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## PREDICTING FACTORS FOR SEIZURES AFTER CEREBRAL VENOUS THROMBOSIS: A RETROSPECTIVE SINGLE CENTER COHORT STUDY

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Background: Seizures are a common complication of cerebral venous thrombosis. In this study, we intended to define clinical and neuroradiological factors associated with early and late seizures and predictors for seizure recurrence.

Materials and Methods: The database of our high-volume tertiary stroke center was screened for patients diagnosed with cerebral venous thrombosis between April 2006 and July 2021. Demographics, clinical, imaging, and instrumental data were collected. We described general characteristics of the population with summary statistics, furthermore, we tested univariate and multivariate associations for early/late seizures and relapses.

Results: Out of a total of 80 patients, 30 had seizures, either within the first week after onset (22 patients) or after (8 patients). Speech impairment and intracerebral bleeding were statistically associated with seizures in univariate analysis, but in a logistic regression model, only

brain damage with hemorrhagic infarct and/or presence of brain hematoma [OR 6.051; 95% CI 1.881−19.468] (p = 0.003) were predicting factors for seizures. Late seizures were significantly more frequent in younger age [OR 0.864; 95% CI 0.763−0.978] (p = 0.020). Early seizures resulted as protective factors for recurrence; an altered state of consciousness at baseline and late seizures resulted as predictive factors for relapses (0.0% vs. 81.0%, p = 0.005, and 100.0% vs. 19.0%, p < 0.005, respectively).

Discussion: Our study underlines that primarily hemorrhagic lesions are highly predictive of seizures during the acute phase. The need to identify patients with CVT at risk for seizure recurrence is relevant, as a definition of specific predictors may determine whether or not epilepsy can be diagnosed and thus treated. Our study points out that seizures occurring beyond 7 days from onset are highly predictive for relapses. Overall, we suggest that CVT patients with hemorrhagic supratentorial brain lesions should be strictly monitored in the acute phase to tackle possible epileptic complications. Besides, in case of late-onset seizures, long-term treatment seems reasonable due to an increased risk of recurrence. Indeed, although the presence of seizures appears to have no impact on the final outcome and long-term disability, the adoption of prophylactic measures according to specific predictors might improve the quality of life of patients.

Conclusions: Our study confirms brain bleeding as the strongest risk factor for seizures after cerebral venous thrombosis. Recurrence is unusual after early seizures, while the presence of late seizures seems to raise the risk of recurrence.

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## GENDER DIFFERENCES IN TIME TRENDS OF INCIDENCE AND CASE-FATALITY OF INTRACEREBRAL HEMORRHAGE


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Aims: Intracerebral hemorrhage (ICH) accounts for up to 20% of all strokes, but it is responsible for up to 70% of one-month stroke mortality. Sex-related differences in ischemic stroke have been widely investigated in several studies, nevertheless, there is still a lack of knowledge on this topic in spontaneous ICH. Thus, the purpose of this observational work is to provide information on ICH incidence during the study period and outcome in terms of case-fatality rate in spontaneous ICH in relation to gender.

Materials and Methods: We recruited patients from a prospective population-based stroke registry, admitted from 2011 to 2020 to the hospitals of the district of L'Aquila with first ever ICH. We evaluated the overall incidence of spontaneous ICH in men and women over the whole study period, the premorbid performance status according to the modified Rankin Scale (mRS). We also assessed case-fatality rates in both sex groups.

Results: The study included a total of 439 (58.7%) males and 309 (41.3%) females, with males having a mean age of 73.2 ±13.6 years and females having a mean age of 78.9 ±12.6 years (p<0.001). The overall incidence rate was 250.7 cases of ICH per 100.000 population per year (95% CI 243.4-257.7). The incidence rate was 30.2 cases per 100,000 person-years (95% CI 27.4-33.2) in men and 20.2. cases per 100,000 person-years (95% CI 18.0-22.6) in women. 51 (13.1%) of men and 48 (18.5%) of women had a premorbid-mRS ≥3 (p=0.026). The global 1-year case-fatality rate was 43.6% (95% CI 34.4-46.5); it was 40.1% (95% CI 43.2-50.0) in males and 48.5% (95% CI 41.1-57.0) in females (p=0.026).

Discussion: ICH seems to be a predominantly male pathology: according to our analysis, the overall ICH incidence rate was higher in men than in women. Females were, on average, 6 years older than males in the study population and, subsequently, more liable to develop comorbidities. Furthermore, men had slightly better outcome in terms of lower 1-year case-fatality rate compared to women, probably, because of their older age and worse premorbid condition.

Conclusions: Gender differences in primary spontaneous ICH is not explored enough field, in which there are still discordant results of studies. Understanding the burden of comorbidities and the underlying mechanisms of these differences on the incidence and outcome in ICH patients, may pave the way to more patient-tailored preventive and therapeutic strategies.

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## SUCCESSFUL INTRAVENOUS THROMBOLYSIS IN CENTENARIANS: AN ITALIAN CASE REPORT


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Introduction: Intravenous thrombolysis (IVT) for acute ischemic stroke (AIS) in oldest-old is never an easy decision. Lot of comorbidities and higher pre-stroke disability are the main reasons for IVT withholding in such patients. Sometimes the age itself is the only reason to rule out patients from the treatment, probably due to the lack of data about the safety of alteplase in these patients.

Methods: We report the case of a 101-year-old woman with acute partial anterior circulation syndrome, who received intravenous thrombolysis (rtPA), with complete regression of symptoms at discharge.

Results: The patient was admitted to our Emergency Department for acute blurred speech, left side hemiparesis, left lateral hemianopsia and gaze preference to right side (NIHSS 11) lasting for 1 hour. Her past medical history was remarkable for paroxysmal atrial fibrillation, arterial hypertension and chronic kidney disease. No significant disability was reported (mRS 1). On arrival, a basal CT scan was performed with no evidence of acute bleeding. The CT angiography highlighted right

M3 occlusion and perfusion CT (pCT) showed a wide parietal-temporal penumbra area with a limited ischemic core (Tmax >6s: 54.35 mL, CBF <20%: 3.4 mL, CBF <30%: 23.9 mL). Intravenous alteplase was started 2 hours from symptoms onset with early neurological improvement (NIHSS 4) and without complications. The 24-hs CT did not documented intracranial bleeding neither ischemic lesion. A complete remission occurred during the next 36 hours, and she was discharged asymptomatic after 4 days (NIHSS 0 and mRS 1). Apixaban 2,5 mg twice daily was given for secondary prevention.

Discussion: Searching in medical literature, we selected 28 cases of centenarians treated with rtPA in which outcome and pre-admission disability were available. Only 18 patients have low disability (mRS <3) before the event. Death within three months occurred in 11 patients but it was not related to the treatment. Risk-to-benefit ratio should always be evaluated for each oldest–old patient eligible for intravenous thrombolysis. Our case suggests that age should not itself be considered a reason to withheld IVT, in particular in patients with low pre-stroke disability.

Conclusion: To the best of our knowledge, this is the first case of centenarian's stoke treated with intravenous thrombolysis in Italy. As life expectancy will likely continue to increase, further studies about efficacy and safety of AIS therapy in oldest-old are needed.

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## NEUROIMAGING IN MONOZYGOTIC TWINS WITH CADASIL DUE TO A NOVEL NOTCH3 VARIANT


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Background and Aims: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominantly inherited cerebral small vessel diseases caused by mutations in NOTCH3 gene. The main clinical features include migraines with aura, recurrent ischemic strokes and dementia. In literature, reports of twins with CADASIL are scarce [1,2]. Herein we describe a pair of monozygotic twins with CADASIL carrying a new NOTCH3 variant.

Materials and Methods: Both twins underwent extensive clinical, laboratoristic and neuroradiological evaluation as well as genetic analysis of NOTCH3 gene.

Results: Twin A: he was a 45-year-old male, suffering from migraine, obesity, arterial hypertension and polycythemia; he referred to our Emergency Department because of a short-lasting (~ 5 minutes) episode of speech difficulties. Neurological examination was normal. Head CT showed extensive leukoencephalopathy. Brain MRI revealed diffuse, symmetrical, confluent periventricular white matter vascular lesions in the frontal, parietal and temporal lobes as well in external capsules, with sparing of anterior temporal poles. Clinical and neuroimaging data suggested the diagnosis of CADASIL. Genetic analysis of NOTCH3 gene demonstrated the presence of missense c.3329G>A, p.(Cys1110Tyr) variant. Genetic analysis for essential polycythemia (JAK2, BCR/ABL, MPL) was negative. Twin B: he suffered from migraine and polycythemia. He came for a 2-months history of trigeminal neuralgia (involving the 2nd branch of the left trigeminal nerve). Neurological examination was otherwise normal except for left facial hyperalgesia. Head CT showed diffuse leukoencephalopathy. Brain MRI demonstrated lesion distribution similar to his twin with an adjunctive T2-FLAIR hyperintense area in the left middle cerebellar peduncle along the intracisternal course of the fifth cranial nerve. Genetic analysis revealed the same NOTCH3 gene variant as his twin. He was given carbamazepine up to 600 mg/day with almost complete pain relief.

Discussion and Conclusions: We report clinical and neuroimaging features of a pair of twins with CADASIL due to a new missense NOTCH3 gene pathogenic variant, showing strikingly similar brain MRI findings. Sparing of anterior temporal poles represent an uncommon finding, mainly occurring in cysteine-sparing NOTCH3 mutations [3]. To date, only two pair of twins with CADASIL have been reported [1,2]; one family only showed similar neuroimaging pictures [2]. In our family, it remains to be elucidated if polycythemia is a casual comorbidity or represents a manifestation of this new NOTHC3 variant, expanding the spectrum of CADASIL phenotype.

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## TRANSIENT ISCHEMIC ATTACKS IN A MIDDLE-AGED WOMAN WITH UNFUSED/TWIG-LIKE MIDDLE CEREBRAL ARTERY TREATED WITH ENCEPHALOMYOSYNANGIOSIS


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Objective: Twig-like middle cerebral artery (MCA) is a rare unilateral vascular anomaly characterized by a replacement of the M1 segment of the MCA by a plexiform network of small vessels. Its prevalence rate ranges from 0.11% to 1.17%, especially in middle-aged females in East Asia [1]. It may be found incidentally or may present with headache or symptoms secondary to cerebral ischemia, transient ischemic attack, hemorrhage or aneurysm, usually not present before late adulthood.

Patient and Methods: A 49-years old woman was admitted to our Neurology Department for acute onset of recurrent right brachial-crural hyposthenia with gradual spontaneous resolution. No meaningful events in medical history or chronic pharmacological therapy were detected.

Results: The patient underwent to a brain computed tomography (CT) scan with no acute lesions demonstration; brain/neck CT angiography (CTA) showed unfused/twig-like feature of left MCA, no aneurysmal anomalies or intracranial stenosis were reported. Brain magnetic resonance imaging (MRI) scan detected micro-ischemic foci in the left frontal lobe cortex. Digital subtraction angiography (DSA) of brain found complete absence of left M1 branch, instead arterio-arterial

anastomoses which ensured distal opacification of orthograde ipsilateral M2 branches were marked. Furthermore leptomeningeal branches from the left anterior cerebral artery (ACA) and the posterior cerebral artery (PCA) supplied the distal left hemispheric territories and the left temporal lobe. In order to grade the possible hypoperfusion state of the brain, the patient was evaluated with a brain CT perfusion scan which demonstrated asymmetry of the cerebral blood flow (CBF) map in the left temporal area, an increase in the mean transit time (MTT) map diffused in the left hemisphere and in the right ACA area and similarly, time to peak (TTP) map had a lower value in the right hemisphere. According to our Neurosurgical department, patient was treated with an indirect revascularization technique like encephalomyosynangiosis (EMS) with a temporalis muscle flap placed directly over the cerebral cortex [2]. Then, indication to antiplatelet therapy was given.
Discussion and Conclusions: Currently, there is no consensus about the treatment of unfused/twig-like MCA, owing to its small prevalence and paucity of treatment data. Case reports in literature described successful extracranial-intracranial bypasses and combined direct/indirect revascularization. According to the low symptoms burden of our patient, the treatment was chosen to promote over time low-flow collateral neoangiogenesis in order to reduce hemodynamic insufficiency of the brain and to augment the vascular supply distal to the twig-like MCA.
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## AN ATYPICAL CASE OF CAROTID ARTERY DISSECTION

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A 57-year-old man was admitted to our emergency department in September 2021 for persistent tightening headache with fluctuations throughout the day. He also noted mild articulatory clumsiness and mild swallowing difficulty for solid food over the past three days. There was no history of notable medical conditions and home therapies. On arrival in the emergency department, he had normal vital parameters except for mild increase of blood pressure (150/95 mmHg). He underwent brain CT scan from which no ongoing acuities were evident. He was transferred to the neurology department for further evaluation. On admission to the ward, the headache appeared attenuated and lateralized to the right parietal site. Clinical examination revealed mild speech articulation impairment and tongue deviation to the right during protrusion. No other neurological deficit was discernible. A lumbar puncture was performed during the hospital stay: CSF cells and proteins were normal and virological examination negative. Brain MRI with gadolinium excluded acute cerebral ischemia or pathological enhancement. However, the presence of altered endoluminal signal at the level of the distal extracranial third of the right internal carotid artery (ICA) with filiform opacification of the vessel lumen was reported. In the suspicion of carotid dissection, CT angiogram of the neck was urgently performed. The scan documented the presence of irregular and filiform vessel caliber of the right ICA in its distal extracranial tract with the extension up to the intracranial segment. In particular, there was evidence of an endoluminal hypodense image, in a circumferential arrangement, which wrapped the opacified vessel lumen "sleeve-like". The diagnosis of right ICA dissection was confirmed. According to the equal effectiveness between antiplatelet and anticoagulant therapy [1], the patient was treated with Cardioaspirin and Statin. Compression neuropathy of the ipsilateral hypoglossal nerve due to ICA enlargement was presumed. The patient underwent short-term corticosteroid therapy with gradual improvement of tongue weakness. Following ultrasound checks documenting normalization of carotid artery caliber and, in relation to the absence of absolute indication for continuing antiplatelet therapy, Cardioaspirin was discontinued after 9 months.
Discussion: This case documents that the clinical presentation of carotid dissection can be atypical [2]. Isolated hypoglossal nerve palsy associated with unilateral headache can be a warning sign for vascular disease even in the absence of specific risk factors [3].
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## CEREBRAL FAT EMBOLISM: A CLINICAL AND PATHOPHYSIOLOGICAL CHALLENGE

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Introduction: Cerebral fat embolism (CFE) is a rare incomplete type of fat embolism syndrome (FES) characterized by purely cerebral involvement. It usually occurs 12-72 hours after the initial trigger mainly represented by fractures of lower extremities. CFE pathophysiology is still not completely understood.

Case presentation: The patient was a 24-year-old male who was admitted to our ER for a right traumatic femoral bone multiple fracture. Twenty-four hours after he was admitted, he presented severe psychomotor agitation and confusion without focal neurological deficits. Brain CT and EEG were normal. Symptoms were diagnosed as a psychiatric disease triggered by pain. Afterwards, patient became anartric with severe drowsiness and consciousness impairment without meningeal or focal signs. A new brain CT was again normal. Symptoms at that point were considered collateral effects of sedation with neuroleptics. Because of neurologic worsening, he underwent to a brain MRI which showed a "starfield pattern" characterized by multiple, scattered, small and hyperintense lesions on DWI and T2 sequences localized in both white matter and deep grey matter in bilateral centrum semiovale, corona radiata and basal ganglia. This MRI pattern is typical of CFE. Pulmonary, abdomen and lower limbs CT angiography were irrelevant. Transoesophageal echocardiography with bubble study ruled out a PFO. Patient started desametaxone 8 mg BID, aspirin and enoxaparine. He underwent to surgery for fracture reduction and gradually improved along 2 weeks. Follow-up brain MRI after 2 weeks showed near disappearance of the previous pathological findings. He was dismissed at home with normal neurological examination.

Discussion: CFE symptoms, as in our patient, are non-specific leading to possible misdiagnosis. Brain CT and EEG are not relevant but MRI findings such as the "starfield pattern" if recognized is typical of CFE. The pathophysiological hypothesis is that fat droplets from the bone marrow are released in the venous system and through arteriovenous shunts (i.e. PFO) travel into the systemic circulation and reach the brain. In patients without PFO, as in our patient, the hypothesis is that very small fat droplets pass directly through the pulmonary capillary bed.

Conclusions: CFE diagnosis is challenging mainly in patients without systemic symptoms of FES. Brain MRI is needed for the typical

"starfield pattern". The way of travel of fat droplets to the brain circulation in patient without PFO and pulmonary vascular abnormalities is still debated.

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## STARTING INTRAVENOUS THROMBOLYSIS IN IMAGING AREA IS ASSOCIATED TO EXCELLENT OUTCOME IN PATIENTS WITH ACUTE ISCHEMIC STROKE

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Introduction: Door-to-needle time (DNT) is an established predictor of outcome in acute ischemic stroke (AIS), when intravenous thrombolysis (IVT) is indicated. Several strategies have been proposed to streamline in-hospital pathways, in order to achieve shorter DNT, and starting IVT directly in the CT/MRI suite appears to be among the most useful ones.

Aim: To explore the impact of starting IVT in the CT/MRI suite, here defined as imaging area (IA), on functional outcome in patients with AIS treated only with IVT.

Methods: All patients with AIS treated with IVT at our center in 2020, 2021 and 2022 were included. Patients undergoing endovascular treatment were excluded, to reduce heterogeneity. To assess the effect on outcome, we only included patients without any previous disability. The cohort was divided into two groups, depending on the IVT site. One group started IVT inside the IA, right after eligibility was confirmed, the other received the treatment outside the IA (emergency department or stroke unit). Regression analysis assessed the association between IVT site and 3-months outcome, defined by the modified Rankin Scale score.

Results: 301 patients who received only IVT were included in the analysis. 112 (37.2%) were in the IA group and 189 (62.8%) in the not-IA group. The groups had similar baseline characteristics. In the IA group DNT was 42 minutes shorter. Although a similar rate of functional independence at 3-months (mRS 0-2), the IA group showed a higher rate of excellent outcome (mRS 0-1) when compared to the not-IA group (54.8% vs 41.7%, p=0.03). The multivariate regression analysis demonstrated starting IVT in IA was independently associated to excellent outcome (OR 2.09 [1.05-4.18]).

Conclusions: Starting IVT in IA enables to noticeably cut down DNT, showing a significant impact on the outcome in AIS patients treated with IVT. Our study therefore emphasizes the importance of this treatment strategy and reinforces the idea it should be encouraged as standard-of-care.

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## ISOLATED ACUTE ONSET AMNESIA DUE TO BILATERAL FORNIX INFARCTION. A CASE REPORT

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Introduction: Isolated acute-onset amnesia is a rare neurological syndrome and may represent a challenging diagnosis. Cerebrovascular etiology is uncommon, accounting for only about 1.2% overall. In these cases, the most frequent mechanism is represented by cardioembolism and the most commonly affected vascular territory is the posterior circulation. Acute amnestic syndrome due to bilateral fornix infarction is even rarer and only a few cases have been reported in the literature. Also known as "the amnestic syndrome of the subcallosal artery", this entity is the result of an acute infarction in the territory of the subcallosal arteries, which are perforating branches originating from the anterior communicating artery. However, in the few cases in which bilateral fornix infarction was reported, MRI abnormalities also involved the corpus callosum and anterior cingulate gyrus, while isolated bilateral infarction of the anterior fornix has rarely been described. Hereby, we present the case of a 61 year-old woman with acute onset of persistent anterograde amnesia due to bilateral anterior fornix infarction secondary to the occlusion of both anterior cerebral arteries.

Case presentation: About one hour after being involved in a minor car accident, a 61-year-old woman suddenly developed memory disturbances characterized by not being able to recollect recent events, including the collision itself. Her medical history included rheumatic mitral valve repair and pulmonary embolism due to venous thrombosis, but she was not taking any anticoagulant drugs. Except for amnesia, neurological evaluation on admission was normal and brain CT was unremarkable. At first, transient global amnesia was suspected and she was discharged from the E.R. However, due to persisting memory disturbances she was hospitalized four days later. Brain MRI showed T2-FLAIR hyperintensities with diffusion restriction in both columns of the fornix, anterior commissure and ventral hypothalamus, consistent with recent infarction. AngioMRI revealed a bilateral anterior cerebral artery occlusion (A1 segment), along with a persistent left trigeminal artery. CTA of cervical arteries, prolonged EKG monitoring and blood tests were within limits. Transoesophageal echocardiography showed moderate mitral regurgitation and left atrial enlargement, without signs of left atrial appendage thrombosis. Neuropsychological testing revealed an impaired episodic memory with encoding and recalling deficits, while remaining cognitive functions were preserved. Given the risk of thromboembolism due to structural atrial cardiopathy, anticoagulant therapy with warfarin was started.

Conclusions: Bilateral fornix infarction should always be taken into account in the differential diagnosis of a persistent acute onset amnestic syndrome, especially in patients with significant cerebrovascular risk factors.

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## SAFETY AND EFFECTIVENESS OF SHORT-TERM DAPT AFTER MINOR ISCHEMIC STROKE OR HIGH-RISK TIA IN A REAL-WORLD SETTING. DATA FROM READAPT STUDY

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Background and aims: According to international guidelines [1], based on the results of randomized controlled trials (RCTs), short-term (21-90 days) dual antiplatelet treatment (DAPT) is the gold standard for secondary prevention of minor ischemic stroke (NIHSS score ≤5) or high risk-TIA (ABCD2 score ≥4). We aim at evaluating DAPT benefits and risks in a real-world setting (RWS), even in patients not strictly following RCTs inclusion/exclusion criteria and procedures (timing and DAPT loading dose). [2]

Materials and Methods: The Real-life study on short-term dual antiplatelet treatment in patients with ischemic stroke or transient ischemic attack (READAPT) is a prospective, nationwide, multicentre, observational study, which has included patients with non-cardioembolic minor ischemic stroke or high-risk TIA receiving short-term DAPT in clinical practice since February 2021 with a follow-up of 90 days. Primary efficacy outcome is a new stroke event (ischemic or hemorrhagic) or death at 90 days. The primary safety outcome is a moderate-to-severe bleeding event.

Results: Up to 15th May 2023, 60 centers included 1554 patients who completed the follow-up period, 31 (2.0%) discontinued DAPT due to conditions requiring anticoagulation and were excluded, so 1523 (98.0%) patients were included in the follow-up analysis. Overall, most patients were male (1014, 65.25%) with a median age of 72 years (IQR 62-79). According to symptoms duration, 1077 (69.0%) patients had an ischemic stroke with a median NIHSS of 3 (IQR 2-4) and 477 (31.0%) a TIA with a median ABCD2 score of 4 (IQR 4-5); 296 (18.0%) received acute revascularization procedures. Only 118 (7.74%) followed both RCTs criteria and procedures. Median DAPT duration was 21 (IQR 21-68) days, 110 (7%) of patients early discontinued DAPT due to atrial fibrillation or need for anticoagulant (n=31, 2%), adverse event (n=20, 1.3%), lack of compliance/unknown cause (n=59, 3.8%). During the follow-up, 63 (4.0%) patients had a recurrent ischemic event, of which 37 (58.7%) were ischemic strokes and 26 (41.3%) were TIA. Eight (0.5%) patients died from any cause, 3 (0.2%) died due to vascular causes; 4 (0.3%) had intracerebral hemorrhages; and 46 (3.1) had bleedings. No significant differences, in terms of effectiveness or safety, were found between patients following and not following RCTs criteria/procedures.

Discussion and Conclusions: In RWS, patients with minor ischemic stroke or high-risk TIA treated with short-term DAPT, had similar proportion of ischemic recurrences and similar proportion of hemorrhagic events than in RCTs.

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## THE USE OF ALTEPLASE, ALTHOUGH SAFE, DOES NOT OFFER CLEAR CLINICAL ADVANTAGES WHEN MILD STROKE IS NON-DISABLING

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Objectives: It is unknown if alteplase is effective and safe in patients with mild acute ischemic stroke (AIS). Determining whether symptoms are "disabling" or not is the crucial factor in the management of these patients. The aim of this study was to investigate the efficacy and safety of alteplase in subjects with mild, non-disabling AIS.

Materials: We included all consecutive patients admitted at our institution from January 2015 to May 2022 for AIS with a baseline NIHSS score of 0-5 and suitable for intravenous thrombolysis. In order to select only subjects with non-disabling AIS, we excluded patients who scored more than 1 point in the following NIHSS single item: vision, language, neglect and single limb. Patients who scored at least 1 point in

the NIHSS consciousness item were excluded as well. This study is a retrospective analysis of a prospectively collected database.
Methods: After application of the excluding criteria, we included 319 patients, stratified into patients receiving and not receiving alteplase just because of non-disabling symptoms.
Results: The two groups were comparable regarding demographic and clinical data. Rates of three-month favorable outcome, defined as three-month mRS score 0–1, were similar, being 82.3% and 86.1% in treated and untreated patients, respectively. Hemorrhagic complications and mortality occurred infrequently and were not affected by alteplase treatment.
Discussion and conclusions: This observational study demonstrates that the use of alteplase, although safe, is not associated with a better outcome in highly selected patients with non-disabling AIS.
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## A CHALLENGING CASE OF VASCULAR MYELOPATHY DUE TO POSTERIOR SPINAL ARTERY INFARCTION


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Purpose: Diagnostic accuracy for myelopathies is challenging due to the multitude of possible pathophysiologic mechanisms, including inflammatory and vascular aetiologies amongst the most common. Spinal cord infarction is an important and underrecognized cause of acute spinal syndrome, although it is the most frequent non-inflammatory myelitis mimic. We present the case of a posterolateral bulbomedullary infarction due to focal stenosis of a vertebral artery [1,2].

Materials and Method: We reviewed the patient's medical history and performed Computed Tomography (CT) angiography and cerebral angiography, brain and cervical spine MRI, lumbar puncture and an immunological panel.

Results: A 46-year-old man was admitted to our division complaining dysesthesias which began in the left parieto-occipital region and subsequently spread to the left laterocervical area and to the left arm over the course of a few days. The neurological examination showed an impaired proprioception of the left upper limb, fine movement impairment of the left hand with dysdiadochokinesia and sensory loss of the left hemi-head, left arm and left hemithorax. CT angiography showed narrowing of the left vertebral artery in the intracranial tract (V4), distally to the emergence of the posterior inferior cerebellar artery (PICA). Brain MRI showed an area of altered signal at the left bulbomedullary junction, characterized by T2 and FLAIR hyperintensity, T1 hypointensity, DWI hyperintensity with unclear ADC restriction and minimal contrast enhancement. Lumbar puncture showed a slight increase in CSF proteins (53 mg/dL; normal values: 15-45 mg/dL). An immunological panel (including anti-MOG and anti-Aquaporin 4 antibodies) was performed which resulted negative. We then performed a cerebral angiography (DSA) which showed a focal stenosis at V4, at the usual origin of the posterior spinal artery. We decided to repeat a brain MRI, including vessel wall imaging, which showed enhancement at the site of the stenosis where a limited signal hyperintensity in FLAIR was evident [3].

Discussion: The case presents unusual aspects: although the gradual onset of symptoms and the site of the lesion in the posterolateral bulbomedullary junction would lean towards an inflammatory aetiology, the vascular alteration documented by the angiographic study and by MRI sequences leant towards an ischemic cause, in the territory of the posterior spinal artery.
Conclusion: We documented a rare case of posterior spinal artery infarction thanks to the neuroradiological study of vascular anatomy.
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## A POTENTIALLY FATAL CAUSE OF VERTIGO: ROTATIONAL VERTEBRAL ARTERY SYNDROME


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Purpose: We present the case of a patient with recurrent strokes and a history of vertigo.

Materials and methods: We reviewed the patient's medical history and performed a diagnostic work-up for embolic sources and a digital subtraction angiography (DSA) of cerebral arteries.

Results: A 69-year-old woman with a history of hypertension, dyslipidemia, diabetes and episodes of unexplained vertigo, experienced acute onset of vertigo, paresthesias in the left hemi-face, dysarthria, and diplopia. She was admitted to the hospital where the neurological examination showed dysarthria, left lower facial droop, right inferior rectus muscle weakness with contralateral nystagmus (NIHSS 4). The brain computed tomography (CT) was unremarkable (ASPECTS 10) while neck and brain computed tomography angiography (CTA) revealed a basilar apex occlusion with patency of both posterior cerebral arteries (PCA). Endovenous thrombolysis with rt-PA was started and then a DSA study was performed which documented patency of basilar apex and occlusion of the left PCA at P3. The diagnostic work-up was negative for embolic sources (normal atrial volume, ECG monitoring during hospitalization was negative for emboligenic arrhythmias, Transcranial Doppler Ultrasound was negative for shunts). CTA of cerebral arteries showed narrowing of the right vertebral artery (VA) at V2, between vertebraes C3-C4, where vertebral canal appeared markedly deformed by degenerative spondyloarthrosis. Vertebral DSA was performed: angiograms after rotation of the patient's head to the right documented occlusion of the right VA at C3 level, which led to the hypothesis of rotational vertebral artery syndrome (Bow Hunter's syndrome). The patient was discharged and a double antiplatelet therapy

was started. Twenty days after discharge, the patient suffered from a transient ischemic attack in the territory of posterior cerebral circulation (right visual field impairment, motor impairment of right upper limb and dysarthria), with resolution of symptoms after 20 minutes. Given the failure of initial conservative management, the patient underwent decompressive surgery of the right VA at C3-C4 level and subsequent Anterior Cervical Discectomy and Fusion of C3-C4.

Discussion: Stenosis or occlusion of VA due to head rotation can lead to downstream hypoperfusion of brain or thromboembolism. Mechanical compression can occur anywhere along its course and aetiologies include osteophytes, herniated discs, spondylosis, tendinous bands or tumours. [1]

Conclusion: Bow hunter's syndrome is a rare but potentially treatable cause of strokes.

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## EARLY NEUROLOGICAL DETERIORATION IN ISOLATED PONTINE STROKE: CLINICAL AND IMAGING FEATURES


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Objectives: Patients with isolated pontine ischemic stroke may face early neurological deterioration (END). We aimed to assess clinical and neuroimaging factors associated to END in pontine stroke.

Materials and Methods: We analysed 112 consecutive patients, admitted to our Stroke Center, with MRI/CT-defined isolated pontine infarction, without basilar artery occlusion. END was defined as persisting NIHSS increase ≥2 points, occurring <48h after admission. Lesion anatomy was classified by neuroimaging. Pontine warning syndrome (PWS) was defined as transient neurological symptoms, typical for posterior circulation, occurring 2-7 days before stroke onset.

Results: Among 112 patients with isolated pontine infarction, END was recorded in 36 (32.1%). Demographic data and stroke risk factors did not differ between END and clinically stable patients. While median baseline NIHSS was similar in both groups (3 vs. 4, p=0.25), median increase of 5 NIHSS points (range 1-12) was observed at discharge in END patients (p<0.001). PWS occurred in 14/36 (38.9%) subjects with END vs. 16/76 (21.1%) subjects without END (p=0.067). Significant chronic small vessel disease (MRI-based Fazekas score ≥2) occurred in 24/32 (75.0%) patients with END vs. 39/70 (55.7%) without END (p=0.08). Anteromedial lesion location was the most common (N=27 deep, N=38 superficial), followed by anterolateral (N=19), tegmental (N=16) and other (N=12). END was observed in 8/27 (29.6%) deep anteromedial, 18/38 (47.4%) superficial anteromedial, 4/19 (21.1%) anterolateral, 0/16 (0.0%) tegmental, 6/12 (50.0%) other (p=0.0061 overall).

Discussion and Conclusion: Early neurological deterioration is common in pontine stroke patients. We described possible association with significant chronic small vessel disease, ventral stroke location and occurrence of pontine warning syndrome.

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## ISCHEMIC STROKE AS PRESENTING MANIFESTATION OF ESSENTIAL THROMBOCYTHEMIA DUE TO V617F MUTATION IN JAK2 GENE


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Introduction: Essential Thrombocythemia (ET) is a myeloproliferative syndrome characterized by increased number of blood platelets and most patients with ET harbor a V617F mutation in JAK2 gene. ET is a rare cause of cerebrovascular thrombotic event and hereby we describe a case of ischemic stroke as presenting manifestation of ET in a patient carrying a JAK2-V617F mutation.

Case Report: A 51-year-old female presented to our center with acute aphasia, right hemianopsia, hemiparesis and hypoesthesia (NIHSS:23), The CT angiography of neck and intracranial arteries showed a 90% occlusion at the origin of the left internal carotid artery (ICA). Neither thrombolysis was performed because the patient arrived at our center out of the ''window" time, nor acute carotid stenting surgery. The patient was scheduled for elective carotid stenting ten days later and in the meantime, she was treated with loading dose of aspirin 300 mg plus clopidogrel 75 mg followed by dual antiplatelet therapy (DAPT= aspirin 100 mg + clopidogrel 75 mg). Atorvastatin 80 mg once a day was also added in therapy. Blood tests revealed an increased platelet count (677 x 103/microL; normal values 150-450 x 103/microL) while no other common risk factor for stroke including hypertension, hyperlipidemia, diabetes mellitus, coronary heart disease, smoking, alcohol consumption, low physical activity, and obesity was recorded. Ten days later, CT angiography of the neck and intracranial arteries demonstrated a 60% reduction of carotid stenosis, with a residual atherosclerotic plaque of ICA (30% stenosis) and stenting procedure was not performed. The persistent increased platelet count led to hematological evaluation and the patient underwent genetic analysis revealing V617F mutation in JAK2 gene. Accordingly, she started additional treatment with hydroxyurea 1000 mg and allopurinol 300 mg daily.

Discussion: The present case suggests that ICA stenosis might have favored thrombus formation in a patient with ET due to V617F mutation in JAK2 gene. Patients with ET have reduced overall survival and increased risk of thrombotic events compared with the general population. The degree of elevation of the platelet count has not been shown to be predictive of developing a thrombotic event whereas patients with a history of thrombosis or those older than 60 with a JAK2-V617F mutation are considered at high risk.

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## EARLY P-WAVE PREDICTORS OF AF IN PATIENTS WITH ACUTE ISCHEMIC STROKE: EVIDENCE FROM INSERTABLE CARDIAC MONITORS

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Background and Aims: Asymptomatic atrial fibrillation (AF) is a risk factor for ischemic stroke. Active search of subclinical AF in cryptogenic stroke (CS) patients is crucial to define the optimal secondary prevention strategy since AF patients need anticoagulant therapy to significantly reduce their ischemic risk and, therefore, avoid new ischemic events [1]. Insertable cardiac monitors (ICM) are employed in clinical practice to reveal AF, and recent evidence indicates that they can detect AF in up to 40% of patients with CS [2]. Nevertheless, accurate analysis of some cardiological features, such as left atrial and ventricular strain, during the acute phase of ischemic stroke (i.e., during hospitalization) may help clinicians to suspect asymptomatic AF [3]. In this study, we investigated the role of p-wave predictors of AF in the acute phase of ischemic stroke, in patients followed with ICM.

Methods: This is a single-center retrospective study. An expert cardiologist blindly reanalyzed ECGs obtained at hospital admittance of forty-three patients discharged with a diagnosis of CS and then followed with ICM. The analysis was focused on p-wave features, such as enlargements, humps, and spikes.

Results: Continuous ECG monitoring revealed subclinical AF in 19 patients (44%). The analysis of p-wave features showed abnormalities in 19 patients. Among them, 12 received a diagnosis of AF at ICM follow-up. P-wave abnormalities were significantly associated with the occurrence of AF (OR = 4.16, CI 95% 1.15 - 15, p = 0.02). Interestingly, in the AF group the duration of hospitalization was significantly higher than in the nonAF group ($p<0.01$).

Conclusions: In patients with CS, p-wave analysis should be considered a useful step, to select patients at high risk of asymptomatic AF who need a careful follow-up and a prompt therapeutic switch to anticoagulation.

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## A RARE COMPLICATION OF GIANT CELL ARTERITIS

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Introduction: Giant cell arteritis (GCA) is a granulomatous medium and large-vessel vasculitis. It is the most common form of systemic vasculitis, affecting both extracranial and rarely intracranial vessels, with an incidence of 15-25 cases per 100,000 persons over 50 years of age. Stroke is a serious though uncommon complication of GCA: in a large series on 287 biopsy-proven patients with GCA, stroke was observed in 2.8% in a period from the symptom's onset to 4 weeks after the beginning of the treatment.

Case Report: We present a case of a 65-year-old man who developed suddenly nausea and vomiting with transient vertigo, without fever. The patient had no history of hypertension, headache or diabetes mellitus. Blood tests shows slightly elevated PCR levels of 3,7 mg/dl and VES of 62 mm/h. Brain CT revealed no abnormality. After 1 week he developed persistent imbalance, slurred speech and psychomotor slowing. MRI with gadolinium showed bilateral middle cerebellar peduncles infarction, angio-CT of the supra-aortic vessels showed irregular aspect of the vertebral arteries and an intracranial obstruction of the left vertebral artery, suggestive of vasculitis. Doppler of the supra-aortic trunks revealed a typical dark hypoechoic area around the vessel lumen, the so called "halo sign" in the left vertebral artery. Temporal artery doppler ultrasound revealed a diffused mild intima-media thickness; ophthalmological examination was normal. According to clinical symptoms and radiological signs we made a diagnosis of GCA The patient was submitted to intravenous corticosteroids at the dose of 1 g/d for 5 days, followed by an oral dose of 1 mg/Kg/ die. Subsequently he started therapy with Tocilizumab.

Discussion: Ischemic stroke is a relatively rare complication in GCA patients, especially in vertebrobasilar territory. Moreover, an early recognition of stroke is very important because cerebrovascular disease are one of the predominant causes of death in patients with GCA. The absence of clinical symptoms in the first phase of the disease is not a prognostic criterion of ischemic cerebral events. Our patient showed a good recover, with a complete improvement of the symptoms. Patient who developed vertebrobasilar stroke may have brainstem involvement and poor outcome despite steroid therapy.

Conclusion: In patients with ischemic stroke of the vertebrobasilar territory and a radiological assessment compatible with a vasculitis, a diagnosis of GCA should be considered, even in the absence of clinical symptoms, especially when multiple concentric stenosis of vertebral arteries are present. Delay of immunosuppressive treatment could worsen clinical outcome.

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## POST-PARTUM HEADACHE AS PRESENTING SYMPTOM OF CAROTID ARTERY DISSECTION

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Introduction: Carotid artery dissection is an important cause of stroke or TIA, especially in young people. Bilateral dissection occurs less frequently. The classical presentation involves headache or neck pain, Horner's syndrome, TIA and stroke.

Case presentation: A 41-year-old woman came to our attention about 10 days after complicated vaginal delivery, for gradual onset of occipito-temporal headache, phono-photophobia, transient numbness in the left upper limb and production speech disorder. Vomiting, fever or neck stiffness were absent. Her anamnestic history revealed Hashimoto's thyroiditis in euthyroidism, pituitary adenoma in regular follow-up,

homozygous mutation of MTHFR gene. Neurological examination was normal. Brain MRI showed lesions involving the right parietal cortex, the left frontal lobe and the left head of the caudate, that were hyperintense with restricted diffusion, compatible with recent ischemic lesions. Ultrasonography of the internal carotid arteries (ICAs) documented double vascular lumen with intraparietal hematoma bilaterally, compatible with bilateral mid-distal level dissection, determining hemodynamically significant effects (PSV: 330 cm/sec, ICA/CCA ratio: 2.72). Computed tomography angiography confirmed multiple steno-dilatations and parietal thrombotic appositions at the mid-distal level of ICAs, suggested for dissection. In relation to bilateral localization of the pathology, no indication for endovascular treatment was placed. The patient underwent pharmacological interruption of lactation and was treated with double antiplatelet therapy and statin. After 2 weeks, a minimal progressive recanalization of the vessels lumen was highlighted by carotid ultrasonography. The patient began outpatient follow-up. Forty-five days after the event, carotid ultrasound test showed normalization of flow velocities at the mid-distal level of ICAs, so single antiplatelet and statin therapy was maintained.

Discussion: During puerperium the incidence of stroke increases. Postpartum dissection is a rare occurrence. Our patient's symptoms have several differential diagnosis, including intracerebral hemorrhage, cerebral venous thrombosis and reversible cerebral vasoconstriction syndrome. Although carotid dissection is not a frequent cause of headache during post-partum, it should be considered, assessed by imaging and promptly treated. As evidenced by the CADISS study, there is no difference in efficacy of antiplatelet and anticoagulant drugs at preventing stroke and death in patients with symptomatic carotid artery dissection.

Conclusions: Although bilateral carotid dissection is an extremely rare condition, it should be included among the differential diagnoses of headache in pregnancy and post-partum period, especially in the case of complicated deliveries, with the aim of a rapid radiological evaluation and individual targeted therapy.

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## PEDIATRIC ARTERIAL ISCHEMIC STROKE: A SINGLE CENTER'S EXPERIENCE


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Objectives: Acute ischemic stroke in children (AISc) represents a rare condition with a great short- and long-term burden [1]. The aim of our study is to present our single-center case series data of patients with AISc.

Methods: We conducted a retrospective analysis from 2006 to 2023 of all AISc evaluated at our Pediatric Neurology Center. Children with age of onset between 28 days-of-life and 18 years were included and hemorrhagic strokes were excluded. Epidemiological, clinical, biochemical, neuroradiological and therapeutic data were collected by consulting our hospital database.

Results: Our case-series included 30 children: the onset mean age is 5.7 years (range: 6-months to 13-years), 15/30 have onset within the first 5 years of life (M/F:1). The cause was identified in 20/30 of patients: a predisposing genetic condition was found in 5 patients, cerebral vasculitis in 8, cardiogenic stroke in 5, 1 with arterial dissection and 1 intra-infective. The most frequent onset symptoms were hemiplegia or monoplegia (27/30), seizures (8/30) or amnesic-confusion state (7/30), while constitutional symptoms were present in 6 patients. None of our patients showed overt abnormalities of routine blood tests, except for one patient with sickle cell anemia. CSF analysis was conducted in 11/30 and only in 1 case was suggestive of HSV1 infection. On neuroradiological scans, the ACM territory was the most affected (28/30), while in 2 patients the lesions were present in the cerebellar-ponto-mesencephalic region. 22/30 were treated with acetylsalicylic acid, 13 with low-molecular-weight heparin and 7 with steroid. 12/30 received a combined treatment with at least 2 drugs. Only 2 patients presented with relapsing strokes.

Discussion and conclusions: We confirm that most AISc occur within the first 5 years of life. Our diagnostic-etiologic yield rate is high (66%), although not yet in line with international standards (80%), presenting, however, a high prevalence of vasculitis and low for cardiogenic and sickle-cell-related-stroke. The onset with focal neurological deficits is the most frequent, followed by seizures. Most AISc occur in the anterior circulation territory, whereas the posterior circulation failure is rarer (93% vs 7%). Treatments vary according to the individual patient's risk factors, although antiplatelet therapy or anticoagulant alone or add-on to steroid is the most common.

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## CHARACTERIZATION OF A PANEL OF SERUM BIOMARKERS TO DEFINE FUNCTIONAL OUTCOME IN ISCHEMIC STROKE PATIENTS: FOCUS ON INFLAMMATION


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Objectives: Inflammation is known to exacerbate ischemic injury leading to secondary delayed damage [1]. Although inflammation comprises several mediators, most of the studies have so far evaluated single molecules involvement in acute ischemic stroke patients' outcome [2], but the quest for biomarker panels is open [3]. The aim of this ongoing study is to determine the relationships between selected inflammatory serum biomarkers and functional outcome evaluated by mRS at discharge and at 3 months.

Materials and Methods: In this longitudinal prospective observational study, we included patients with acute ischemic stroke fulfilling these criteria: >18y, onset <24h, NIHSS >1, pre-stroke mRS=0-1, evidence of acute stroke at neuroimaging. Exclusion criteria: >80y, Transient Ischemic Attack, previous stroke/traumatic head injuries, other neurological disease, immunosuppression before stroke, eGFR<30mL/min, pregnancy. Patients were treated as standard of care. The following markers have been considered: Interleukin-6 (IL6) and receptor for advanced glycation end-products (RAGE) for inflammation,

neurofilament-light-chain (NfL) as a measure of neuronal damage. Biomarker serum concentrations were determined with ELLATM Automated Immunoassay System on samples collected within 24h (T0) and after 7±2 days from onset (T1).

Results: At present, we included 54 patients (31 males, mean age 61.48[±14.28]); 75.9% with minor, 16.7% moderate, 5.71% severe stroke. Biomarker median values were IL6=6.09pg/mL (IQR=5.79), RAGE=722pg/mL (IQR=532.00), NfL=26.30ug/mL (IQR=42.10) at T0; IL6=8.04pg/mL (IQR=15.85), RAGE=670.50pg/mL (IQR=386.50), NfL=92.95ug/mL (IQR=116.40) at T1. IL6 and NfL were higher at T1 vs T0 (p=0.012 and p<0.001, respectively). NfL positively correlated with both IL6 and RAGE serum concentrations at T0, and only with IL6 at T1. At discharge, RAGE-T0 and IL6-T1 correlated with mRS score while, at 3 months, no correlations were observed for either the inflammatory markers, being IL6-T0 at the limits of significance (p=0.058).

Discussion: Results confirmed the distinctive kinetics of RAGE and IL6 release in the blood after stroke, influenced by the extension of brain damage particularly at T0. Moreover, these inflammatory biomarkers differently correlated with functional outcome at discharge, reflecting their release kinetics and the intrinsic differences in the activation timing of inflammatory mediators. On the contrary, no correlations were observed at 3 months: this could be due to the small sample size and to the fact the majority of so-far enrolled patients had minor strokes.

Conclusions: These preliminary results are part of a larger Study to identify a biomarker panel to better characterize the physiopathological complexity and clinical evolution of ischemic stroke patients.

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## PREDICTORS OF GOOD FUNCTIONAL OUTCOME IN PATIENTS WITH TANDEM OCCLUSION AFTER REVASCULARIZATION TREATMENT: SINGLE CENTER EXPERIENCE WITH 12-MONTH FOLLOW-UP

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Objectives The primary aim of this study is to identify good clinical outcome predictors for patients presenting with tandem occlusion (TO), analyzing a series of demographics, clinical and radiological data, all compared to outcome measure at 3, 6 and 12-month follow-up. Secondly, we investigated what variables were able to influence mortality.

Background: TO is defined as a severe stenosis/occlusion of the cervical internal carotid artery ipsilateral to the intracranial occlusion. TO clinical features may be similar to other stroke subtypes due to isolated intracranial occlusion but with more severe neurological symptoms and worse outcome.

Patients and Methods: We collected data of 100 patients with TO that underwent revascularization treatments in our Stroke Unit Center. We studied different cohorts with good clinical outcomes, defined as a mild disability with mRS 0-2 at 3, 6 and 12-months versus those with poor clinical outcomes defined as mRS 3-6. Moreover, we analyzed what studied factors were able to influence mortality (mRS 6).

Results: Using univariate analysis, we noticed that at 3- and 6-month follow-up, smoker patients with younger age and low NIHSS at admission and at discharge showed better clinical outcomes than others. Besides, low burden of leukoaraiosis and combined use of mechanical thrombectomy (MT) with acute stent of extracranial lesion, were associated with good functional outcomes up to one year follow-up. About other variables related to death, higher age and high NIHSS, at 24h and at discharge, were associated with high percentage of mRS-6 at 90 days. At 6- and 12-month follow-up, patients with high rate of leukoaraiosis demonstrated higher risk of death. About treatment, patients who underwent MT alone, had a higher death rate than patients treated differently.

Conclusions: As a single Center experience, it has been demonstrated after one-year follow-up in patients with TO, what kind of variables might influence outcomes and mortality.

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## ANTIPLATELET THERAPY IN PATIENTS WITH ACUTE ISCHEMIC STROKE TREATED WITH EMERGENT CAROTID ARTERY STENTING

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Background and Purpose: Carotid stenting in acute ischemic stroke is sometimes necessary to maintain the patency of the vessel during endovascular procedures in acute ischemic stroke. However, there are few data regarding antiplatelet management for carotid stenting placement in this setting and the optimal antithrombotic regimen in this setting is still unclear. This study aimed to investigate the difference between early single and dual antiplatelet therapy on short term outcomes in patients with acute ischemic stroke treated with carotid stenting.

Materials and Methods: A multicentre retrospective study was conducted in patients with acute ischemic stroke treated with emergent carotid artery stenting placement. Early antiplatelet treatment before 24 hours was made by neurointerventionalist and stroke neurologist according to local protocols and was single or dual antiplatelet therapy (SAPT and DAPT, respectively). Outcomes of interest were: any hemorrhagic transformation (HT) and at 24 and 48 hours after stroke and stent reocclusion. Independent associations were investigated with logistic regression assessing for confounders.

Results: We enrolled 181 patients, mean (+-SD) age 67.4 (+-12.1) years, 132 (73%) males, median (IQR) NIHSS 15 (10-20), 92 (51%) patients received rt-PA before endovascular treatment. Internal carotid artery was occluded in 148 (82%) and stenotic in 33 (18%) patients. Aspirin was the most frequent drug after stent placement (51%). After stent placement, 131 (72%) received DAPT and 50 (28%) received SAPT. HT at 24 hours was present in 51 (28%) patients (of whom 14 had HT soon after the endovascular procedure and were therefore administered with SAPT), 20 (40%) SAPT and 31 (24%) DAPT (p=0.029); HT within 48 hours occurred in 54 (30%) patients, 21 (42%) SAPT and in 33 (25%) DAPT patients (p=0.027). Considering patients without HT soon after endovascular treatment, HT at 24 hours was present in 6 (12%) SAPT and 31 (24%) DAPT patients (p=0.082), HT at 48 hours in 7 (14%) SAPT and 33 (25%) DAPT patients (p=0.105). Number of passes >3 increased risk of hemorrhagic transformation (ORmulti=4.78; 95%CI=1.33-17.11), length of endovascular treatment and treatment with rt-PA were not associated with HT. Stent reocclusion within 48 hours occurred in seven (5%) patients, two SAPT and five DAPT patients.

Conclusions: In patients with acute ischemic stroke, early single antiplatelet therapy was not associated with an increase of both hemorrhagic complications and stent reocclusion.

## ROLE OF TRANSCRANIAL DOPPLER ULTRASONOGRAPHY IN THE MANAGEMENT OF ACUTE POSTERIOR CIRCULATION ISCHEMIC STROKE RELATED TO BASILAR ARTERY STENOSIS

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Objectives: To demonstrate the relevance of neurosonology in the management of acute ischemic stroke.

Materials and method: We present a case report of posterior circulation stroke related to basilar artery stenosis (BAS).

Results: A 79-year-old man awoke at 5 a.m. with right deviation of the head and right hemiparesis. His last known normal was 11 the previous night. His past medical history revealed arterial hypertension, diabetes mellitus and dislypidemia. The patient presented to the emergency department at 06 a.m. The neurological examination showed coniugate left gaze palsy, dysarthria and right hemiparesis. The National Institutes of Health Stroke Scale score was 16. Head Computed Tomography (CT) did not show acute lesions and the CT perfusion documented an area of ischemic core in the left pons and penumbra in pons, medulla and bilateral superior cerebellar hemispheres. CT angiography (CTA) documented distal BAS. An urgent brain MRI confirmed a right paramedian pontine diffusion-weighted imaging hyperintensity, in the context of which a moderate hyperintensity on fluid-attenuated inversion recovery (FLAIR) sequences was observed. Although BAS was associated with brainstem hypoperfusion, the FLAIR-positive lesion determined a significant risk for hemorrhagic transformation in case of revascularization. Hence, neurosonologic exam was performed and did not reveal hemodynamic demodulation in the proximal tract and in the top of basilar artery. Thus, digital subtraction angiography (DSA) and basilar artery stenting were avoided. Dual antiplatet therapy was administered. In the following days the patient showed a gradual progressive improvement.

Discussion: Posterior circulation stroke represents approximately 20% of all strokes, and It is associated with higher risk of recurrence (1), mortality and morbidity rates than anterior circulation ischemic stroke. BAS is one of the main causes of posterior circulation ischemic stroke, especially symptomatic stenosis greater than 50%, which is associated with multiple transient ischemic attacks (TIAs) and recurrent stroke (2). Currently, DSA is the gold standard for diagnosing BAS. However, DSA is invasive and expensive. Transcranial color-coded sonography (TCCS) can be employed to detect BAS. Moreover, TCCS allows dynamic real-time observation of the flow imaging of the BA, intracranial vertebral artery (IVA) and posterior cerebral artery, detecting the presence of collateral flow through the posterior communicating artery, assessing velocities and evaluating vascular stenosis using the Doppler spectrum (3).

Conclusion: The use of neurovascular ultrasound is a reliable and effective tool in acute posterior circulation stroke management as it can guide the choice of further investigation and treatment options.

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## STROKE-LIKE SYMPTOMS IN A PATIENT WITH NEWLY DISCOVERED ATRIAL FIBRILLATION AND A HISTORY OF MULTIPLE SCLEROSIS

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Objectives: Male, 67-year-old. In 1995 he experienced an optic neuritis in the left eye, treated effectively with corticosteroids. In 2021 he had transient paresthesia and a Brain MRI revealed hyperintense lesions in the white matter on the T2/FLAIR sequences.

Materials and Methods: A lumbar puncture revealed only a slight increase in cerebrospinal fluid protein levels and no oligoclonal bands. Due to three new periventricular lesions at follow-up Brain MRI, the patient was diagnosed with multiple sclerosis and started on dimethylfumarate on 2020. On 2022, ha was admitted to hospital for the sudden onset of right homonymous hemianopsia (NIHSS 2). Brain MRI showed a lesion with restricted diffusivity and FLAIR hyperintensity in the left temporo-occipital cortico-subcortical region not involving a specific vascular territory, with cortical hemosiderin deposits and without blood-brain barrier alterations. No stenosis of the main intracranial vessels was found on MRI angiography and vessel-wall imaging (black blood sequences) showed no areas of abnormal wall enhancement. Extensive cardiovascular assessment was performed and a 24-hours ECG monitoring revealed a 4 hours episode of atrial fibrillation so DOAC therapy was initiated for primary prevention of embolism.

Results and Conclusions: Considering the patient's history and the radiological findings, the diagnosis of multiple sclerosis has been revised and Dimethyl-fumarate therapy was discontinued. A primary vasculitis of the central nervous system has been hypothesized. The patient is under consideration for cerebral biopsy to verify this hypothesis. At 3 months follow-up the patient had complete recovery from visual deficits (NIHSS 0) and did not experience any new neurological symptom.

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## ACUTE STROKE IN INTERMEDIATE THALASSAEMIA

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Intermediate Thalassaemia (IT) is an autosomal inherited condition, characterized by decreased beta-chain synthesis, with clinical onset at childhood or adolescence. Altered beta globin loci may account for recessive or, less frequently, dominant genetic pattern [1,2]. Abortive erythropoiesis, haemolysis, increased intestinal iron absorption, extramedullary erythropoiesis and hypercoagulability are the hallmark of the disease. Thromboembolic events (TEE) are reported 0.9-4% in Major Thalassaemia (MT) and 3.9-29% in IT [3]. A 64 year old female came to our observation for transient right arm hypoesthesia in already diagnosed IT, with negative neurological, cardiological, radiological examinations, except arterial hypertension. She was dismissed on low dose antiplatelet therapy. At the age of 67 years, she was again admitted to neurological unit for recurrence. CT showed chronic, ischaemic encephalopathy and hypodense, left cerebellar area, unrelated to the acute event. Thrombocytosis and first-degree atrioventricular block with mild mitral prolapse were revealed. Moreover, episodes of atrial fibrillation with low ventricular rate were detected at Holter's ECG. Therefore, a pacemaker was implanted, and anticlotting therapy was prescribed. Nonetheless, after nine months, she presented left hypoesthesia and lower limb hyposthenia. There were moderate mitral, and tricuspid prolapse, mild aortic stenosis with insufficiency at echocardiography, pulmonary nodules at chest CT. Cerebral TC confirmed chronic, ischaemic encephalopathy and showed extramedullary intracranial and paravertebral erythropoiesis / hemosiderosis in already mesylate deferoxamine undergoing treatment, because of repeated, regular transfusions. At the age of 70, in the context of coronavirus 19 paucisymptomatic infection, a vertebrobasilar event recurred. Lastly, after seven months, she arrived at emergency department with right complete hemisyndrome, because of wide, left fronto-temporo-parietal ischaemia in the territory of middle cerebral artery with haemorrhagic infiltration. Hypercoagulability in IT is related to membrane changes in erythrocytes, haemolysis, hemosiderosis, chronic platelet aggregation, increased expression of adhesion molecules in endothelial cells, activation of clotting system, cardiac dysfunction, splenectomy, hormonal disorders, accounting for resistance to therapeutical strategy. The prevalence of overt strokes in IT patients with a history of thrombosis ranges between 5% and 9%. A rate of 37,5% ischemic lesions at MRI is reported in IT who were neurologically intact and had no conventional stroke-related risk factors. High incidence of silent brain infarction, large cerebral vessel disease, and impaired neuronal function are reported in splenectomized patients with TI. Accurate examination of neuroimaging is important to discern among extramedullary erythropoiesis, hemosiderosis and haemorrhagic infiltration.

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## NSE IN ACUTE STROKE

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Background and Aims: Neuron-specific enolase (NSE) is a dimeric, intracellular, glycolytic enzyme, which is released after stroke, cardiac arrest, traumatic brain injury [1,2,3]. Its level may help in identification of patients at risk of poor outcomes, in decision making on intensive care, rehabilitation or palliative treatments. The aim of our study was to assess Neuron Specific Enolase (NSE) in Acute Strokes (AS) patients.

Methods: We recruited 210 patients affected with acute cerebrovascular syndromes (ACVS), subgrouped according to age (A: up to 29 years; B: 30-44 years; C: 45-64 years; D: 65-76 years; E: beyond 77 years) and volume of infarcted areas (1: small vessel occlusions, lacunes (SVO-L); 2: large-medium vessel occlusions (L-MVO). They underwent blood withdrawal within 24 hours, Computerized Tomography at Emergency Department and after 24 hours, Magnetic Resonance Imaging after 24 hours.

Results: NSE was not significantly higher in group D and E compared with A and B. Mild significance was detected in A1 vs B1 and C1 and between C2 vs D2, especially in patients with concomitant chronic ischaemic encephalopathy (CIE) (b) compared to those without CIE (a)

and in L-MVO. Pearson's test showed correlations of NSE with age, day1 GCS, day7 GCS, day7 MRS, PAP, LAD, BNP.

Conclusions: Altogether, our results highlight the importance of age consideration for a precise interpretation of haematological parameters. NSE release may increase by aging. It occurs in AS. As expected, its entity may decrease in CIE, when gliosis becomes predominant. It correlates with worst acute neurological and cardiological conditions, especially in elderly patients, as expression of acute sufferance and reduced clearance. Higher standard deviations and lower correlations related to concomitant multisystemic, chronic organ failure, especially in advanced age, may lessen statistical significance. Nonetheless, NSE may be a useful parameter of acute neuronal body death and blood brain barrier disruption, considering the brief half-life (24-72 hours in serum), while biomarkers with longer half-life, as tau protein (10 hours in plasma, 23+6,4 days in brain), Neurofilament light chain (several weeks to 2 months) may better indicate the burden of retrograde, anterograde and transneuronal neurodegeneration in CIE. Further biological and radiological data are needed to shed light on conflicting results of published studies on the issue. This would allow better prediction of brief and long-term prognosis and drawing up protocols of rehabilitation based on benefits/costs analysis.

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## HYPERDENSE ARTERY SIGN (HAS) AS A MARKER OF ACUTE ISCHEMIC STROKE (AIS): ETIOPATHOGENETIC, HISTOLOGICAL AND NEUROSONOLOGICAL CORRELATES

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Objectives: The focal hyperdensity of the middle cerebral artery (MCA) or of other large vessels, on non-enhanced cranial CT (NECCT), is the earliest radiological marker of AIS, being an indicator of occluding clot. The aim of this study is to evaluate the possibility to correlate thrombus features to stroke etiopathogenesis, thus suggesting effective therapies.

Materials and Methods: We extracted data from 20 subjects with AIS. All patients exhibited HAS on NECCT and Large Vessel Occlusion on CT-MR angiography. Sixteen patients underwent combined (bridging) or isolated treatment (IV-TL or TM), 4 subjects were excluded for intraprocedural complications (I° Group); the presence/absence of HAS was retrospectively evaluated in 19 patients with AIS and histological analysis of the extracted thrombi (II° group) was conducted. Ultrasounds and neuroimaging monitoring were given at Stroke Unit.

Results: The outcome was good in both groups, resulting in recanalization, except for 6 cases. Median thrombus length was 12-14 mm and MCA, M1 or M2 tract, was the principal occlusion site. The histological examination of the thrombi revealed, in the 16 subjects with HAS, an almost homogeneous distribution of fibrin, predominantly white thrombi in 9 patients and red thrombi in 7 patients, plus concomitant atrial fibrillation in 11 cases; in the 3 subjects without HAS a prevalence of white thrombi (2 vs 1) and absence of atrial fibrillation was observed; a slight prevalence of white, fibrin-rich thrombi, was also detected in longer procedures. An association trend between thrombi size and proximal occlusion, as well as extra-intracranial atheromatous load, highlighted by ultrasound, was observed; no association between the greater thrombus length and collaterals was detected, because longer thrombi occlude the vessels able to provide collateral compensations. The correlation between thrombus length and atrial fibrillation was almost significant (P=0,05).

Conclusions: The latest correlation suggests that cardiac thrombi are extended in length and their composition would give the hyperdensity to neuroimaging. Particularly, fibrin-rich thrombi are hyperdense and, if from cardio-embolic source, they have a solid component of red blood cells (RBCs), which is moreover responsible for the hyperdensity, unlike athero-thrombotics ones, less rich in RBCs; the cellular part decreases over time, leading to the organization of fibrin meshes: the fresher the thrombus is, the richer it is in RBCs. HAS is therefore an early marker of stroke and provide information both on the presence and on the features of the thrombus, suggesting to employ alternative thrombolytics and Thrombectomy with EA-TL.

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## BILATERAL PTOSIS AND DIPLOPIA AS SYMPTOMS OF STROKE: A CASE REPORT

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Introduction: Bilateral ptosis and diplopia are unspecific symptoms of brain or cranial nerve injury. We hereinafter report a case of bilateral ptosis and diplopia as the only symptoms of stroke.

Materials and methods: A 59-year-old man was referred to our institution for a sub-acute presentation of bilateral ptosis and diplopia. His medical history was unremarkable except for a recent diagnosis of diabetes. On neurological examination a fixed bilateral ptosis was observed, associated with an abducent nerve palsy in the left eye. No other neurological signs nor signs of fatigable weakness were recorded. Blood exams were normal except for an increment of blood glucose and glycated hemoglobin, consistent with the history of diabetes. These signs are often found in neuromuscular transmission disorder and patient underwent to repetitive nerve stimulation and single fiber EMG: both of these exams were negative. AChR and MuSK antibody assays were negative. Myasthenia gravis was excluded and a brain MRI was performed, showing a minimal ischemic lesions in pons.

Then a transcranial doppler was done and it revealed a severe stenosis in the middle of the basilar artery associated with a moderate stenosis of the left posterior cerebral artery in the P2 segment. Finally, an angio-CT scan confirmed this datum. The patient was diagnosed with ischemic stroke and for the intracranial stenosis a treatment with dual antiplatelet therapy (acetylsalicylic acid and clopidogrel) and statin was administered.

Discussion: In a patient with only bilateral ptosis and diplopia often a neuromuscular transmission disorder is hypothesized. Actually, myasthenia gravis showed an increment of incidence in the last decades, especially in male patients with more than 60 years. Despite the incidence of increment, myasthenia gravis remains a rare disease and, in front of ptosis and diplopia, often other causes, such as tumors or neurodegenerative disorders, should be taken into account. Ischemic stroke has an highest incidence in male with more than 60 years, especially for those patients who have comorbidities such as hypertension, diabetes or hearth diseases. Posterior circulation infarction is more rare than anterior infarction and it is often associated with dysarthria, dysphagia and ataxia.

Conclusion: This case should be taken into account as it shows how posterior circulation infarction may be underhand and misdiagnosed.

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## ASSOCIATIONS OF RISK SCORES WITH SVD BURDEN AND PROGRESSION IN ELDERLY PATIENTS ON ORAL ANTICOAGULANTS FOR ATRIAL FIBRILLATION: THE STRAT-AF STUDY

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Objectives: Guidelines recommend CHA2DS2-VASc and HAS-BLED scores, based on clinical variables, for thromboembolic and hemorrhagic risk in atrial fibrillation (AF), however, their predictive value is limited. MICON-ICH and MICON-IS, including the imaging variable microbleeds (MBs), have been recently proposed in patients on antithrombotics.

Aims: In a cohort of elderly AF patients on oral anticoagulants we assessed the associations between MICON, CHA2DS2-VASc and HAS-BLED scores and small vessel disease (SVD) markers (baseline and progression), as anatomical substrate for both ischemic and hemorrhagic stroke.

Methods: Strat-AF study is an observational, prospective, single-center study that enrolled patients over 65 years, taking oral anticoagulants for AF. Brain MRI was performed at baseline and after 18 months. On MRI, SVD burden and progression were visually assessed with validated scales. Risk scores were calculated at baseline.

Results: 170 patients were enrolled (mean age:77.7+/-6.8 years, male:65%). At baseline, MICON-ICH was significantly associated with presence of all SVD markers (with severe White Matter Hyperintensities: 6.8±2.5 vs. 5.8±2.2, p=.001; with MicroBleeds: 9.4±2.0 vs. 5.3±1.7, p=.001; with lacunes: 6.6±2.4 vs. 5.9±2.3, p=.032; with Basal Ganglia-Enlarged PeriVascular Spaces: 6.5±2.4 vs. 5.4±2.0, p=.001; with Centrum SemiOvale-EPVS: 6.5±2.6 vs. 5.7±2.0, p=.015) and MICON-IS (with severe WMHs: 8.3±2.6 vs. 7.6±2.1, p=.034; with MBs: 9.6±2.2 vs. 7.4±2.0, p=.001; with lacunes: 8.8±3.0 vs. 7.4±1.9, p=.006; with BG-EPVS: 8.0±2.3 vs. 7.3±1.9, p=.012) with all but CSO-EPVS (p=.092), while CHA2DS2-VASc and HAS-BLED showed few significant associations (CHA2DS2-VASc with MBs: 4.2±1.2 vs. 3.6±1.5, p=.034; HAS-BLED with severe WMHs: 2.0±1.0 vs. 1.7±0.8, p=.034, and with lacunes: 2.0±1.0 vs. 1.7±0.8, p=.010). At follow-up, between neuroimaging SVD progression markers, only incident MBs (13%) were associated with MICON-ICH (7.3±3.0 vs. 5.7±2.3, p=.030) and MICON-IS (8.7±1.9 vs. 7.6±2.4, p=.046), while no significant associations were found for CHA2DS2-VASc and HAS-BLED.

Conclusions: Compared to CHA2DS2-VASc and HAS-BLED, MICON-scores were more consistently associated with the presence of microangiopathic neuroimaging markers, suggesting a potential stronger predictive ability for hemorrhagic and ischemic events in AF patients. Funded by Tuscany Region and Italian Ministry of Health.

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## SUBARACHNOID HEMORRHAGE ASSOCIATED WITH ESSENTIAL THROMBOCYTHEMIA: A CASE REPORT OF A PATIENT WITH A CALRETICULIN MUTATION

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Objectives: Essential thrombocythemia (ET) is a myeloproliferative neoplasm characterised by thrombocytosis and dysfunctional platelets. A recent review identified 63 cases of ET and stroke, of which only 6 were haemorrhagic and 4 mixed (ischaemic and hemorrhagic) [1]. We describe a rare case of subarachnoid hemorrhage (SAH) in a patient affected by ET, in therapy with oncocarbide, aspirin and anagrelide, bearing a calreticulin (CALR) mutation, to enrich the literature on the subject.

Materials: We describe the case of a 54-year-old woman.

Method: Electronic medical records, neuroimaging and laboratory results were reviewed.

Results: The patient was admitted to the emergency department after developing a sudden severe frontal headache, associated with nausea and vomiting. A brain Computer Tomography (CT) scan revealed a left frontal SAH. The angio-CT study showed focal dilatation (3 mm) of the right middle cerebral artery, without vascular malformation. Aspirin and anagrelide were discontinued. On admission, platelets were raised (709.000/μL), as well as her International Normalized Ratio (1.22), and activated partial thromboplastin time was normal. Repeated CT scan showed no further intracranial bleeding during headache relapses and a regular evolution of the lesion. A cerebral Magnetic Resonance showed no venous intracranial abnormalities. The cerebral

angiography described slight calibre irregularities on atheromasic basis in the right anterior cerebral artery and both posterior cerebral arteries, but no intracranial high-flow vascular malformations. After 12 days, the patient was discharged on oncocarbide alone, with normal neurological examination except for a moderate headache. At haematological re-evaluation the indication to discontinue anagrelide and aspirin was maintained.

Discussion: To date, only one other case report of SAH has been described in association with a CALR mutation. Several mechanisms underlying hemorrhagic manifestations have been hypothesised, including a predisposition to aneurysm formation and rupture due to a weakened vessel wall or the induction of a condition mimicking a reversible cerebral vasoconstriction syndrome due to altered vessel tone (both attributed to a disturbance of the microcirculation within the vasa vasorum); an acquired Von Willebrand syndrome in the presence of severe thrombocytosis; furthermore, some studies have shown an increased incidence of bleeding in CALR-mutated patients undergoing antiplatelet therapy.

Conclusions: Management guidelines for ET mainly focus on thrombosis risk stratification and prevention [2]. However, haemorrhage (with an incidence ranging from 1.39 to 6.6 per 100 patient-years) is a rare but well-known complication that involves the central nervous system in 9.8% of cases [3] and that physicians must take into account.

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## ANTICOAGULANT-RELATED INTRACEREBRAL HEMORRHAGE: NO SIGNALS OF IMPROVEMENTS OVER 10 YEARS IN ITALY

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Background: Direct oral anticoagulants (DOACs) are increasingly adopted as alternatives to vitamin K antagonists (VKAs) [1]. This change in practice of anticoagulation might have impacted the incidence and characteristics of oral anticoagulant-related intracerebral hemorrhage (OAC-ICH) in recent years.

Aim: The aim was to provide an updated account on the epidemiology of OAC-ICH over a decade of increasing use of DOACs to assess whether the introduction of DOACs was associated with a change in time trends in incidence and case-fatality rates (CFRs) of ICH.

Methods: All patients with a first-ever spontaneous ICH residing in the district of L'Aquila (298,343 inhabitants) from 2011 to 2020 were prospectively included. We defined OAC-ICHs as an ICH occurring within 48 hours from intake of VKAs - regardless of the measured International Normalized Ratio (INR) value on hospital admission - or DOACs. Global and yearly incidence of OAC-ICH were calculated according to a Poisson model. To assess whether OAC intake was independently associated with 30-day and 1-year CFR, Cox regression analyses were performed with ICH score components [2] (age, NIHSS and Glasgow Coma Scale (GCS) scores, systolic blood pressure at ICH onset, ICH volume at onset, hemorrhage location, intraventricular extension) plus intake of OACs.

Results: We recorded 748 ICHs of whom 108 (14.4%) were OAC-related, 75 (69.4%) with VKA and 33 (30.6%) with DOAC intake, respectively. There was a non-significant trend toward an increase in OAC-ICHs from 2.35 (95% confidence interval [CI], 0.94-4.83) in 2011 to 4.02 cases per 100,000 person-years (95% CI, 2.08-7.03) in 2020 (p=0.482). Among OAC-ICHs, we observed a relative increase of DOAC-ICHs (0% in 2011; 83.3 % in 2020). 30-day and 1-year CFRs for OAC-ICHs were 48.1% and 51.9%, with a non-significant increase over time (p=0.847 and p=0.941). Univariate Cox regression revealed that OAC use was not a predictor of 30-day CFRs (HR 1.33, 95% CI, 0.98-1.80; p=0.064). GCS (HR 0.82, 95% CI, 0.68-0.97; p=0.025), non-lobar location (HR 0.45, 95% CI, 0.20-1.00; p=0.049), uncertain location (HR 3.28, 95% CI, 1.08-10.02; p=0.037) and intraventricular extension (HR 4.60, 95% CI, 1.94-10.86; p<0.001) were the only factors independently associated with 30-day CFRs for OAC-ICHs.

Discussion: During the study period, VKA-ICHs were gradually overcome by DOAC-ICHs. However, the incidence and case-fatality of OAC-ICH did not significantly change.

Conclusions: Despite the wider adoption of DOACs representing a safer alternative to VKAs, OAC-ICH remains a devastating complication of the use of oral anticoagulants with a huge impact on public health.

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## PREDICTING ATRIAL FIBRILLATION AFTER CRYPTOGENIC STROKE WITH CLINICAL RISK SCORES: A RETROSPECTIVE ANALYSIS

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Objectives: Atrial fibrillation (AF) is the most common cardiac arrhythmia and represents a frequent cause of acute ischemic stroke (AIS) but is often underdiagnosed in cryptogenic stroke (CS), mostly due to inadequate cardiac monitoring. The identification of a clinical risk score to predict AF among CS patients, could improve patient selection for prolonged monitoring.

Materials: We retrospectively collected the data of CS patients discharged from our Stroke Unit from February 2018 to March 2023.

Methods: A time-to-event analysis was performed to investigate variables associated to AF. Furthermore, we compare the predictive role of two published clinical risk scores: AF ESUS score (high sensitivity and negative predictive value with a relative risk of new incident AF 13 times higher in patients with score >0) and Graz AF risk score (high sensitivity and acceptable specificity, with cutoff level of 4 points). All statistical analyses were performed using IBM SPSS Statistics version 25.0.

Results: We collected demographic and clinical data of 156 patients with AIS and median age at time of event of 70,5 years old. Eighty-nine (57%) were male. Median follow-up from discharge was 16 months.

Thirty patients underwent to loop recorder implantation during hospitalization of whom 11 revealed AF after a mean time of 7 months. AF was discovered in 12 patients without implantable device after a mean time of 15 months. Overall, 23 patients (15%) experienced AF. Among all the demographic and clinical variables, univariate analysis identified hypertension (AH) (p=0.039), left atrial (LA) dilation expressed as diameter >40 mm (p<0.001), supraventricular premature beats (SPB) >125 on 24-hs electrocardiogram (EKG) (p=0.001) as significant predictors of developing AF. Comparing AF ESUS score and Graz score, the first showed an AUC of 0.565 (p=not significant), whereas the latter evidenced a sensitivity of 87% and a specificity of 62% with an AUC of 0.747 (p<0.0001).

Discussion: Our data confirmed previous studies reporting a significant association between AF and AH, LA dilation and SPB >125 on 24-hs EKG. The comparison between AF-ESUS score and Graz AF risk score showed an undoubtedly higher predictive ability of the latter one. Indeed, Graz AF score consist of an extended combination of EKG, neurological and cardiac imaging findings and blood biomarkers, strongly associated with occult AF.

Conclusion: Herein we demonstrated the utility of selecting CS patients for expensive cardiac long-term monitoring. Therefore, it is important to find a score that better identify CS patients at high suspicion of occult AF.

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## CAROTID EAGLE SYNDROME: A CASE SERIES


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Background and Aims: Carotid Eagle Syndrome (CES) is a rare disease due to the conflict of the elongated Styloid Process (SP) with the Extracranial Internal Carotid Artery (EICA), causing vessel dissection or compression. Currently, the diagnosis is defined by an SP longer than 25-30 mm and by a suggestive clinical presentation, like syncope, stroke, Transient Ischemic Attack (TIA), or headache. [1] However, there has yet to be a widely approved consensus regarding the diagnostic criteria or the management of this pathology. [1] The aim of this single-centre study is to describe the clinical and radiological features of CES cases and the adopted therapeutic approach.

Methods and Materials: In this case series study, we reported patients with suspected CES, who have been admitted to the Stroke Unit of the University Hospital of Messina since February 2014. Symptoms at the onset, NIHSS at admission, and diagnosis at discharge were collected. Characteristics of the SPs (length) and the EICAs (presence of kinking, coiling, atherosclerotic plaques and dissection) were described using CT Angiography (CTA) images. We also reported the follow-up data and if the styloidectomy was performed.

Results: Among 14 CES patients, 9 (64%) were males (mean age: 54±11 years). The majority (79%) had an NIHSS < 5 at admission. At discharge, we reported 8 ischemic strokes, 4 TIAs, 1 syncope and 1 headache. Evaluating CTA images, the stylo-carotid conflict was evident in all cases, with an average styloid length of 30±6 mm. Furthermore, 7 patients (50%) showed carotid dissection and 8 patients (57%) had an abnormal course of the ICA, whereas in only one case were there relevant atherosclerotic plaques. Styloidectomy was performed in 4 patients and none of the 14 patients reported any recurrence at the follow-up.

Discussion and Conclusion: Even though most patients presented with mild symptoms, half of them developed an ischemic stroke and several carotid dissections were reported. Therefore, it is essential to suggest not underestimating the CES, which could lead to potentially life-threatening diseases (like stroke or carotid dissection) and whose incidence could be higher than expected. [1] In some cases, the abnormal course of the ICA may contribute to the genesis of the stylo-carotid conflict and it could predispose to vessel dissection. [2] The surgery approach seems safe, but the course of ICA should be taken into account pre-operatively because it may cause vascular accidents. [3]

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## BRAIN IS NOT ONLY TIME: THE ROLE OF BRAIN CT PERFUSION IN ACUTE ISCHEMIC STROKE PATIENTS IN THE EARLY TIME WINDOW


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Aims: According to international guidelines, only non-contrast CT (NCCT) is required in acute ischemic stroke (AIS) patients who are eligible for intravenous thrombolysis (IVT) in the early time window. Aim of this study was to evaluate the possible role of advanced neuroimaging in predicting clinical and radiological outcome in AIS patients receiving IVT within 4.5 hours of stroke onset.

Materials: Patients presenting within 4.5 hours of AIS onset who underwent multimodal CT protocol (including NCCT, CT-perfusion (CTP) using RAPID software, CT-Angiography) and thrombolytic treatment between July 2021 and August 2022 were enrolled.

Methods: Demographic, clinical and neuroradiological data were recorded. CTP parameters as rCBF<30%, Tmax>6 seconds and volume mismatch were collected. We evaluated final infarct volume (FIV) at 24-36 hours follow-up neuroimaging (CT or MR), and 3-month clinical functional outcome using modified Rankin Score(mRS).

Results: 262 AIS patients were included. Compared to patients with 3-month good clinical outcome (mRS 0-2), patients with 3-month mRS 3-6 were older (p<0.0001), had higher baseline NIHSS score (median 10, IQR 5-17 vs 4, IQR 3-9; p<0.0001) and a longer onset-to-needle-time (p=0.03). Baseline ASPECTS was similar between the two groups (p=0.04), while all CT perfusion parameters were higher in patients with 3-month unfavourable outcome (rCBF<30% p=0.004; Tmax>6 seconds p=0.004; volume mismatch p=0.0001). Patients with 3-month mRS 3-6 had a larger FIV at follow-up (p<0.0001). In multivariable binomial logistic regression analysis rCBF<30% (OR 1.12, 95% CI 1.06-1.19, p<0.0001), baseline NIHSS score (OR 1.08, 95% CI 1.01-1.15, p=0.02) and TICI 0-2a (p =0.005) independently predicted FIV>10 ml; while age (OR 0.90, 95% CI 0.86-0.94, p<0.001), baseline NIHSS score (OR 0.93, 95% CI 0.87-0.99, p= 0.036), onset to needle time (OR 0.99, 95% CI 0.99-0.99, p=0.02) and rCBF<30% (OR 0.95, 95% CI 0.92-0.98, p=0.002) independently predicted 3-month mRS 0-2. In multivariable ordinal logistic regression analysis rCBF<30% was an independent predictor of 3-month mRS 3-6 (OR 1.04, 95% CI 1.01-1.06, p=0.001).

Discussion and Conclusion: In our study on early time window IVT, the extent of ischemic core predicted FIV and 3-month clinical outcome, performing better than the ASPECTS. The use of this latter to select patients to be submitted to revascularization treatments in the early time window should be reconsidered.

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## CLINICAL AND LABORATORY PREDICTORS OF RESPONSE TO ANTIPLATELET THERAPY MEASURED BY ELECTRICAL IMPEDANCE AGGREGOMETRY IN SECONDARY STROKE PREVENTION


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Background: Ischemic stroke is a neurological disease with an enormous social impact. The introduction and improvement of revascularization treatments in the acute phase, together with a more careful and specific secondary prevention therapy, of which antiplatelet therapies are the cornerstone, have revolutionated the prognosis of this neurological disease. Their use, guided by tools capable of measuring their effectiveness, such as aggregation tests, could allow to a more targeted therapy.

Goals: The aim of our study was to identify any clinical or laboratory test factors that could influence the response to the antiplatelet therapy, evaluated with the aggregometric tests (Multiplate®), therefore potentially predictive of better or worse response to antiplatelet agents.

Materials and Methods: This is a retrospective study on 2400 patients in secondary prevention therapy with antiplatelet drugs, evaluated with a electrical impedance aggregometric test (Multiplate®). Information was collected on various clinical and laboratory variables, for which the possible correlation with the aggregometry values (defined by the parameters ASPI, ADP, ASPI/TRAP and ADP/TRAP) was evaluated, identifying with multivariate potential independent predictors of antithrombotic response.

Results: For the ASPI test, the number of platelets resulted as an independent predictor of high residual platelet activity in response to ASA (OR 0.99, 95% CI 0.98–0.99, p < 0.001), and the same is for the RDW (OR 0.86, 95% CI 0.75-0.99, p < 0.001). For the ADP test, the platelets predict the high residual platelet reactivity to the inhibitor of P2Y12 receptor (OR 0.99, 95% CI 0.98-0.99, p < 0.001). The use of SSRI predicts a lower response to ASA in the ASPI/TRAP ratio (OR 0.63, 95% CI 0.41-0.97, p = 0.03), and the same is for the WBC (OR 0.89, 95% CI 0.85-0.94, p < 0.001). For the ADP/TRAP ratio, the SSRI use is related to a higher response to P2Y12 inhibitor (OR 3.80, 95% CI 1.59-9.07, p = 0.003) while alcohol use and PCR are related to a lower response (OR 0.94, 95% CI 0.88-0.99, p = 0.03).

Conclusions: Aggregometry is proposed as a potentially useful tool in identifying patients at increased risk of new cerebrovascular events. The evaluation of the predictive factors of residual platelet hyperreactivity could be a valid criterion for the selection of patients at greater risk of resistance to therapy and therefore candidates for monitoring with an aggregometric test. Our study needs confirmation, but it might be helpful to personalize treatment for patients with cerebrovascular diseases.

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## NEURO-BEHÇET'S DISEASE: A RARE CAUSE OF STROKE IN YOUNG PATIENTS


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Introduction: Behçet's disease (BD) is a recurrent, multisystemic, inflammatory disorder that frequently affects blood vessels; the involvement of central nervous system is reported in 10%-25% of patients, known as

neuro-Behçet disease (NBD). Although the pathogenesis of stroke in BD patients may be multifactorial, recurrent inflammation of cerebral blood vessels could play a crucial role in the development of ischemic stroke.

Case description: A 28-years-old male patient, with a history of recurrent oral aphthae and scrotal ulcerations, presented with acute diplopia, nausea/vomiting and postural instability. Evaluated several times in the past for papular lesions in the lower limbs and for alternate alvus, with finding of rectal and descending colon linear ulcers, associated lymphoplasmacytic infiltrate and increased IgG4 in the serum, the patient denies arthritis, Raynaud's phenomenon, inflammatory low back pain or uveitis. He only reported an episode of sudden memory loss for recent events, with gradual spontaneous recovery; since then he complained of increased memory difficulties. During hospitalization, a brain MRI documented a small ischemic lesion in the pontine tegmentum on the left side; MR Angiography and transcranial color-coded duplex (TCCD) excluded alterations of extra- and intracranial vessels. An extensive infectious, neoplastic and autoimmune screening, including screening for chronic inflammatory bowel disease, was inconclusive, except for IgG4 and IgE elevation. Due to hypovitaminosis B12 and B9 and the previous episode of confusion with transitory memory impairment, Wernicke's encephalitis was suspected, although the neuroimaging features were not quite typical, and supportive therapy with parenteral multivitaminic integration, including thiamine, was set ex juvantibus. Neuropsychological tests revealed marked attentional-executive deficits. In order to search for potential deficient neuropathies, electroneurography was performed. It showed a predominantly demyelinating sensorimotor asymmetric multineuropathy. Cerebro-spinal fluid examination was normal, including autoimmune encephalitis and onconeural antibodies research on CSF, as serum Anti-ganglioside. A cardiological screening excluded cardiac abnormalities or major arrhythmias, and the genetic investigation for Fabry disease was negative. HLA B51 and B08 were found, and, considering clinical presentations, diagnosis of Behçet's disease was made; according to rheumatologists, the patient started steroid therapy with progressive clinical improvement and regression of postural instability and diplopia reported on admission.

Conclusion: Behçet's disease may be an important cause of ischemic stroke, especially in young patients; therefore in patients who have no risk factors for ischemic stroke, but experienced cerebral small-vessel lesions, NBD should be considered.

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## ISCHEMIC STROKE AND SUBARACHNOID HEMORRHAGE WITH REVERSIBLE VASOSPASM IN ACUTE BACTERIAL MENINGITIS: A CASE REPORT


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Objectives: To report the clinical features and course of a patient with ischemic stroke and subarachnoid hemorrhage with reversible vasospasm during an acute bacterial meningitis.

Materials and Methods: A previously healthy 72-year-old woman presented to our hospital in January 2023. For a few days she had been experiencing headache and neck pain unresponsive to over-the-counter anti-inflammatory drugs. On admission, she had fever, high blood pressure and blood tests showed neutrophilic leukocytosis. Computed tomography (CT) scans of brain and chest were normal. Cerebral spinal fluid (CSF) analysis showed high cell count (8633 cells/microliter) and low glucose (24 milligrams/deciliter). Polymerase chain reaction test on CSF was positive for streptococcus pneumoniae. Antibiotic therapy with ceftriaxone and vancomycin was started. The patient was then admitted to the infectious diseases ward. Four days later, however, her consciousness worsened despite an improvement in lab tests.

Results: Brain CT showed a hypodense lesion in the left caudate nucleus and a subarachnoid hemorrhage near the anterior falx. CT angiography showed irregular appearance of both anterior cerebral arteries as effect of vasospasm. Cerebral angiography subsequently confirmed the presence of vasospasm in both anterior cerebral arteries. Intra-arterial infusion of nimodipine resulted in vasospasm regression. Nimodipine was orally continued for two weeks and imaging controls revealed no new vascular event. On discharge, although a complete motor recovery occurred, the patient lost her independence in activities of daily life, due to severe multi-sectorial cognitive deficit caused by strategic territory ischemic stroke [1].

Discussion: Cerebrovascular complications are commonly reported in patients with acute bacterial meningitis. The pathophysiological processes involved are vasculitis, vasospasm and arterial or venous thrombosis [2]. Streptococcus pneumoniae is the most common pathogen involved. Intracranial hemorrhage can be seen in up to 3% of patients with bacterial meningitis. The most frequently seen cerebral hemorrhage types are intraparenchymal and subarachnoid3. In this patient, ischemic stroke and subarachnoid hemorrhage were observed with delayed onset in respect of the acute infectious disease despite an improvement of systemic condition.

Conclusions: Neurological deterioration in a patient with acute bacterial meningitis should always lead to the suspicion of a cerebrovascular complication, of ischemic or hemorrhagic type. Diagnostic evaluation should include CT Angiography to exclude potentially treatable acute vasospasm.

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## VARIANT ASCENDING PHARYNGEAL ARTERY MAINTAINING FLOW IN A SYMPTOMATIC OCCLUDED INTERNAL CAROTID ARTERY IN A PATIENT PRESENTING WITH SUBACUTE EMBOLIC STROKES. A CASE REPORT


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Purpose: We present a case of successfully treated internal carotid artery occlusion (ICAO) in the presence of a variant ascending pharyngeal artery (APA) providing flow to an internal carotid artery (ICA).

Materials and method: Review of patient's medical history, carotid ultrasound, head and neck Computed Tomography Angiography and endoarterectomy.

Results: A 55-year-old man with a history of diabetes, hypertension, hypercholesterolemia and smoking presented with mild right hemiparesis and impaired walking. A markedly increased differential blood pressure was observed between right and left arm. Neurological examination revealed motor aphasia, right lateral homonymous hemianopsia, mild right hemiparesis. Aortic dissection was ruled out by aortic CT-angiography. Brain CT showed an area of subacute stroke in the left temporo-occipital region and a chronic stroke in the left parietal region. Carotid ultrasound was performed showing patency of left common carotid artery with high resistance flow and occlusion of the left ICA in a short segment near its origin. Orthodromic flow was evident 1 cm distally to carotid artery bifurcation. Left ICA flow was secured by a collateral vessel with high peak velocity and prominent diastolic flow. A head and neck CT-angiography was performed which demonstrated mixed density atherosclerotic plaque at the carotid bulb extending longitudinally for 15 mm to the origin of the internal carotid artery, thereby causing a 3-4 mm occlusion of the left ICA. Flow to the left ICA was granted by a thin tortuous vessel corresponding to a variant left APA which was connected through anastomotic branches to the left thyro-cervical trunk. A subocclusive stenosis of the brachiocephalic artery was detected explaining the increased differential blood pressure. Because the left ICA was fed by APA and its occlusion was short and likely the embolic source of the strokes, patient underwent carotid endoarterectomy. After surgery, carotid ultrasound demonstrated patency of left ICA and inversion of flow of APA with increased resistance, reduced peak systolic velocity and absent diastolic flow.

Discussion: The presence of variant APA in a patient with ICAO (rarely reported in literature) granted flow to ICA probably preventing hemodynamic strokes and making the surgical approach safer. On the other hand, the presence of APA probably contributed making ICAO symptomatic by creating turbulent flow in proximal ICA in the presence of orthodromic flow. This prompted us to give indication to endoarterectomy.
Conclusion: We described a rare case of symptomatic ICAO in the presence of variant APA, successfully treated with endoarterectomy.
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## BILATERAL CAROTID ARTERY DISSECTION IN HYPER-IGE SYNDROME: A CASE REPORT


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Objective: To describe a case of hyper-IgE syndrome (HIES), with emphasis on vascular involvement as a possible manifestation of the disease in adulthood.

Materials: Review of the patient's medical history, clinical assessments and laboratory tests, neurologic and cardiologic evaluation, imaging tests.

Methods: We report the case of a 54-year-old patient who was admitted to the emergency department for rapid onset of sharp pain in the right neck and narrowing of the palpebral fissure in the right eye with ipsilateral headache. Some relevant comorbidities were present: previous left carotid dissection in 2018, permanent atrial fibrillation (AF), previous lung abscess and multiple episodes of sinusitis, recurring joint dislocations.

Results: The patient had previously worked as contortionist in a circus. At neurological examination a deficit of left IX cranial nerve and left Horner syndrome was present. Cranial-CT and angio-CT displayed findings indicative of right internal carotid (ICA) dissection. The patient was diagnosed with HIES through a gene segregation test following her daughter's HIES diagnosis. A dominant-negative (DN) IL6ST mutations (p.Cys733Leu fs Ter6) was documented. Blood examination showed high serum immunoglobulin E (IgE) concentrations 1584 kUI/L (nv <100). Xrays examination confirmed bone dysmorphism and retained deciduous teeth. Consensus was reached on conservative medical management with anticoagulation therapy. In the first few days, the patient had a favourable evolution with resolution of the pain in the right neck and headache and improvement of the signs and symptoms of Horner syndrome.

Result and Discussion: HIES are multi-system disorders and a rare primary immunodeficiency disease. It is characterized by staphylococcal abscesses, eczema, respiratory infections, chronic mucocutaneous candidiasis, elevated levels of serum IgE, eosinophilia and low levels of inflammatory markers during infection. Extrahematopoietic features, include various connective tissue, skeletal, and vascular abnormalities with mainly large vessel involvement that contributes to morbidity and mortality in HIES patients. Hypereosinophilia, defective angiogenesis or vasculitis are supposed to contribute to vascular damage. However the patient's job (contortionist due to joint hypermobility) could have had a role in facilitating carotid dissection at the neck, being responsible of microtraumas.
Conclusion: To our knowledge, this is the first report of bilateral ICA dissection in HIES in the medical literature. ICA dissection can be a manifestation of HIES in adult. We suggest to evaluate thoroughly patients with HIES for vascular involvement. The study of mechanisms involved in large vessels dissections in these patients may shade light on the disease pathogenesis also in non-genetic, sporadic cases.
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## REVERSIBLE FOCAL CONTRAST-INDUCED NEUROTOXICITY FOLLOWING CORONAROGRAPHY MIMICKING ACUTE STROKE


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Background: Transient contrast-induced neurotoxicity (TCN) is a rare but well-known complication of intra-arterial contrast administration (REF). The putative mechanisms are still partially unknown, yet iodinated contrast-driven endothelial damage and blood-brain barrier disruption arguably play a pivotal role. TCN may present with a wide

spectrum of neurological manifestations, including seizures, cortical blindness, altered mental status, and focal neurological deficits (REF). Therefore, accurate and prompt diagnosis is challenging.

Case report: We report the case of a 64-year-old man who underwent a coronary angioplasty with stent placement. At the end of the procedure, the patient exhibited acute-onset severe left hemiparesis and gaze palsy. A stroke multimodal study CT was unremarkable. Nonetheless, in the suspicion of an acute ischemic stroke, intravenous thrombolysis was administered. Following reperfusion therapy, the patient rapidly developed a cognitive-motor slowing. A follow-up brain CT revealed the disappearance of cerebral sulci and cortical blurring in the right frontoparietal cortical areas. Notably, a brain MRI did not reveal any restriction diffusion or other abnormalities. the clinical-radiological status resolved completely within 72 hours.

Conclusions: Contrast-induced neurotoxicity is an important clinical entity to consider in the differential diagnosis of stroke following coronarography. A temporal correlation between neurological dysfunction and the administration of iodinated contrast is required to diagnose this neurological condition. Even though it usually presents with encephalopathy and contrast stagnation in subarachnoid spaces, focal manifestations accompanied by atypical radiological features may occur.

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## A LONGITUDINAL STUDY IN PATIENTS WITH CHRONIC DISORDERS OF CONSCIOUSNESS: COMPARISON BETWEEN PATIENTS WITH POSITIVE AND NEGATIVE OUTCOME


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Objective: The evidence about outcomes in chronic Disorders of Consciousness (DOC) is poor, therefore we compared sociodemographic and clinical variables between patients who died (negative outcome) and the ones who did not (positive outcome).

Materials: We collected socio-demographic and clinical data of 129 DOC patients at the admission to long-term care structures in the geographic area of Milan (Italy) from the 2017 to 2021. Specifically, age, sex, time since injury (TSI), aetiology, number of infectious events and bedsores, Body Mass Index (BMI), Coma Recovery Scale-revised (CRS-r), Glasgow Coma Scale (GCS), and Disability Rating Scale (DRS) scores, were collected.

Method: Data were collected at the admission to the long term-care structure (T0) and twice a year until 2021 or at discharge (T1), occurred either because of death or other reasons (e.g. discharge). We divided the sample into two groups depending on the outcome (positive, negative). We compared the two groups considering each socio-demographic and clinical data, one at the time, as dependent variable. Mann-Whitney U test was used for continuous variables whilst Chi-squared test was used for categorical ones.

Results: Among the 129 patients (73 M; 60.8±14.4 years), the 83% was diagnosed with Unresponsive Wakefulness Syndrome whilst the 17% with Minimally Conscious State. At T1, 69 patients had a negative outcome (mean time from acute event to death: 2.57±2.92 years) and 60 a positive outcome. There were no significant differences between groups when considering the aetiology, TSI, number of bedsores, BMI, CRS-R, and the GCS (all p>.05). A trend was found for the patients' age (U=1685; p=0.07) and the total number of infectious events (U=1691; p=0.06). The two groups differed for the sex (X2= 6.13, p=.013), where the number of males was higher for negative outcome patients (n=46) than positive outcome patients (n=27), conversely the number of women was higher in positive outcome patients (n=33) than negative outcome patients (n=23). Significant difference was found also on the DRS score (U=1566; p=.015) where patients with a negative outcome had higher scores (25±2) than patients with positive outcomes (24±2).

Discussion: This is one of the few studies following a cohort of chronic DOC patients across the time.

Conclusions: Being a male and having a higher level of disability, at the time of the admission to the long term care structures, could increase the chance for an unfavourable outcome. However, future studies are needed to better explore the predictive values of such variables.

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## ACUTE BILATERAL HORNER SYNDROME BY CERVICAL ARTERO-VENOUS MALFORMATION


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Background: Horner syndrome (HS) usually consists of unilateral ptosis, an ipsilateral miotic but quite normally reactive pupil (with delayed dilation), and ipsilateral facial anhidrosis. It is caused by a damage of the ipsilateral oculosympathetic pathway that is divided into three groups of neurons including first-order neurons (from hypothalamus through brainstem and extends into the upper portion of the spinal cord), second-order neurons (from spinal column, across the upper part of the chest and into the side of the neck) and third-order neurons (along the side of the neck to iris and eyelids). The first order may be disrupted by stroke, cerebral tumors, demyelination, syringomyelia or neck trauma (central HS); second order by lung cancers, schwannoma, aortic dissection, chest surgery (pre-ganglionic HS); the third order may be involved in carotid artery damage in the neck, migraine, and cluster headache (post-ganglionic HS). Very rarely it may be bilateral, due to bilateral interruption of the cervical sympathetic pathway or widespread autonomic neuropathy.

Case report: A 51-year-old man complained of a sudden onset sensitive and motor impairment in his left upper limb with difficulties in breathing when lying down. In about 30 minutes he reached the hospital. In the emergency room, he rapidly showed a progressive four limbs flaccid paralysis and breathing arrest with necessity of intubation. He remained vigilant, with face-mouth and tong grimaces, in the effort to inspire. Cranial nerves were functioning. Pupils were symmetrically pinpoint in room light. No drug was detected in the blood. Cerebral CT was normal. An angio-CT of brain, neck and chest showed normal

carotid and vertebral arteries and no aortic dissection. The patient, even intubated, was vigilant, collaborative, quadriplegic, bilaterally miotic, with a complete impairment of both spontaneous and voluntary breathing: the clinical presentation focused on a cervical spine acute disorder. CT scan did not show bleeding but spinal vessels seemed to be dilated and detectable with this method. An MRI scan showed a cord swelling from C3 level, with winding images T2-ypointense into the cord and around it at C3-C4 level. More caudally (D1-D3), a T2-hyperintense lesion without enhancement, resembling an ischemic lesion, was present. A type III artero-venous malformation was then diagnosed. The angiographic exam confirmed this suspect. No bleeding observed. An endovascular procedure was done. Autonomous breathing and walking were recovered in 4 months.

Discussion: No other cases of acute bilateral Horner syndrome induced by a spinal vascular malformation have been described before.
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## PERSISTENT LEFT SUPERIOR VENA CAVA: AN UNUSUAL CAUSE OF RIGHT-TO-LEFT SHUNT AND EMBOLIC STROKE

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Introduction: Juvenile ischaemic stroke in the young might be particularly challenging for definitive diagnosis and often requires a major diagnostic effort. Persistent left superior vena cava (PLSVC) is a congenital malformation caused by abnormal development of the left cardinal vein, resulting in a possible source of right-to-left shunt and embolic stroke.

Methods: We describe the case of a 23-year-old male patient admitted to our Neurology ward. Electronic medical records, neuroimaging and laboratory results were reviewed.

Results: Our patient presented to the emergency department with acute left hemiparesis (NIHSS 18). One week prior, he suffered a blunt trauma playing football, with consequent localized oedema in his left arm. CT angiography showed an occlusion of right MCA, which was submitted to intravenous thrombolysis with rTPA and mechanical thrombectomy. MRI identified a large infarct in the fronto-temporo-insular area, the deep nuclei and bilaterally in the occipital region. Screening for autoimmune/thrombophilic disorders was negative as well as genetic testing. Transthoracic (TTE) echocardiography was normal. A micro-bubble transcranial Doppler, conducted on his right arm, was negative for right-to-left shunt. A transoesophageal (TEE) echocardiography was performed: upon injection of the sonicated solution in the left antecubital vein, early opacification of the left atrium was noted. Computed tomography of the chest was performed, which objected the anatomical anomaly. Since the possible recurrence of strokes due to the congenital defect, the patient was then referred to a cardio-thoracic surgery center, where was submitted to PLSVC disconnection from the left atrium and connection with the right cava with interposition of a reinforced prosthesis. A presence of a thrombus inside the accessory vein was confirmed during the surgery process. The patient was transferred to a rehabilitation facility to provide tailored neuro-motor rehabilitation.

Conclusion: This case highlights the relevance of the correct choice of the venous side in performing a micro-bubble transcranial Doppler: echo contrast injection from the right antecubital vein may indeed give a false negative result and misunderstand a rare cause of paradoxical embolism. While the arm choice can be serendipitous, a possible misdiagnosis could also be achieved in the case of an inverted SVC injecting microbubbles from the left side: our advice is to perform the exam on both arms and, if a shunt is confirmed, to further investigate with investigations capable of optimally delineating the venous system and its anomalies.
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## COMPARISON OF TROPONIN PEAK VALUES BETWEEN CEREBRAL HEMORRHAGES AND UNTREATED ISCHEMIC STROKES

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Purpose: Stroke-heart syndrome (SHS) is a documented complication of acute stroke. It consists in cardiac injury following an acute stroke, with consequent ECG changes, arrhythmia, myocardial injury, ACS heart failure, Takotsubo and sudden cardiac death. The interrelationship with acute myocardial injury also applies to cerebral hemorrhage, especially when extensive. The etiopathogenesis underlying this process is partly unknown, however inflammatory cytokines, the autonomic nervous system, the humoral system with catecholamines, cortisol and various cellular mediators appear to be involved [1-2]. Any or few studies have investigated the difference in this mechanism between ischemic and hemorrhagic stroke. The aim of this study is to compare the heart injury markers between cerebral hemorrhages and untreated ischemic strokes.

Materials: We included 152 patients hospitalized in 2022 in our Stroke Unit, 40 of whom with hemorrhagic stroke (HS) and 112 with untreated ischemic stroke (IS).
Methods: We compared demographic, clinical features (sex, age, cardiovascular risk factors) and markers of cardiac injury (maximum TnI level reached, NT-proBNP >3 times upper limit, maximum TnI > 3 times 99th percentile). Statistical analysis was performed with SPSS using $X^2$ test/Fisher-Yates test/Mann Whitney U test as needed.

Results: No statistical differences between the clinical/laboratory features were observed in the two cohorts (HS and IS untreated), except the NIHSS on admission (7.5; IQR 4-13 in HS and 4; IQR 2-85 in IS) with p=0.015 and discharge (4; IQR 1-7.25 in HS and 1; IQR 0-3 in IS) with p=0.004 and the mRS on discharge (4.5; IQR 1-5 in HS and 2; IQR 1-4 in IS) with p=0.011; the cardiac marker of injury were not statistically significant between the two groups, in particular NT-proBNP (33% in HS and 36% in IS; p=0.714), maximum TnI level reached (ng/l) in HS (15; IQR 8.75-35) and IS (12; IQR 7-30.75) with

p=0.278. The troponin elevation pattern up to 20% was 30% in HS and 28% in IS (p=0.779).

Discussion This study suggests there are no differences in TnI levels between HS and IS in the acute phase. The raise and fall pattern is superimposable. These data suggest that there could be a mechanism of cardiac damage independent of the nature that generated it.

Conclusions More studies are suggested to better investigate if there are substantial differences between HS and IS in the context of SHS, possibly by comparing the trend of the markers if single brain areas are specifically considered.

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## PROXIMAL BASILAR ARTERY STENOSIS "SPONTANEOUS" RESOLUTION AFTER STA-MCA BYPASS IN A SUSPECTED MOYA MOYA DISEASE WITH POSTERIOR CIRCULATION INVOLVEMENT

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Introduction: Moya Moya angiopathy is still a challenging issue for vascular neurologist, despite recent literature updates on diagnosis and treatment. An extensive diagnostic work up is mandatory for an accurate diagnosis to choose best therapy option. Surgical revascularization procedures can improve cerebral perfusion and lower recurrency of ischemic attack and intracranial bleeding.

Methods: We report a case of suspected Moya Moya disease with posterior circulation involvement which underwent to direct revascularization with superficial temporal artery – middle cerebral artery (STA – MCA) anastomosis.

Results: A 46-years old male was admitted to the emergency department for recurrent transient episodes of expressive aphasia. Brain magnetic resonance (MRI) imaging showed multiple subacute subcortical ischemic lesions in the left middle cerebral artery territory. Brain MR angiography (MRA) and digital subtraction angiography (DSA) highlighted multiple intracranial stenoses involving bilaterally carotid siphon, middle (M1), anterior (A1-A2) and posterior (P1-P2) cerebral artery, and also proximal basilar artery. These findings were confirmed on transcranial doppler (TCCD). Extensive diagnostic work-up to rule out primary or secondary vasculitis was perfomed, unless the patient refused lumbar puncture. Aspirin and Clopidogrel was started at the admission and he was discharged asymptomatic as "suspected Moya Moya syndrome". TCCD follow up after 3 months showed worsening of the proximal left middle cerebral artery stenosis. MRA and TCCD at 4-months showed no new ischemic lesions neither progression of stenoses. DSA did not reveal pathologic findings on basilar artery. At 6-months from clinical presentation, direct revascularization with STA–MCA anastomosis was done. In the meanwhile, HLA B51 aplotipe positivity was discovered.

Discussion: Moya Moya differential diagnosis can sometimes be very challenging, particularly when there is both anterior and posterior circulation involvement. This stenotic pattern could be difficult to differentiate from primary cerebral vasculitis. Reliability and reproducibility of diagnostic procedures and a complete differential diagnostic work up are essential to avoid inappropriate therapeutic choice.

Conclusion: STA-MCA bypass was performed in a suspected case of Moya Moya disease (MMD). Changes in stenotic intracranial pattern with basilar stenosis resolution after the surgical procedure raised doubts about diagnosis, as MMD has a chronic progressive evolution. A careful follow-up to better assess the disease progression could be very useful also for correct diagnostic and therapeutic decisions.

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## THERAPEUTIC STRATEGIES IN VASCULAR COGNITIVE IMPAIRMENT: A SYSTEMATIC REVIEW OF POPULATION, INTERVENTION COMPARATORS AND OUTCOMES

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Vascular cognitive impairment (VCI) is a common and heterogeneous condition, both from the clinical and pathophysiological viewpoint. Currently, no approved treatment exists for VCI or one of its subtypes. We performed a systematic review of randomized and non-randomized clinical trials in VCI with the aim of assessing flaws in previous studies and exploring whether any therapeutic option warrants further investigation. 1756 unique medical entries indexed by two widely employed search engines, PubMed® and Embase®, on clinical interventional studies and published from inception to December 31, 2021, were reviewed. We initially searched the two databases with a composite research string assessing the presence in title or abstract of the following keywords (and derivatives, truncations or synonyms thereof) alone or in combination: "vascular", "small vessel", "post-stroke", "subcortical vascular", "multi-infarct, "cognitive impairment", "dementia", "MCI", "therapy", "management". We then conducted a cooperative 3-person review of matching entries using Covidence systematic review software. Abstracts and then full texts were randomly screened for adherence to inclusion criteria by at least two reviewers. Any conflict was resolved by consensus and eventually by a fourth reviewer. Data from included studies were extracted, focusing on study characteristics, design, and population, employed interventions and any relevant outcome. Data were available from 118 trials including 19,223 participants with five different diagnostic VCI categories. Sixty-three different types of intervention were found (51 pharmacologic, 5 employing physical agent application, 7 rehabilitation approaches), the most frequently reported being acupuncture, donepezil, rivastigmine, and ginkgo-biloba extracts. Comparators were either placebo, best medical treatment, or other interventions. Treatment efficacy was assessed by means of 125 outcome measures (49 cognitive-behavioral, 29 instrumental, and 47 functional). A primary outcome measure was clearly pre-specified in only 50.8% of studies. Our review outlined that therapeutic trials in VCI have been heterogeneous in terms of populations, types of interventions, and outcomes. Overall, a lack of a clear pathophysiological rationale for the tested interventions emerges. To tackle more effectively this complex scenario, a change in the approach is needed. Future studies should focus on evaluating treatments with plausible clinical efficacy, employing reproducible outcomes, throughout an adequate timespan to observe possible effects.

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## RISK OF RECURRENT STROKE IN PATIENTS WITH ATRIAL FIBRILLATION TREATED WITH ORAL ANTICOAGULANTS ALONE OR IN COMBINATION WITH ANTI-PLATELET THERAPY

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Introduction: Ischaemic stroke patients with atrial fibrillation (AF) are at high risk of stroke recurrence despite oral anticoagulation therapy. Patients with cardiovascular comorbidities may take both antiplatelet and oral anticoagulation therapy (OAC/AP). Our study aims to evaluate the safety and efficacy of OAC/AP therapy as secondary prevention in people with AF and ischaemic stroke.

Patients and methods: We performed a post-hoc analysis of pooled individual data from multicenter prospective cohort studies and compared outcomes in the OAC/AP cohort and patients on DOAC/VKA anticoagulation alone (OAC cohort). Primary outcome was a composite of ischaemic stroke, systemic embolism, intracranial bleeding, and major extracranial bleeding, while secondary outcomes were ischaemic and haemorrhagic events considered separately. A multivariable logistic regression analysis was performed to identify independent predictors for outcome events. To compare the risk of outcome events between the two cohorts, the relation between the survival function and the set of explanatory variables were calculated by Cox proportional hazard models and the results were reported as adjusted hazard ratios (HR). Finally another analysis was performed to compare the overall risk of outcome events in both OAC/AP and OAC cohorts after propensity score matching (PSM).

Results: During a mean follow-up time of 7.5±9.1 months (median follow-up time 3.5 months, interquartile range ± 3), 2284 stroke patients were on oral anticoagulants and 215 were on combined therapy. The multivariable model demonstrated that the composite outcome is associated with age (OR: 1.03, 95% IC: 1.01-1.04 for each year increase) and concomitant antiplatelet therapy (OR:2.2, 5% IC:1.48-3.27), the ischaemic outcome with congestive heart failure (OR: 1.55, 95% IC: 1.02-2.36) and concomitant antiplatelet therapy (OR:1.93, 95% IC: 1.19-3.13), the haemorrhagic outcome with age (OR:1.03, 95% IC: 1.01-1.06 for each year increase), alcoholism (OR: 2.15, 95% IC: 1.06-4.39) and concomitant antiplatelet therapy (OR:2.22, 95% IC: 1.23-4.02). Cox regression demonstrated a higher rate of the composite outcome (hazard ratio of 1.93 [95% CI, 1.35–2.76]), ischaemic events (HR: 2.05 [95% CI, 1.45–2.87]) and bleeding outcomes (HR: 1.90 [95% CI, 1.06-3.40]) in OAC/AP cohort. After PSM analysis, the composite outcome remained more frequent in people treated with OAC + AP (RR: 1.70 [95% CI, 1.05-2.74]).

Discussion: Secondary prevention with combination of oral anticoagulant and antiplatelet therapy after ischaemic stroke was associated with worse outcomes in our cohort.

Conclusion: Further research is needed to improve secondary prevention by investigating the mechanisms of recurrent ischaemic stroke in patients with atrial fibrillation.

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## IMPACT OF INFLAMMATORY INDEXES ON THE PROGNOSTIC PERFORMANCE OF ICH SCORE IN SPONTANEOUS INTRACEREBRAL HEMORRHAGE

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Introduction: Systemic inflammation could lead to secondary cerebral damage after spontaneous intracerebral hemorrhage (sICH) with a potential detrimental effect on the functional outcome. Multiple parameters have been proposed to evaluate the systemic inflammatory response after sICH including Systemic Immune-Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), and red-cell index (RCI). However, the impact of their inclusion on the performance of the existing clinical-radiological scores, as the ICH score, is still not known.

Methods: All patients admitted from January 2013 to December 2022 to the Stroke Unit of IRCCS Mondino and from January 2017 to September 2017 to the Stroke Unit of Udine University Hospital were retrospectively evaluated. Patients with secondary ICH, lacking neuroradiological, follow-up or laboratory data were excluded. Inflammatory indexes were calculated as follow: SII=platelets*(neutrophils/lymphocytes); SIRI=monocytes*(neutrophils/lymphocytes); RCI=(red blood cells*hemoglobin)/(lymphocytes*platelets). Area under the curve (AUC) of receiver operating characteristic curves (ROCs) were used to evaluate the performance of ICH score alone and in association with the inflammatory indexes and compared with DeLong test. A poor outcome was defined as a modified Rankin Scale 4-6 at 3-months.

Results: 206 patients were included in the final analysis, 88 (43%) were female and had a mean age of 75 (±11) years. 119 (58%) patients had an unfavorable 3-months outcome. Patients with a 3-months poor functional outcome had higher median SII (1367.6 vs 754.1, p<0.001) SIRI (4.0 vs 2.3, p<0.001), RCI (0.3 vs 0.2, p=0.01) and had more frequently ICH score >=2 (55% vs 9%, p<0.001). ICH score alone demonstrated a good prognostic performance (AUC 0.82 [95%CI: 0.77-0.87]). Among the inflammatory response markers, the addition to the model of SII (ICH score + SII: AUC 0.86 [95%CI: 0.80-0.91] ) and SIRI (ICH score + SIRI: AUC 0.85 [95%CI 0.80-0.90]) was able to improve its performance vs ICH score alone (p-values 0.004 and 0.01 respectively).
Discussion: Our data suggest that the addition of SII or SIRI to ICH score would allow to improve its performance in predicting the outcome of ICH patents at 3-months. The use of these biomarkers would be cost-free and very feasible in clinical practice, as they are calculated from routine blood tests. A better outcome prediction would be useful to tailor patients care and communications with relatives in the acute phase of ICH.

Conclusions: SII and SIRI could improve ICH score performance in predicting a poor 3-months outcome in sICH patients, without the need of additional diagnostic tests.

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## THE ROLE OF THE OXFORD COGNITIVE SCREEN (OCS) IN ASSESSING COGNITIVE IMPAIRMENT IN STROKE UNIT - A PILOT STUDY

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Background: The Oxford Cognitive Screen (OCS) is a comprehensive battery of neuropsychological tests designed to evaluate cognitive deficits following a stroke. It covers five cognitive domains, including attention-executive function, language, memory, number processing, and praxis. Unlike widely used instruments such as the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA), which were developed for neurodegenerative diseases, the OCS is specifically tailored to be inclusive and unaffected by aphasia and neglect. Thus, it holds significant potential for accurately assessing cognitive deficits in stroke patients.

Objective: This study aimed to compare the effectiveness of the OCS and MoCA in detecting cognitive impairments among stroke survivors. Additionally, we sought to examine differences in the cognitive profiles of patients with milder versus more severe outcomes three months after the acute phase.

Materials and Methods: Fifty patients consecutively admitted to our Stroke Unit for acute stroke with an average NIHSS score of 5 were enrolled. Patients were evaluated within five days of onset by means of the MoCA and OCS. Follow-up assessments were conducted three months later using the modified Ranking Scale (mRS) to stratify patients into good (n=39, mRS < 3) and worse (n=11, mRS > 2) outcome groups. Spearman's correlation coefficient was used to assess correlations between continuous variables, while the Mann-Whitney-U-test was employed to compare groups.

Results: Of the patients, 90% (n=45) exhibited abnormal scores on the MoCA (below 26/30), while all patients demonstrated impairment in at least one OCS subtest, indicating the higher sensitivity of the OCS in detecting even mild cognitive impairments. Significant correlations were observed between various MoCA and OCS subtest scores. NIHSS scores were correlated with OCS subtests involving sentence reading, number writing, and MoCA subtests assessing orientation. Patients with more severe outcomes at three months performed worse on OCS subtests related to sentence reading, number writing, and trails task, but no statistically significant difference was found in the MoCA global score.

Discussion and Conclusions: The OCS scale demonstrates greater sensitivity than the MoCA in identifying post-stroke cognitive disorders, particularly in cases of mild stroke, which may have significant implications for early intervention and tailored rehabilitation strategies. Additionally, the OCS appears to be a more valuable tool for predicting stroke outcomes. Further research with larger patient cohorts is warranted to validate and expand upon these findings and to explore this association more comprehensively. Moreover, incorporating longer longitudinal assessments may offer a better understanding of the predictive utility of this tool.

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## ROLE OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN EVALUATING ISCHEMIC STROKE DESPITE ADEQUATE ANTICOAGULATION THERAPY

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Objective: This study aims to evaluate the role of transesophageal echocardiography (TEE) in the assessment of patients with ischemic stroke despite adequate anticoagulation therapy with direct oral anticoagulants (DOACs) or properly managed Coumadin therapy (within the therapeutic range). Methods: Sixteen patients (9 females and 7 males) who were on DOACs or Coumadin therapy (5 Apixaban, including 1 at reduced dosage; 3 Edoxaban, including 1 at reduced dosage; 3 Rivaroxaban; and 5 Coumadin) and were admitted to our department for ischemic stroke in 2022 with DOAC dosage or international normalized ratio (INR) within the therapeutic range underwent TEE. The average age of the patients was 72.8 years. TEE findings were analyzed and categorized.

Results: Among the 16 patients studied, 4 exhibited normal TEE findings. Six patients were diagnosed with endocarditis, one of whom also had an auricular thrombus. One patient had a ventricular thrombus, while 4 patients had an atrial thrombus. Three patients were found to have valvular pathology.

Discussion: TEE plays a crucial role in the evaluation of patients with ischemic stroke despite optimal anticoagulation therapy. It allows for detailed assessment of cardiac structures, identification of potential sources of embolism, and detection of coexisting pathologies such as endocarditis, thrombi, and valvular abnormalities. The presence of these conditions may contribute to the occurrence of embolic events despite therapeutic anticoagulation.

Conclusion: In this study, TEE revealed various cardiac abnormalities in patients with ischemic stroke despite adequate anticoagulation therapy. These findings emphasize the importance of TEE in the comprehensive evaluation of such patients, as it provides valuable information for guiding further management decisions. Early identification of endocarditis, thrombi, and valvular pathology through TEE can help optimize treatment strategies and potentially reduce the risk of recurrent embolic events. Considering the few available data [1, 2], larger studies are warranted.

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## POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME DURING TREATMENT WITH LENVATINIB PLUS PEMBROLIZUMAB IN A PATIENT WITH METASTATIC ENDOMETRIOID ADENOCARCINOMA: A CASE REPORT OF AN UNCOMMON ADVERSE EVENT

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Aims: Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder characterized by a subcortical white matter reversible vasogenic edema typically located bilaterally in the parieto-occipital region. Immunosuppressive and cytotoxic drugs can predispose for this uncommon condition. In a few case reports lenvatinib, an inhibitor of the tyrosine kinases of vascular endothelial growth factor receptor (VEGFR) used for the treatment of several cancers, has been shown to predispose to PRES. The mechanism is still unclear, but it seems to be linked to induced hypertension and endothelial dysfunction. Recently a combination therapy of lenvatinib plus pembrolizumab was approved for the treatment of advanced endometrioid adenocarcinoma. Pembrolizumab is an immune checkpoint inhibitor which is associated with the development of autoimmune diseases including encephalitis.

Materials: Here we report a case of PRES developed by a patient treated with lenvatinib plus pembrolizumab.
Method: A 63-year-old woman with a metastatic endometrioid adenocarcinoma presented with headache and a generalized epileptic seizure with consequent head trauma 6 months after initiation of lenvatinib plus pembrolizumab.

Results: The patient was referred to the emergency room where she underwent a CT scan of the brain with evidence of frontal and temporal cerebral contusions. Lenvatinib was immediately discontinued due to its association with increased bleeding risk. The electroencephalogram showed left fronto-temporal epileptic activity and the MRI revealed multiple bilateral areas of subcortical white matter edema. The patient rapidly recovered after lenvatinib discontinuation with a complete clinical and radiological recovery one week later. A diagnosis of lenvatinib induced PRES was then made.

Discussion: According to clinical presentation and neuroimaging the two main diagnostic hypotheses were PRES and autoimmune encephalitis. The rapid recovery of neurological symptoms after lenvatinib discontinuation led to encephalitis exclusion and PRES diagnosis without the need of a lumbar puncture. To the best of our knowledge this is the second case of PRES in a patient treated with lenvatinib plus pembrolizumab and the ninth linked to lenvatinib.

Conclusions: In the future there will certainly be a progressive increase in the use of these new targeted therapies for the treatment of a variety of malignancies. Linked to this, there will therefore also be a consequent increase in their life-threatening adverse effects, such as PRES, and their rapid recognition and treatment will be essential.
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## FAST IS FINE, BUT ACCURACY IS FINAL

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Introduction: Arm and leg weakness is part of the FAST acronym used as a mnemonic to help detect and enhance responsiveness to the needs of a person having a stroke. However, a vascular neurologist should learn to be slow in a hurry, as good management is dependent on good assessment.

Case report: A 79-year-old woman with a history of hypertension, hypercholesterolemia, and remote right leg deep vein thrombosis was admitted to our emergency department due to an abrupt onset of intense cervical pain irradiated to her right shoulder, immediately followed by a marked weakness of the right extremities. The patient denied a recent trauma or infection. The neurological examination revealed a right hemiparesis: NIHSS 5 (2 points for arm weakness, 3 points for leg weakness). Cerebral CT and CT-Angio were unremarkable, therefore in the absence of clear contraindications, thrombolysis was promptly administered in the CT room. When the patient arrived at the Stroke Unit, an experienced vascular neurologist noted the absence of a right facial paresis, urging a spinal MRI which disclosed a spontaneous epidural hematoma extending from C1 to T3. A digital subtraction angiography did not document arteriovenous malformations or dural fistulas and a surgical approach was ruled out. On the following days, there was a progressive improvement of her right hemiparesis, although the patient still reported a persistent but slight cervical pain. On day 4, a spinal MRI showed a complete reabsorption of the hematoma. On day 5, the patient was completely asymptomatic and was discharged without any neurological deficits.

Discussion: Spontaneous spinal epidural hematoma (SSEH) is a rare condition defined as blood within the epidural space without known traumatic or iatrogenic cause compressing the spinal cord and leading to acute neurological deficits. Standard therapy is decompressive laminectomy, although spontaneous recoveries have been reported, as in our patient. Acute hemiparesis with cervical pain is a possible presentation of SSEH mimicking stroke secondary to a cervical dissection. Not recognizing SSEH can lead to a stroke misdiagnosis with an unjustified and potentially dangerous treatment.

Conclusions: An insufficient understanding of a patient's condition in a stroke-related emergency setting should slow down the process enough to gather the necessary information before choosing the optimal treatment, as an inaccurate assessment might be fatal.
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## FRAILTY AS PREDICTOR OF IN-HOSPITAL COMPLICATIONS IN PATIENT WITH ACUTE ISCHEMIC STROKE

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Background: Frailty is the most important short- and long-term predictor of disability in the elderly and thus might influence the clinical outcome of acute stroke [1,2].

Objective: To evaluate whether frailty predicts short-term complications during hospitalization in Neurology setting in elderly patients with stroke.

Methods: The study included consecutive patients older than 65 years admitted to a single Acute Neurology Unit. Predictors of stroke outcomes were assessed including demographics, baseline National Institute of Health Stroke Scale (NIHSS), comorbidities and treatment. Premorbid Frailty was assessed with a comprehensive geriatric assessment (CGA) including functional, nutritional, cognitive, social and comorbidities status [3]. Predictors of death, medical complications and duration of hospitalization were assessed in linear and logistic regression analyses.

Results: One-hundred and twenty patients with stroke entered the study (median age 73.5, 66.3-81.2 years). Frailty was diagnosed in 60 out of 120 patients and associated with older age ($p<0.001$), higher premorbid disability and stroke severity. Frailty status was associated with higher risk of complications (48.3% vs 11.7%, $p<0.001$) and longer median hospitalization (14 vs 9 days, $p<0.001$). Multidimensional frailty increased the risk of in-hospital complications (odds ratio (OR) 15.61, 95% confidence interval (CI) 1.43-170.47, $p=0.024$) independently of age and baseline NIHSS.

Discussion: Frailty is an important predictor of stroke short-term complications beyond age and severity. Larger on-going longitudinal studies are warranted to evaluate the clinical impact of multidimensional frailty evaluation on clinical management of patients in acute and chronic settings.

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## FUNCTIONAL OUTCOME PREDICTION IN STROKE: LOCAL AND DISTAL LESION PROPERTIES

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Objective: Predicting clinical recovery in stroke using neuroimaging features is an emerging field of research. Previous studies have attempted to predict clinical recovery based on lesion volume and topology with disappointing results. Here, we investigated whether a multivariate clinical approach incorporating advanced lesion properties could improve functional outcomes prediction in stroke.

Materials: We enrolled stroke patients who had undergone T1-weighted imaging or CT scan and completed the stroke impact scale (SIS) at 6/12 months post-stroke. For each lesion we computed local measures (lesion shape, tract density index - number of white matter fibers affected by the lesion - and within-lesion diffusion properties) and structural and functional network measures (percentage of networks disconnected by the lesion). Except for lesion shape, all other features were computed using a normative structural/functional connectome. A factorial analysis was performed on the SIS subitems. the resulting components were used as dependent variables in a ridge regression model with a bagging procedure. Three models were tested: one incorporating local measures as predictors, another including structural disconnected networks, and a third model using functional disconnected networks as predictors. The models were compared based on R-square values.

Results: Sixty patients were included (mean age 66). Three SIS components were identified, explaining over 70% of the variance. The first component was associated with motor items (renamed as physical), the second component with cognitive items (cognitive), and the third with emotional/social items (emotion/social). The first model (local measures) explained a small amount of variance (cognitive: 14%; physical: 11%; emotion/social: 6%). The structural disconnection network model explained a slightly higher, yet still low, amount of variance (cognitive: 17%; physical: 13%; emotion/social: 9%). The functional disconnection network model yielded higher variance prediction for the physical component (28%), increasing to 35% when sociodemographic variables were included. In contrast, both cognitive and emotion/social components were not well explained by functional disconnection (7% and 10%, respectively).

Discussion: The SIS scale comprises three components that can be predicted differently based on lesion properties. However, the prediction of cognitive and emotion/social outcome was low based on local lesion and network disconnection measures. In contrast, the physical component was more accurately predicted by functional network dysconnectivity.

Conclusions: These results emphasize the potential of network dysconnectivity as an important predictor of motor outcomes. Cognitive and emotional aspects may necessitate direct measures (e.g., diffusion-weighted imaging, resting-state fMRI) to better understand the complex alterations after a stroke.

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## INTRALUMINAL NON-OCCLUSIVE THROMBUS AND EMBOLIC STROKE IN A PUERPERAL WOMAN

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Introduction: Intraluminal non-occlusive thrombus (ILT) is a rare finding in patients with acute ischemic stroke, with a prevalence ranging

from 1.6%-to-3.2%. Although in most cases ILT is associated with atherosclerotic disease or arterial wall disorders, this finding has been also described in patients without any underlying vessel disease, but with a hypercoagulable state due to several etiologies. To the best of our knowledge there are no reports of ILT during pregnancy or puerperium.

Case report: We report a case of a 38-year-old puerperal woman with acute onset of mental confusion and left-sided weakness. She had no vascular risk factors and her medical history was unremarkable. After in-vitro fertilization pregnancy (IVF), she had a spontaneous vaginal delivery with post-partum hemorrhage (PPH, 900mL) treated with uterotonic agents and prophylactic anticoagulation (enoxaparin 4,000UI once-daily). Neurological examination confirmed mild dysarthria and mild left-sided hemiparesis, NIHSS score was 5. Brain CT and CT angiography showed sub-occlusion of the right distal MCA at the bifurcation and an intraluminal filling defect at the right carotid bulb, suspected to be a thrombus. Brain MRI was also performed and showed acute ischemia in the right caudate and lenticular nucleus. The patient underwent to urgent cerebral angiography and mechanical thrombectomy was performed with complete reperfusion. Intravenous thrombolysis was not administered due to the recent delivery and because the patient was out of therapeutic window. To better study the CTA finding, carotid ultrasound (CUS) was performed which revealed a homogeneous intraluminal isoechoic formation, adhering to the carotid wall, suggestive of a thrombus. She was treated with acetylsalicylic acid 100mg and enoxaparin 6,000UI. All other tests excluded other potential sources of embolism. Complete blood tests were normal, excluding any hereditary or acquired thrombophilia. In follow-up imaging the intraluminal thrombus gradually decreased in size and then disappeared without revealing any underlying carotid defect. At discharge the neurological examination was normal.

Conclusion: In pregnant or puerperal women the hypothesis of an ILT as cause of an embolic stroke should be considered. In our case the pregnancy-induced changes (hypercoagulability and endothelial dysfunction), further enhanced by IVF and PPH, may have led to thrombus formation in a vascular region, such as the carotid bulb, usually characterized by wall shear stress due to a non-laminar and turbulent blood flow. Little is known about the best therapy, both antiplatelets and anticoagulants are used in clinical practice and outcome is generally good with complete thrombus resolution at follow-up.

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## CARDIAC INJURY AFTER STROKE, A COMPARISON BETWEEN TRANSIENT ISCHEMIC ATTACKS AND ISCHEMIC STROKE


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Purpose: Transient ischemic attack (TIA) is defined as transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction [1]. In this type of ischemic event, there are no data about a possible cardiac injury tested with troponin. After a stroke the cardiac involvement due to a neuroinflammatory response (recently defined as Stroke Heart Syndrome) is well established [2]. The aim of this study is to compare troponin levels after a stroke or TIA.

Materials and methods: This is a retrospective, single center study on 565 patients (73 TIAs, 492 stroke). We collected demographic characteristics, cardiovascular risk factors, cardiac data such as troponin, NT-proBNP, left atrial dilatation, etiology of the ischemic event (TOAST classification).

Results: We compared IS to TIA for each TOAST subtype. In all groups no substantial differences were found in demographic and past medical history ($p>0.05$). Maximum troponin levels were significantly lower in TIAs than in IS ($p<0.05$), except in lacunar etiology strokes were troponin levels were similar in both groups. In multivariate analysis troponin levels over the 99 th percentile (18 ng/l) were inversely associated with TIAs (OR 0.118; 95%IC 0.050-0.277 and lacunar strokes (OR 0.180, 95%IC 0.085-0.379)), and directly correlated to NT-proBNP (OR 4.071, 95%IC 2.521-6.573) and age (OR 1.057; 95%IC 1.035-1.080).

Discussion and Conclusions: Troponin level after TIAs is significantly lower than IS. Troponin levels after an ischemic event are also independently correlated to NT-proBNP, age and lacunar strokes subtype.

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## TAKOTSUBO AFTER LEFT BULBAR ISCHEMIC STROKE (WALLENBERG SYNDROME): A CASE REPORT


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Purpose: Takotsubo syndrome (TTS) is a well known cardiac complication after stroke. It is more commonly reported after subarachnoid hemorrhage (SAH) or ischemic stroke involving insular areas. Rare case reports of TTS after massive involvement of posterior circulation strokes are described (basilar artery occlusion). However there are no data about TTS after Wallenberg Syndrome (WS).

Materials: We describe one case of TTS after a left bulbar ischemic stroke (WS).

Methods: We performed a PubMed search using the following MeSH terms “(Takotsubo) AND (ischemic stroke)” or “(takotsubo) AND (brainstem stroke)”, looking in particular for articles that explain any relationship between small brainstem infarction and TTS.

Results: A 91 years old woman, affected by arterial hypertension, dyslipidemia, previous PTCA-treated myocardial infarction (2014), was admitted to our Stroke Unit for sudden onset of mild left ataxic hemiparesis and dysmetria, vertigo and nystagmus. Brain CT scan did not show ischemic lesions while CT angiography demonstrated a distal left vertebral occlusion. The patient was treated with rtPA with mild improvement. During the standard blood tests, a troponin (up to 2364 ng/l) and NT-proBNP increase (4703 pg/ml) were correlated to a cardiac dysfunction at transthoracic echocardiography (left apical akinesia), with clear disproportion between the diffuse left wall dysfunction and the moderate troponin rise. Moreover new ECG alteration

appeared (as QT prolongation and negative T waves), without ECGrafic signs of acute AMI.

Discussion: In literature TTS is commonly described after an involvement of the autonomic network (insulae, diffuse lesions of the brainstem) [1-2]. The role of small medullary infarction as in Wallenberg syndrome in inducing TTS may be linked to a general stress response following a stroke wherever it is located, not only insular or massive posterior circulation strokes.

Conclusions: TTS is a rare complication after stroke. More studies are needed to better evaluate the role of small infarctions as possible triggers of autonomic stress response leading to TTS.

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## THE EFFECT OF CITICOLINE IN MODULATING BRAIN CORTICAL PLASTICITY IN SUBACUTE/CHRONIC ISCHEMIC STROKE PATIENTS

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Objectives: Ischemic stroke is the first cause of persistent disability and it frequently affects cognitive abilities, with a series of syndromes ranging from mild cognitive impairment to dementia. Research on animal models of ischemic stroke supports the idea that pharmacological treatments potentially enhancing intrinsic brain repair and plasticity could reduce acute brain damage, improving functional recovery. Citicoline (an exogenous form of cytidine-5'-diphospho-choline) is a molecule potentially able to enhance brain plasticity, and it has been extensively studied in several neurological disorders [1, 2]. A previous experimental study showed that patients who had experienced an ischemic stroke and started citicoline for 8 weeks within 36 hours from the event had an improvement in intracortical excitability measures, assessed through transcranial magnetic stimulation (TMS) protocol [3]. Taking into account these findings, the present experimental study will evaluate the effect of a longer treatment with citicoline on cholinergic neurotransmission using TMS protocols, in ischemic stroke patients within three months from the event.

Methods/Design: This single-blind, multicentric, randomized clinical study will include 100 patients, aged 60 to 80 years, who experienced a stroke in the past three months and have a National Institutes of Health Stroke Scales (NIHSS) < 14. Patients will be randomly assigned to two different groups with a ratio 1:1. Patients randomized to the first group, will receive conventional treatment and oral citicoline 1000 mg once daily for 16 weeks. Patients in the second group, will receive conventional therapy for 8 weeks, then oral citicoline 1000 mg once daily will be added for 8 additional weeks. Patients will be evaluated at baseline (T0), after 8 weeks (T1), after 16 weeks (T2) and after a 8-week follow-up (T3). At all timepoints (T0, T1, T2 and T3) enrolled patients will be evaluated with TMS and clinical scales (MMSE-Mini Mental State Examination, NIHSS, RAVLT- Rey's auditory verbal learning task, Trail Making Test A and B and Test of everyday attention).

Discussion: TMS techniques have been widely used to assess vascular pathology and can be useful to detect brain changes in patients with ischemic stroke. As citicoline has been shown to have effects on animal models of ischemic stroke as well as enhancing brain plasticity in ischemic stroke patients, this randomized experimental study will shed lights on the effect of citicoline on neurotransmission pathways and specifically will confirm the effect on citicoline on the cholinergic pathway using an objective measure, such as TMS.

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## ATRIAL FIBRILLATION DETECTION WITH LOOP RECORDER IN ESUS (EMBOLIC STROKE OF UNDETERMINED SOURCE): A PROSPECTIVE MONINSTITUTIONAL SERIES

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Objectives: We aim to determine the prevalence of occult atrial fibrillation (AF) in patients with diagnosis of ESUS through continuous cardiac monitoring using ILR.

Materials and methods: We prospectively collected data from 2019 to 2023 of 48 patients with ESUS implanted with ILR including risk factors and home therapy before the event, clinico-radiological elements and the complete diagnostic work-up data. We also evaluate any correlations between risk factors and AF.

Results: The median age was of 66,5 (37-82) years. The majority of patients were men (60%) and the median time of cardiac monitoring was of 14,5 months (1-45). The main cerebrovascular risk factors were collected (hypertension, diabetes, dyslipidemia, previous stroke, cardiopathy, vasculopathy, smoking) and 71% of patients had at least 1 of them, while the 52%, 27%, 12,5% had at least two, three or four of them respectively. 29,2% of patients were on antiplatelet or anticoagulant treatment before stroke. The median NIHSS was 4 (1-24) at onset and 0 (0-4) at discharge, with a mRS ≤2 in 87,5% of patients. In 50% of patients multiple ischemic lesions, suggestive of embolic events, were found on CT or MRI scans. Atrial fibrillation was detected in 16 patients (33,33%) with a median time from the implantation of the ILR and from the ischemic stroke to the AF registration of 29 days (2-267) and of 89 days (7-622) respectively. To univariate analysis age was the only significant predictor, with an OR of 15,0 (95% CI 1,7 - 127,4) for patients older than 60 years.

Discussion: Prolonged monitoring with ILR can give a high percentage of occult AF detection and our data regarding overall prevalence is in line with those from literature. The majority of the events were recorded in the first 2 months after implantation and data analysis on possible predictive factors is still ongoing. Our detection rate (20,83% at 2 months, 33,33% at 9 months) is much higher than in

CRYSTAL AF study and other studies and series from literature. Age was the only significant predictor found in our study, as in literature; no other risk factors were found to be statistically significant.

Conclusion: We confirmed the data available in literature about AF detection in ESUS with ILR. An accurate selection of the patient, after a complete work-up analysis, and definition of ESUS is mandatory to increase the sensitivity of the continuous cardiac monitoring. Further research is needed to determine more risk factors of AF other than age.

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## EPIDEMIOLOGY AND OF ANEURYSMAL AND NON-ANEURYSMAL SUBARACHNOID HEMORRHAGE AND ITS SUBTYPES OVER 10 YEARS IN A POPULATION-BASED STUDY

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Objectives: We aimed at giving an updated report of either aneurysmal (a-) or non-aneurysmal (na-) SAH epidemiology over the last 10 years. Materials and Methods: Our prospective population-based registry included patients with first-ever SAH occurring from January 2011 to December 2020. Clinical and neuroimaging records were screened to evaluate the presence of intracranial aneurysms in order to differentiate aneurysmal (aSAH) from non-aneurysmal SAH naSAH) and to retrieve information on surgical treatments. Incidence rates were standardized to the 2011 Italian and European population. We also estimated 30-days and 1-year case-fatality rates (CFRs).

Results: 194 patients (60.8% women; mean age 62.5±16.0 years) were included (76.8% aSAH and 23.2% naSAH). The crude incidence rates per 100,000 person-years of SAH, aSAH, and naSAH were 6.5 (95% CI 5.6-7.5; p for trend=0.764), 5.0 (95% CI, 4.2-5.9; p for trend=0.831) and 1.5 (95% CI, 1.1-2.0; p for trend=0.815), respectively. SAHs 30-day and 1-year CFRs were 28.4% (95% CI 21.4-36.9%) and 37.1% (95% CI 29.0-46.7%) respectively. Compared to aSAH, naSAH patients had older age (68.8±19.7 vs 60.6±14.2 years; P=0.012), lower prevalence of cigarette smoking (17.9% vs 36.4%; p<0.001), and higher prevalence of atrial fibrillation (15.7% vs 2.8%; p=0.005). Considering the two types of naSAH, the perimesencephalic form affected younger patients compared to non-perimesencephalic naSAH (57.8±16.2 vs 75.5±18.7 years; P=0.002) and 30-day and 1-year CFRs were higher for non-perimesencephalic naSAH (p=0.022). Discussion: Although literature reported a globally decline in SAH incidence, in our cohort remained almost stable and was highest in patients aged >75 years. Those last data are in line with worldwide trends pointing toward an increasing age at SAH onset probably due to prevalence of vascular risk factors, mainly arterial hypertension and cigarette smoking. Our 30-day case-fatality rate was slightly higher and may be explained by the relatively high mean age of our sample. In line with literature, most patients had aSAH, despite naSAHs cases were a higher proportion compared with similar population-based studies. In naSAHs subtypes we found difference in CFRs, in particular non-perimesencephalic naSAH is associated with worse prognosis compared with perimesencephalic one.

Conclusion: We found a low and stable incidence of SAH and a shift towards older age at SAH presentation compared with previous data. naSAH is an emerging and heterogeneous entity and the distinction between its two subtypes is of prognostic relevance; considering the lower frequency, larger epidemiological studies are warranted.

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## CAROTID-CAVERNOUS FISTULA COMPLICATED BY ACUTE ISCHEMIC STROKE DUE TO INTERNAL CAROTID ARTERY DISSECTION IN VASCULAR EHLERS-DANLOS SYNDROME

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Background: Vascular Ehlers-Danlos syndrome (EDS) is a collagen genetic disorder caused by COL3A1 gene mutations. It is a rare cause of stroke by ruptured aneurysms, cervical artery dissections and carotid-cavernous fistula (CCF).

Case report: A 42-year-old woman with a genetic diagnosis of EDS, was admitted for sudden onset of headache and paralysis of 3rd and 6th cranial nerves. She had a history of hypertension, bowel perforations, and splenic artery aneurysm. CT-angiography showed left fronttemporal subarachnoid hemorrhage (SAH) and a CCF. After seven days she presented recurrent episodes of motor aphasia that became persistent two days later. Aphasia furtherly worsened, CT-angiography with CT-perfusion was repeated showing severe left internal carotid artery (ICA) stenosis due to dissection in C1 segment and hypoperfusion in the left MCA territory (ischemic core 31 ml, penumbra/core 1.8). Urgent endovascular stenting of ICA was performed and in the same intervention CCF was transarterially embolized. Post-intervention

time was complicated by left temporal hematoma with initial transuncal herniation and acute respiratory insufficiency requiring invasive intracranial pressure (ICP) monitoring and tracheostomy. Progressively, patient improved with suspension of air support and ICP monitoring. At demission (40 days after the intervention) she presented sporadic anomies, left ptosis and slight sixth cranial nerve palsy.

Conclusions: Our patient presented two types of vascular complications due to EDS: CCF with SAH and spontaneous homolateral ICA dissection, partly consequent to high flow compensating arteriovenous steal. Endovascular procedure was technically difficult for high risk of hemorrhage in vessels fragility; carotid stent was implanted to treat acute ischemic stroke.

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## MOVING FROM CT TO MRI IN ACUTE ISCHEMIC STROKE: EFFECTS ON DIAGNOSIS, REVASCULARIZATION METRICS AND MEDIUM TERM OUTCOMES

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Background and Aims: The relative value of CT and MRI in acute ischemic stroke (AIS) is debated. In May 2018, in Lausanne University Hospital (CHUV) we switched from CT to MRI as first line imaging for all suspected AIS. Here, we aimed to retrospectively assess the effects of this paradigm change on diagnosis, revascularization metrics and safety and disability outcomes.

Methods: From the Acute STroke Registry and Analysis (ASTRAL) we selected an identical number of patients during the MRI-first-period (05/2018-08/2022) and the preceding CT-first-period (until 2012). We compared outcome measures in the two periods by univariate and multivariate analysis and we performed time-trend analyses for the main outcomes.

Results: The median age of the 2972 included consecutive AIS patients was 76 (IQR=65-84) years, and 1361 (46%) were female. In the MRI-period, 80% underwent MRI as first acute imaging. The proportion of patients requiring a second acute imaging modality for diagnostic ± revascularization reasons increased from 2.1% in the CT-period to 5% in the MRI-period (puniv<0.05) while the rates of subacute imaging (until the end of hospitalization) decreased from 79% to 60% (padj <0.05). The rates of initially missed AIS diagnosis (chameleons) was similar (3.8% vs 4.4%, padj=0.32). Stroke mimics treated by intravenous thrombolysis (IVT) decreased by half (8.6% vs 4.3%, padj<0.05). The MRI-paradigm was not associated to the rates of undetermined stroke mechanism at the end of hospitalization. We assessed 1131 consecutive IVT and 662 endovascular (EVT) treated patients. Median door-to-needle-time was 31min (IQR=24-48) in the CT-period vs. 43min (IQR=33-58) in the MRI-period (+12 min, puniv<0.01), while median door-to-groin-time was unchanged. In the CT vs. MRI periods, rates of missed IVT opportunities were respectively 3.1% vs. 0.8% (puniv<0.01); rates of symptomatic intracranial haemorrhage (SICH) after IVT were numerically, but non-significantly, lower (5.6% vs 3.2%, padj=0.07) and SICH after EVT (±IVT) were similar (6.5% vs 4.2%, padj=0.21). Disability at 3 months was unaffected for both IVT and EVT-treated patients (common adjusted odds ratio for favourable Rankin shift 1.23,95%CI=0.96-1.58; p=0.1 and 0.93,95%CI=0.67-1.29, p=0.674 respectively) and in the overall cohort.

Conclusion: The paradigm shift from CT to MRI as first-line imaging for AIS in a comprehensive stroke centre seems feasible. MRI was associated with reduced IVT for stroke mimics, but not with rates of missed AIS diagnosis and undetermined stroke mechanism at discharge. The MRI paradigm was associated to reduced rates of missed IVT opportunities. We observed longer door-to-needle and stable door-to-groin times during the MRI-period. Safety (SICH) and 90-day disability were not affected.

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## INVESTIGATING TEMPORAL MUSCLE THICKNESS (TMT) AS A PREDICTOR OF FUNCTIONAL OUTCOME AFTER REVASCULARIZATION TREATMENTS FOR ACUTE ISCHEMIC STROKE

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Objectives: The study aims at investigating temporal muscle thickness (TMT) as a predictor of functional outcome in patients with acute ischaemic stroke who received revascularization procedures.

Materials and Methods: Consecutive patients affected by ischemic stroke who underwent thrombectomy and/or thrombolysis at our center were included in this observational retrospective study. Demographic, clinical and radiological data were extracted from electronic reports. TMT was measured on emergent brain Computed Tomography (CT) images acquired at arrival in the emergency room, according to published protocols. Modified Rankin Scale (mRS) scores at 3 months represented the main endpoint of functional outcome. Patients were further divided into two groups: at-risk vs not-at-risk of sarcopenia, based on a literature cut-off of mean TMT. Univariate and multivariate analyses were performed to assess the significance of mean TMT as a predictor of functional outcome.

Results: 126 patients (53 f and 73 m) were included in the study. Mean age was 72 ± 14 SD (range 24 - 95), baseline NIHSS was 11.7 ± 6.9. 34 patients underwent thrombolysis, 50 patients thrombectomy and 42 both. Mean TMT was 5.4 mm ± 1.9 (range 1.2 - 11.7); male patients had higher TMT values compared to female (mean value 5.9 vs 4.6, p<0.0001). We found a correlation between mean TMT and age (r -0.32, p<0.001) and with mean TMT and pre-existing mRS (r -0.34, p<0.001) but not with BMI. In the univariate analysis patients with unfavorable outcomes at 90 days (mRS > 3) had lower values of mean TMT (4.9 vs 5.6 mm, p=0.02), as well as the subgroup of patients who passed away (n = 17, 13.5%; 4.1 vs 5.6 mm, <0.001). We found that patients at-risk of sarcopenia were more likely to die (OR 6.8, 95% IC 2-20, Fischer's exact test p<0.001). In the multivariate analysis, after adjustment, neither mean TMT nor belonging to the at-risk of

sarcopenia group were confirmed as independently associated with worse outcomes.

Discussion: Despite proper care and treatment, functional outcome in patients with acute ischemic stroke isn't always as favorable as expected. There are many known factors that influence patient's recovery (age, gender, initial severity of stroke, functional status at admission, etc.) but many more are under investigation to improve treatment personalization and prognostication. The measurement of temporal muscle thickness (TMT) has been introduced as an easily obtainable new surrogate marker to identify patients at risk of sarcopenia, which is known to be a major cause of disability and frailty, especially among the elderly population, due to its high correlation with skeletal muscle mass, muscle function and nutritional status. It has already been studied as a prognostic factor in other neurological disease (cerebral aneurisms and glioblastoma multiforme). Reliability of TMT evaluation as a tool to identify sarcopenic patients has been confirmed in a mixed stroke population (ischemic and hemorrhagic) but there are no data available regarding its relationship with ischemic stroke outcome after acute phase treatment. In this study a correlations was found between unfavourable outcomes at 90 days (mRS > 3) and lower values of TMT whereas, in the multivariate analysis, neither mean TMT nor belonging to the at-risk of sarcopenia group were confirmed as independently associated with worse outcomes.

Conclusion: A trend in higher frequencies of very severe outcomes for patients at-risk of sarcopenia undergoing revascularization treatments for acute ischemic stroke was identified. Actual evidence fully supports treatment of this frail population according to established guidelines. Further investigations are needed to verify if sarcopenia may be an independent prognostic factor.

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## REFRACTORY AND FATAL STATUS EPILEPTICUS AS PRESENTATION OF CEREBRAL AMYLOID ANGIOPATHY RELATED INFLAMMATION: CLINICAL AND AUTOPTIC FINDINGS


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Introduction: Cerebral amyloid angiopathy related inflammation (CAAri) is a rare yet aggressively relapsing disease. The diagnosis is often based on clinical and radiological data, but the gold standard remains brain biopsy or autopsy. Early diagnosis is important to start immunomodulant therapy that has been proved to be effective. Herein we present a case of an 80 years-old woman who was diagnosed with CAA-ri and died because of super-refractory status epilepticus with no response to high dose steroid therapy. Her diagnosis was confirmed by histopathological examination of the brain tissue.

Aim: To report atypical clinical and radiological findings of CAAri and to describe pathological findings.

Case presentation: An 80-years-old woman with no history of chronic disease complained of sudden intense headache, followed by gaze deviation and clonic movements in the left limbs. At emergency department, a CT scan showed right temporal subarachnoid haemorrhage. Deep sedation was started along with administration of levetiracetam and the patient was admitted to intensive care unit. Cerebrospinal fluid examination was normal. Biomarkers for biological Alzheimer's disease were positive (increased phosphorylated tau and decreased level of β-amyloid protein 1-42 and decreased β-amyloid 1-42/1-40 ratio). APO-E genotype was ε3/ε3. The first EEG showed occasional fronto-central epileptiform features. Follow-up EEG showed non-convulsive epilepticus status not responsive to polytherapy with brivaracetam, perampanel and lacosamide. MRI revealed multiple microbleeds with lobar distribution and bilateral disseminated sulcal superficial haemosiderosis, right parietal subcortical confluent white matter hyperintensities. No post-contrastographic enhancement was noted. High dose steroid therapy was started with methylprednisolone 1000 mg for five days with tapering in the following five days. There was no response to immunomodulatory therapy with persistent super-refractory epilepticus status with more evident epileptiform frontal-temporo-parietal activity (ictal-interictal continuum) without any change after continuous infusion of add-on valproic acid. The patient died 19 days after admission. Brain autopsy confirmed a thioflavin, Congo-red positivity of brain specimens from the right parietal lobe with marked parenchymal oedema.

Conclusion: Refractory status epilepticus has been reported in CAAri but seldom as first manifestation of the disease. Lack of response to high dose steroids in these cases should be immediately followed by second-line immunosuppressive treatment. Histologic characterization of the inflammatory response may prompt deeper understanding of the physiopathology of this malignant form of the disease.

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## EEG NETWORKS TOPOLOGICAL MODIFICATIONS PREDICT CLINICAL EVOLUTION IN ISCHEMIC STROKE ACUTE PHASE


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Background and aims: Following a stroke, EEG-based brain networks' overall balance between local specialization and global integration, known as "Small-worldness" (Sw), experiences complex changes. Sw is characterized both by high segregation (high clustering coefficient, Cw) and high integration (low shortest path length, Lw). We found that acute stroke causes a reduction of delta network Sw and an increase of alpha network Sw. In this multicentric observational study, we aimed to evaluate whether specific networks characteristics at admission and at discharge are associated with different neurological severity and, thus, different clinical evolution.

Materials and methods: We recruited patients admitted for acute anterior circulation stroke; we recorded a first 64-channel EEG within 24 hours and a second EEG within 5 days from stroke onset. We obtained NIHSS at admission and at discharge. Connectivity analysis was performed with eLORETA for each EEG frequency band. We compared connectivity parameters of first vs second acquisition and then we performed a regression analysis using stroke severity as dependent variable.

Results: We enrolled 80 consecutive patients (57% female, median age 75, 53% right hemispheric stroke). Median NIHSS at admission was 11 (IQR:6-15), 5.5 (IQR:2-12) at discharge. We found no difference in terms of clustering between first and second acquisition, while we found a reduced global integration (higher Lw) for alpha 1 and alpha 2 networks at first acquisition ($p=0.041$, $p=0.024$). Concerning overall network balance, we found that alpha 1 network Sw was higher in the second acquisition than in the first ($p=0.014$). The regression model found an indirect association between alpha 1 Sw at first acquisition and NIHSS at admission ($p=0.043$) and a direct association between delta Sw at second acquisition and NIHSS at discharge ($p<0.0001$). Finally, the regression model found a direct association between delta Sw at first acquisition and NIHSS at discharge ($p=0.024$) and delta Cw at first acquisition and NIHSS at discharge ($p=0.029$).

Discussion: While brain connectivity dynamically changes in stroke acute phase, delta network rearrangements have a potential prognostic role. In fact, a higher delta Sw at admission predicts greater stroke severity at discharge. Such rearrangement seems to depend more strongly on modifications of local segregation induced by the lesion itself. The indirect association between alpha 1 Sw and stroke severity probably depends on the perturbation of physiological brain rhythms induced by brain damage.

Conclusions: Delta network rearrangements induced by acute stroke can predict stroke severity at discharge, being a potential prognostic factor.

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## SEX-DIFFERENCES IN SHORT-TERM OUTCOME IN YOUNG ADULT PATIENTS WITH ACUTE ISCHEMIC STROKE WHO UNDERWENT REVASCULARIZATION TREATMENT: A SINGLE CENTER CASE SERIES


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Introduction: There are few data in the literature about short term clinical outcome in young adults with acute stroke after revascularization with thrombolysis (IVT) and/or endovascular treatment (ET) and gender differences in treatment response. [1-3]

Objectives: To assess gender differences in short-term clinical outcome in young adults with ischemic stroke after IVT and/or ET.

Materials and Methods: Clinical and radiological data from 127 consecutive patients aged < 50 years with ischemic stroke were collected. They were admitted in the Stroke Unit of "Cardarelli" Hospital between August 2017 and September 2022 for revascularization with IVT and/or ET. NIHSS and TOAST classification were used to define stroke severity and aetiology. Patients' clinical short-term outcome was assessed by NIHSS.

Results: In the study period 1494 patients with ischemic stroke who underwent revascularization treatment were admitted in our Stroke Unit. 127 patients (8.5%) were aged ≤50 years and were defined young adults. They were 54 females and 73 males. Mean age was 42.2+8.8 years for women and 42.9+7.1 years for men. The most frequent risk factors in the entire population were smoking, hypertension, and dyslipidemia. The only statistically significant difference in risk factors distribution between men and women was the history of stroke (14.8% of females and 4.1% of males). Patent foramen ovale was more frequent in the female population, but gender difference did not gain the statistical significance. All the patients considered in the present study underwent revascularization treatment: 69 patients (26 females, 43 males) underwent IVT, 40 patients underwent IVT plus ET (20 females, 20 males), and 18 patients (5 females, 13 males) underwent primary ET. Mean NIHSS score at admission was 10.55 for women and 10.77 for men. Mean NIHSS score 2 hours after treatment was 6.55 for women and 8.41 for men. Mean NIHSS score 24 hours after treatment was 5.04 for women and 6.78 for men. Mean NIHSS score 7-days after treatment was 2.23 for women and 4.75 for men and this difference in 7-days mean NIHSS score between female and male groups was statistically significant (p 0.013). There was no statistically significant interaction between sex and type of treatment on NIHSS at admission, at 2 and 24 hours, and 7-days after revascularization treatment.

Conclusions: Young female patients with ischemic stroke treated with revascularization (IVT, IVT and ET or ET) had a better short-term outcome in comparison with young male patients, as documented by a lower mean NIHSS score 7-days after treatment, independently from treatment type.

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## BOWHUNTER SYNDROME AND CEREBELLAR STROKE, A CASE REPORT


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Background: Bowhunter syndrome (BHS) is an uncommon cause of vertebro-basilar insufficiency that results from occlusion or injury to the vertebral artery (VA) during neck rotation. The cause is often a bony abnormality that may compress the VA, compromising distal flow. Posterior circulation strokes in young individuals should alert the neurologist to suspect BHS, especially if rostral cervical spine abnormalities are detected on initial head imaging.

Case presentation: A 18 year-old patient came to the Emergency Room for subjective acute vertigo, nausea and vomiting, that lasted about five hours. The initial neurological evaluation (after symptom cessation) revealed no focal deficits, brain Comuted Tomography (CT) revealed no recent lesions and Doppler ultrasound showed a demodulated flow in the left extra- and intracranial vertebral artery, in the absence of other pathological findings. The patient refused hospitalization; antiplatelet therapy was introduced and the patient underwent a brain MRI six days later, which showed a recent left cerebellar ischemic lesion. To investigate the etiopathogenesis of the ischemic stroke, in the absence of any cardiovascular risk factors, the patient underwent a CT angiography with the evidence of left vertebral artery stenosis (especially in V4) and an altered structural morphology of the C1 vertebra which determined a reduction in the diameter of the artery at the vertebral crossing point. Suspecting BHS, he subsequently underwent dynamic cerebral angiography which showed dysmorphic appearance of the atlanto-occipital junction and anterior subluxation of C1 with respect to the occipital condyles bilaterally associated with small bone outgrowth of the posterior arch of C1, with consequent anomalous course of the vertebral artery in V3-V4 especially on the left. When asked, the patient confessed frequent neck rotation maneuvers, which he performed daily to release neck muscle tension. In relation to the risk-benefit ratio, surgical treatment was not recommended, in favor of a conservative medical approach.

Conclusion: Although BHS is among the rarest causes of ischemic stroke, it should be suspected in young patients with no clear cardiovascular risk factors, presenting with symptoms suggestive of posterior circulation stroke.

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## THE PROGNOSTIC ROLE OF C-REACTIVE PROTEIN AND OTHER INFLAMMATION SERUM MARKERS IN STROKE: AN OBSERVATIONAL, RETROSPECTIVE STUDY

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Background: Inflammation plays a significant role in the pathophysiology of ischemic stroke that triggers an inflammatory response [1], including the release of pro-inflammatory cytokines and activation of immune cells. C-reactive protein (CRP) is an acute-phase reactant, commonly used as a nonspecific marker of systemic inflammation.

Aim: The aim of the study was to evaluate the predictive role of CRP for the outcome in patients with ischemic stroke, in comparison with other markers or indices of inflammation. We also tried to identify a useful cut-off in clinical practice to stratify the risk of patients admitted to the emergency department with acute cerebrovascular disease.

Material and methods: We included in the study all consecutive patients affected by ischemic stroke or transitory ischemic attack, referred to the Stroke Unit of Policlinico Agostino Gemelli between December 2019 and June 2021 which performed C-reactive protein (CRP), leukocyte formula, fibrinogen and erythrosedimentation rate (ESR) within the first 24 hours after the stroke. Demographic, clinical features, admission and discharge NIHSS score, risk factors and outcome a 3-month follow-up through mRS score were collected.

Results: Starting from 1058 subjects, we enrolled in the final analysis 339 acute ischemic stroke patients, 215 with a good outcome (mRS=0-2) and 124 with poor outcome (mRS=3-6) after 3-month follow-up. We found significantly higher CRP, ESR, Fibrinogen serum levels and SIRI (systemic inflammation response index) in patients with a 3-months poor outcome. The multivariate analysis confirmed CRP and Fibrinogen values as independent poor outcome predictors. Evaluating death predictors, high serum levels of CRP, ESR and high SII (systemic inflammation index) and SIRI were significantly associated with an increased mortality, and, after multivariate analysis, CRP was confirmed as an independent predictor. Moreover, through a receiver operating characteristic (ROC) curve analysis, we identified a CRP cut-off value of 11,5 mg/L (milligrams/liters) as a good predictor of both 3 months outcome (sensitivity: 58%, specificity: 62%, AUC= 0,642) and mortality (sensitivity: 83%, specificity: 60%, AUC= 0,755).

Conclusion: Elevated CRP appears to be a reliable predictor of poor outcome and mortality in ischemic stroke. The PCR cut-off could be an useful tool in the risk stratification of acute stroke patients already in the emergency department to optimize a more suitable diagnostic-therapeutic path or a more appropriate patient monitoring setting.

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## STROKE-RELATED DELIRIUM IN PATIENTS UNDERGOING REVASCULARIZATION TREATMENTS: A RETROSPECTIVE, OBSERVATIONAL STUDY

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Background: Delirium is a complex neuropsychiatric disorder, which often complicates acute illnesses, including acute stroke [1]. In literature the prevalence of delirium in patients undergoing revascularization treatments for acute stroke is not clearly established, since the available epidemiological data mainly refer to the pre-thrombectomy era [2]. The primary aim of the present study was to evaluate the prevalence of delirium in patients undergoing revascularization treatments for acute stroke. Secondary aims were: 1) risk factors for stroke-related delirium; 2) impact of delirium on stroke outcome.

Materials and methods: We retrospectively reviewed the clinical charts of patients admitted to the Stroke Unit of Policlinico Gemelli from 2018 to 2021. Inclusion criteria were: ischemic stroke; treatment with thrombolysis and/or mechanical thrombectomy. Exclusion criteria were: impossibility to retrieve medical records; coma; mutacic patients. Delirium was diagnosed based on the DSM-V criteria [3] by reviewing nurse and medical records.

Results: The study cohort consisted of 445 patients. Mean age was 73.8±13.1, mean NIHSS was 11.9±7.3. Endovascular treatment (EVT) was performed in 226 (50.8%) patients, thrombolysis in 343

(77.1%) both in 124(27.9%). Delirium prevalence was 165/445(37.1%). Among the subgroup treated with mechanical thrombectomy, 92% of patients underwent general anesthesia during the procedure, and 80% were subsequently hospitalized in Neuro-ICU. In the univariate analysis, delirium was associated with EVT (p=0.01), atrial fibrillation (p=0.024), aphasia (p=0.003), hyperglycemia at stroke onset (p<0.001), use of central nervous system acting drugs (p=0.002), cognitive impairment (p<0.001), pneumonia (p<0.001), oxygen-therapy (p<0.001), antibiotic therapy (p<0.001). Patients with delirium were older (p<0.001), had higher NIHSS at stroke onset (p<0.001), and after treatment (p<0.001), and higher disability pre-stroke (p<0.001). In the multivariate analysis, risk factors for delirium were age (OR=1.04; 95% C.I.=1.02-1.07; p=0.001), NIHSS after treatment (OR=1.18; 95% C.I.=1.12-1.25; p<0.001), oxygen-therapy (OR=1.86; 95% C.I.=1.06-3.26; p=0.032), antibiotic therapy (OR=2.46; 95% C.I.=1.27-4.76; p=0.007), cognitive impairment (OR=3.17; 95% C.I.=1.24-8.14; p=0.016). Patients with delirium were less often discharged home (p<0.001), had prolonged hospitalization (p<0.001) and increased 90-days disability (p<0.001).

Discussion and conclusion: In the last years, stroke management has radically changed, due to the introduction of effective treatments and with the extension of the therapeutic window up to 24 hours. This study adds knowledge to the prevalence and risk factors of delirium in the new clinical scenario of acute stroke care. In our cohort, delirium was not associated with general anesthesia for EVT nor to Neuro-ICU hospitalization after EVT. Delirium is a frequent complication in acute stroke patients undergoing revascularization treatments and negatively affects stroke outcome.

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## INTRAVASCULAR STENTING IS SAFE AND EFFECTIVE IN SECONDARY PREVENTION OF CEREBRAL ISCHEMIC EVENTS IN PATIENTS WITH CAROTID WEB

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Background and aims: A carotid web (CaW) is a thin intraluminal shelf-like lesion along the wall of the internal carotid artery. Although it has been recognised as a common cause of cryptogenic stroke in young adults (9.8-37%), optimal management strategies of CaW cases in primary and secondary cerebral ischemic events (CIE) prevention appear unclear.

Clinical case: We report the case of a 44-year-old woman experiencing transient 10 minutes-long acute left upper limb paresis followed by confusion and multiple short-lasting episodes of aphasia. The week before, she had complained of objective vertigo, nausea and vomiting lasting about 30 minutes. This patient had no medical history of cerebrovascular events and no known risk vascular risk factors. Symptoms had already regressed when she sought medical attention a few hours after the first episode (NIHSS = 0) and she remained asymptomatic throughout hospital stay. CTA and cerebral angiography showed the presence of CaW along the left carotid bifurcation. Diffusion-weighted brain MRI revealed multiple small recent ischemic lesions in left frontal and insular cortex. Appropriate testing allowed to exclude other causes of ischemic events in young individuals (trombophilic, vasculitic and genetic disorders, PFO and drug abuse).

Methods: We conducted a search across Medline via PubMed using the terms [Carotid Web] AND [stroke], which yielded 256 results. After selection of studies describing the recurrence rate of CIE in cohorts of patients with CaW treated with either medical therapy or intravascular stenting, we included 3 studies [1,2,3].

Results: Symptomatic patients with CaW treated with medical therapy have a higher risk of experiencing a new CIE compared to patients who underwent carotid stenting (17-29% vs 0%). Based on these findings, we proceeded with CaW stenting (N days after hospital admission = 12). The procedure was carried out without complications and the patient was then dismissed. By telephone follow-up at 4 months our patient proved to be CIE-free with no complications from intravascular stenting.

Conclusions: Patients with CaW have a high recurrence rate of CIE. Our case confirms safety and efficacy of carotid stenting in a young individual with symptomatic CaW. Despite mounting evidence proving intravascular stenting to be safe and superior to medical therapy in secondary prevention of CIE in CaW cases, latest guidelines are currently lacking definite management indications in such patients. Therefore, strong randomised studies with longer follow-up windows are warranted.

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## CASE REPORT OF MULTIEMBOLIC CEREBROVASCULAR STROKE ASSOCIATED WITH LUNG ADENOCARCINOMA

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Background: Thromboembolic events such as deep vein thrombosis (DVT), pulmonary embolism (PE), arterial thrombosis, non-bacterial thrombotic endocarditis, and ischemic strokes can be the initial event leading to the diagnosis of an underlying malignancy; this is due to abnormalities in the coagulation cascade that often accompanies many oncologic diseases.

Case Report: A 54-year-old Caucasian female, with a medical history of atrial tachycardias and thyroidectomy, was admitted to our emergency department due to an acute onset of slurred speech and right hemiparesis (NIHSS score 8). CT and CTA showed an hypodensity of the middle frontal gyrus and M1 segment occlusion of the left MCA. Mechanical thrombectomy was performed with a complete recanalization (the patient was outside tPA time window). During hospitalization her neurological symptoms progressively improved until they disappeared. An extensive work-up was undertaken to determine the cause of the stroke: supra-aortic trunks ultrasound, transcranial doppler bubble-test, cardiologic evaluation with Holter-ECG and trans-thoracic

echocardiogram were unremarkable. Blood tests including for systemic autoimmunity, infectious screening, hereditary thrombophilia and oncomarkers testing just revealed increasing levels of CA 15-3 and CEA). The patient also reported the presence of dry and persistent cough started four weeks before her hospitalization, so a complete pneumological screening was performed: a non-tuberculous mycobacteria pneumonia and lung adenocarcinoma (ROS-1 mutation positive) were diagnosed and an appropriate antibiotic therapy and treatment with Entrectinib monoclonal antibody were started. In the following days, the patient presented acute onset of dyspnea followed by chest pain and CT angiography scans showed pulmonary embolism so anticoagulant therapy was promptly started (later discontinued because of hemorrhagic pleural effusion). After a few weeks, our patient complained sudden onset of visual disturbance and a brain MRI revealed an ischemic stroke at right occipital lobe. Subsequently a transesophageal echocardiography was performed and it revealed a round 4 mm neoformation adhering to the aortic valve wall that was compatible with a likely embolic source causing stroke.

Discussion: Approximately 30% of patients with ischemic stroke have an embolic stroke of undetermined source (ESUS). An estimated 5% to 10% of patients with ESUS have an active cancer diagnosis and our observation supports that it is required to perform an accurate and complete screening to rule out a possible organic emboligenic source, mainly when malignancy diagnosis coexists, because most cases are discovered incidentally post-mortem. Transesophageal echocardiography allowed us to find the likely emboligenic source causing recurrent cerebrovascular strokes in this patient.

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## STENT PLACEMENT IN ACUTE ISCHEMIC STROKE DUE TO BASILAR ARTERY OCCLUSION: A SINGLE-CENTRE PRELIMINARY EXPERIENCE


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Introduction and Objectives: Ischemic stroke due to basilar artery (BA) occlusion is a rare but highly disabling and deadly pathology. In clinical trials, around two-thirds of patients enrolled were treated with endovascular therapy and stenting placement. Although BA stenting may represent a rescue therapy in selected patients, benefits in clinical settings have not been fully elucidated. We aim to investigate the outcomes of patients with acute ischemic stroke due to BA occlusion treated with stenting compared with thrombectomy/thrombus aspiration.

Materials and Methods: We performed a single-center retrospective study in consecutive patients with acute ischemic stroke due to BA occlusion treated with endovascular procedures from November 2018 until December 2022. Neurointerventionalists and neurologists made the decision to perform thrombectomy/thrombus aspiration or stenting placement. Outcomes of interest were: early neurological deterioration (NIHSS at 24 >=4 points compared to baseline NIHSS), any intracranial hemorrhage at 24 hours, good recanalization of the BA, discharge destination, and death at three months.

Results: We included 38 patients in the analysis. Mean (+-SD) age was 72 (+-12), 24 (63%) were males, median (IQR) NIHSS at onset was 12 (3-18), 12 (32%) patients were treated with stenting, and 26 (68%) underwent mechanical thrombectomy. Sixteen patients received treatment with rt-PA (42%) as bridging therapy, and median (IQR) timing between symptoms onset and endovascular treatment was 405 minutes (295-610). Patients in the stent group were more likely to present early neurological deterioration after the procedure (50% vs. 17%, $p<0.05$); there were no differences regarding intracranial hemorrhage (17% vs. 12%, $p=0.67$) and good recanalization between the two groups (90% in the stenting group and 86% in the control group, $p=0.89$). In the stenting group, 40% of patients were discharged at home compared with 24% of the thrombectomy/thrombus aspiration group ($p=0.34$). Death at three months occurred in 4 patients out of 9 in the control group (44%) and in 3 patients out of 6 in the stent group (50%) ($p=0.4$).

Discussion: In patients with acute ischemic stroke due to BA occlusion treated with endovascular procedures, stenting placement was associated with early neurological deterioration despite similar recanalization and intracerebral hemorrhage occurrence.

Conclusion: Our results suggest that basilar artery stenting should only be adopted as a rescue therapy as it is associated with periprocedural neurological deterioration.

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## AUTOMATED PUPILLOMETRY PREDICTS THREE-MONTH STROKE OUTCOME: AN OBSERVATIONAL, PROSPECTIVE, COHORT STUDY


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Study Objectives: The aim of the study was to analyze the prognostic role of Automated Pupillometry (AP) in patients with acute ischemic stroke, defined through the score of the modified Rankin Scale (mRS) after three months from the Acute Stroke (AS) onset.

Materials and Methods: In this observational, cohort study, we included consecutive adult patients admitted to a comprehensive stroke center with a diagnosis of ischemic stroke from March 2021 to July 2022.

Exclusion criteria included: Clinical history of previous eye surgery, eye trauma, or major eye disease, bilateral strokes, and previous neurological disorders. Automated pupillometry assessment was performed within 72 hours of stroke onset, and parameters of the eye ipsilateral and contralateral to the brain lesion were considered. Stroke outcome was assessed by the 3-month modified Rankin Scale (mRS), obtained from an outpatient follow-up visit or telephone call. The following dichotomizations of the 3-month mRS were used for the statistical analysis: $mRS \leq 1$ vs $mRS > 1$; $mRS \leq 2$ vs $mRS > 2$; $mRS \leq 3$ vs $mRS > 3$. Statistical analyses were performed through univariate and multivariate logistic regression. Optimal thresholds for AP parameters were obtained via Receiver Operating Characteristic (ROC) curves.

Results: 157 patients were included in the study [median age 74.00 (63.00 – 82.00) years, 91 (57.96%) men]. Several AP parameters were

found to be prognostic predictors in the unadjusted analysis, such as dilatation velocity in the eye ipsilateral to the ischemic lesion (DVi), contralateral DV, and contralateral constriction index. In particular, a reduction of DVi was a predictor of poor prognosis for all the outcome models analyzed in the unadjusted analysis (mRS≤1 vs mRS>1: p=0.007; mRS≤2 vs mRS>2: p=0.007; mRS≤3 vs mRS>3: p=0.001) and an independent predictor in the model mRS≤3 vs mRS>3 in the multivariate logistic regression (p=0.022). A DVi<0.875 mm/s predicted an unfavorable outcome with 65% specificity and 56% sensibility.

Discussion and Conclusion: We found that several AP parameters are predictors of ischemic stroke prognosis and that a low DVi is an independent predictor of poor stroke outcome, defined as a three-month mRS>3. Several studies concord on the critical role of AP a in predicting the prognosis of patients with head trauma [1] and after cardiac arrest [2], but only few pieces of evidence are available for patients with stroke [3]. The results of our study suggest that AP may be a useful tool to predict the prognosis of stroke patients and that the automated assessment of pupillary light reflex should be performed routinely in such individuals.

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## NEXT GENERATION SEQUENCING AND WHOLE-EXOME SEQUENCING OF PATIENTS WITH SPONTANEOUS CERVICAL ARTERY DISSECTIONS: A PROSPECTIVE, OBSERVATIONAL STUDY

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Study objectives: This study aims to find the pathogenic genetic variants prevalence in an adult cohort of patients with spontaneous Dissection of the Cervical Arteries (CeAD).

Materials and methods: We enrolled consecutive adult patients admitted to a comprehensive Stroke Unit for non-traumatic CeAD with or without stroke. Patients with CeAD who met at least one of the following criteria were included in the study: 1) multiple structural vessel wall abnormalities; 2) family history of arterial dissections/cerebrovascular diseases in youth; 3) clinical/radiological/dysmorphic findings suggestive of genetic diseases.

Exclusion criteria were: 1) Trauma within 3 months from CeAD diagnosis; 2) previous diagnosis of connective tissue diseases; 3) CeAD risk factors (low alpha-1 antitrypsin levels, uncontrolled hypertension). All patients underwent total-body CT and a dysmorphological examination. For eligible patients, a Next Generation Sequencing (NGS) of the clinical exome using the Clinical Exome Solution® kit was performed, followed by the design of 38 genes virtual panel related to genetic conditions associated with vascular fragility. In patients whose NGS was inconclusive, but who met at least two out of three inclusion criteria, a Whole Exome Sequencing (WES) was performed. Bioinformatics analysis was performed using the SOPHiA DDM platform.

Results: NGS was performed in ten patients [40% female, median age:41]; genetic variants were identified in three patients (30%). One female patient showed a heterozygous c.4565T>C variant of uncertain significance of MYLK gene; another woman was found to be affected by Marfan syndrome (heterozygous pathogenic variant c.67392 T>G of FBN1 gene), and a de novo heterozygous pathogenic variant c.1862G>A of COL3A1 gene was found in a male patient affected by vascular Ehlers-Danlos disease. WES was performed in five out of seven subjects (71.4%) with normal NGS and found a heterozygous pathogenic variant c.2371C>T of COL4A3 gene in a woman. The overall prevalence of genetic mutations was 40%. Among the four patients with genetic variants, positive family history was the most represented risk factor (100%), followed by the evidence of multiple vessel wall alterations (75%), and of suggestive clinical/radiological/dysmorphic findings (50%). 50% of patients had all three risk factors.

Discussion and conclusion: We found a genetic variant in 40% of our selected population with spontaneous CeAD suggesting that, in these patients, family history and whole-body vascular anatomy should always be investigated. In accordance with previous literature [1,2], our results suggest that heritability in spontaneous CeAD plays a major role, and that genetic analyses should be performed in patients with at least one suggestive criterion.

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## FIBRINOGEN DEGRADATION COAGULOPATHY: A MIRROR OF THROMBOLYSIS EFFECTIVENESS IN STROKE PATHOLOGY?

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Background and aims: Thrombolysis during ischaemic stroke degradates fibrin matrix of occluding vascular thrombus, reperfunding cerebral tissue; its effect is extended to circulating fibrinogen because of its incomplete specificity, resulting in fibrinogen depletion. Recently several studies demonstrated importance of monitoring fibrinogen levels after thrombolysis to reduce intracerebral haemorrhage risk. Beyond this, our aim was to investigate if there was a different fibrinogen dynamic profile between patients who underwent high successful thrombolysis and patients who experimented low response to endovenous treatment.

Materials: We retrospectively collected ischemic stroke patients admitted to Trieste Stroke Unit and acutely treated with thrombolysis or bridge thrombectomy between January 1st, 2019 and December 31st, 2021 who underwent to a complete fibrinogen monitoring: peripheral blood samples were drawn at baseline and at predefined time-points of 2, 6, 12 and 24 hours after thrombolysis.
Methods: We divided patients into two groups. Group H ("High" successful thrombolysis) included patients with absolute 3 points-difference or relative 50%-difference between admission- and 24 hours-NIHSS score; remaining patients filled Group L ("Low" successful thrombolysis). We evaluated differences using Mann-Whitney U test for numeric or Chi-square test for nominal variables (statistically significance when $p < 0.05$).

Results: 260 patients were included: 140 in Group H, 120 in Group D, without significant differences in age, gender, cardiovascular risk factors, Bamford Classification, TOAST aetiology, onset-to-needle time. Starting from similar baseline values, we found a trend of lower absolute fibrinogen levels in Group H at 6 (median 210 vs 226 mg/dL, p=0.09), 12 (218 vs 236, p=0.06) and 24 hours (240 vs 246, p=0.08). A sub-analysis including patients who underwent to thrombolysis alone (109 in Group H and 93 in Group L) showed significant high fibrinogen drop from baseline in Group H at 2 (77 vs 47 mg/dL, p=0.01) and 6 hours (92 vs 58, p=0.04).

Discussion: Our study suggest a different fibrinogen profile between ischaemic patients who underwent high or low successful treatment: monitoring step-by-step fibrinogen levels in the first 24 hours after thrombolysis, we noted steady lower values in patients with higher improvement from stroke symptoms. Focusing on thrombolysis alone, fibrinogen drop occurs especially in the first 2-6 hours. In this way, rTPA-related fibrinogen degradation coagulopathy could be a mirror of thrombolysis strength in dissolving local cerebral thrombus.

Conclusions: In addition to preventing intracerebral haemorrhage risk, monitoring the curve of fibrinogen levels in the first 24 hours could be useful to follow thrombolysis efficacy in stroke patients.
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## HISTOLOGIC ASSESSMENT OF CEREBRAL VENOUS THROMBUS RETRIEVED FROM ENDOVASCULAR THROMBECTOMY: FIRST CASE REPORT


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Background: Endovascular thrombectomy (EVT) is a treatment option in patients with cerebral venous thrombosis (CVT) who deteriorate despite anticoagulant treatment. Histologic assessment of the thrombi removed in CVT may provide insights into the pathophysiology of the disease and allow advancements in treatment.

Case report: A 47-year-old woman (smoking habit and estradiol/progesterone-releasing intra-uterine device) diagnosed with massive CVT, underwent EVT (complete recanalization via aspiration catheter and stentriever) due to acute-onset left-sided weakness and dysarthria despite 72h of full-dose subcutaneous low-molecular heparin. Two main reddish clots (maximum diameter 15 mm) were retrieved. Microscopic assessment showed an erythrocyte-rich thrombus (83.9% of entire thrombus surface) with layers of platelets/fibrin: lines of Zahn (13.9% of entire thrombus surface). The scarce inflammatory cells were predominantly (90%) intact neutrophilic granulocytes (MPO+), mixed with scant T-lymphocytes (CD3+) and macrophages (CD68+). We found no evidence of hemosiderin (Iron Stain with Prussian Blue Stain/Pearl's stain), endothelial cells (CD34+), plasma cells (CD138+) or B-lymphocytes (CD20+). Other etiological evaluations were unremarkable, with complete clinical recovery.

Conclusion: This is the first case report of CVT with complete histologic assessment of thrombus retrieved via EVT. Similar to ischemic stroke, thrombus assessment in CVT may provide insights into the pathophysiology of the disease and guide treatment advancements.
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## MULTIMODAL OUTCOME PREDICTION IN LARGE-VESSEL-OCCLUSION ISCHEMIC STROKE, COMBINING PERFUSION-BASED PARAMETERS AND TIME-TO-IMAGING


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Background: Early infarct growth rate ([EIGR] ischemic core / time to imaging [TTI]) is a promising parameter to predict outcome in patients with ischemic stroke (AIS) due to large vessel occlusion (LVO). The prognostic value of other parameters such as the rate of regression of the ischemic penumbra (Early-Penumbra-Reduction Rate [EPRR]: penumbra/TTI) and the Penumbra-to-Core-Rate ([PtCR] (ischemic penumbra/ischemic core)/TTI) has never been studied.

Methods: From ASTRAL registry we included LVO patients with available baseline perfusion metrics. EIGR, EPRR and PtCR were calculated for each patient. The association with outcome (90-day mRS 0-2 and (un)favorable point shift in 90-day mRS) of perfusion-based parameters (considered both as continuous variable and as dichotomized variable [fast versus slow progressors]) was assessed via multivariate regression analysis and comparing area under the receiver operating characteristic curve (AUROC) (via likelihood ratio [LR] tests). Cutoff to define fast/slow progressors, for each perfusion parameter, were defined by maximizing the Youden Index.

Results: Two hundred forty-eight patients were included. All dichotomized perfusion-based parameters were independently associated with

90-day mRS 0-2 (EIGR aOR 3.04 [95%CI 1.48-6.2] p=0.002; EPRR aOR 0.38 [95%CI 0.17-0.81] p=0.012; PtCR aOR 0.38 [95%CI 0.19-0.80] p=0.010). When considered as continuous variable, EPRR (aOR 0.63 [95%CI 0.40-0.99] p=0.046) and PtCR (aOR 0.77 [95%CI0.62-0.96] p=0.022) (but not EIGR) were independently associated with 90-day mRS 0-2. Compared to EIGR and EPRR, PtCR had the best predicting AUROC, both as dichotomized variable (0.62 versus 0.63 versus 0.68 [9%%CI 0.63-0.74] LR test p value < 0.001) and as continuous variable (0.60 versus 0.67 versus 0.73 [95%CI 0.66-0.80; LR test p value < 0.001).

Conclusion: Perfusion-based parameters combined with time-based parameters are promising predicting metrics. The ratio combining (1) ischemic core, (2) penumbra and (3) time-to-imaging (Penumbra-to-Core Ratio) has the highest prognostic predicting value.

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## REPERFUSION TREATMENT IN BASILAR ARTERY OCCLUSION WITH MILD SYMPTOMS

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Background: Endovascular treatment (EVT) improves outcome after basilar artery occlusion (BAO) in patients with moderate to severe neurological deficits. However, optimal treatment for BAO with mild symptoms (NIHSS score 0-5) is unknown, both in the early (0-6 h from onset) and the late (>6 to 24 h) time windows. To determine whether EVT improves outcomes after BAO with mild symptoms we (1) compared EVT+/-IVT versus IVT alone in the early-time-window and (2) mild versus non-mild symptom BAO for EVT+/-IVT in the late-time-window.

Methods: From SITS-International Stroke Thrombolysis and Thrombectomy Register we included consecutive BAO patients between 2015 and 2022 treated by EVT, IVT or both within 24h from symptoms onset. Via Doubly Robust approach (propensity score matching [PSM] plus multivariate logistic regression), we compared efficacy (3-month modified Rankin Scale [mRS]) and safety (symptomatic ICH [SICH] and death at 3-month) outcomes in the early-time-window (onset-to-treatment ≤6h) in mild BAO (EVT+/-IVT versus IVT-alone) and in the late-time-window (onset-to- EVT+/-IVT treatment > 6h): mild-BAO versus non-mild-BAO.

Results: 1862 patients were included (median NIHSS score 13 [IQR 7-23]; 1361 (74.9%) treated in early-time-window). For patients with mild symptoms in the early-time-window (178 matched patients, with 1:1 ratio) functional outcome was significantly worse with EVT+/-IVT than with IVT alone (aOR for mRS 0-2 0.27 [95%CI 08 - 89] p=0.016; aOR for mRS 0-3 0.20 [95%CI 0.06-0.61]; p = 0.05). In the late-time-window (150 matched patients, with 1:2 ratio) mRS 0-2 (aOR 7.89 [95%CI 2.18-28.52];p=0.002), mRS 0-3 (aOR 7.57 [95%CI 2.09-27.42];p=0.002 and mortality (aOR 0.88 [95%CI0.02-0.37];p=0.001) with EVT+/-IVT were significantly better for mild BAO than for non-mild BAO. This difference disappeared after including baseline NIHSS score in adjusted analysis. There were only 2 SICH in both PSM-based analyses.

Conclusion: Our study on BAO patients presenting with mild symptoms suggest that (1) IVT alone may be the preferred choice in the early-time-window, while (2) EVT+/-IVT can be a treatment option even in the late-time-window for these patients. Randomized trials are needed to identify the optimal reperfusion therapy for patients with BAO and mild symptoms.

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## ISCHAEMIC STROKE IN PATIENTS WITH KNOWN ATRIAL FIBRILLATION: THERAPEUTIC DECISIONS IN CLINICAL PRACTICE AND POSSIBLE FUTURE PERSPECTIVES

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Introduction: The best prevention for ischemic stroke due to atrial fibrillation (AF) is oral anticoagulant therapy (OACT) either VKA or DOAC. [1] Left atrial appendage occlusion (LAAO) represents an alternative if OACT is contraindicated. [1] Ischemic stroke despite OACT can occur in patients with AF due to: -stroke unrelated to AF; -cardioembolic stroke due to AF in case of a) poor INR control on VKA; b) poor compliance to or sub-optimal dosage of DOAC, c) despite adequate OACT, i.e Resistant Stroke (RS) [2].

Aims: To describe the secondary prevention strategies undertaken in patients with known AF and ischemic stroke. To estimate the percentage of RS.

Materials and Methods: Retrospective analysis of patients hospitalized for ischemic stroke and known AF. Pathogenesis defined according to TOAST criteria. Prevention therapy on admission, recommended therapy at discharge, therapy at follow-up, outcome were recorded. Definition of adequate OACT: -VKA if INR≥1,7; -DOAC if indications/dosage followed European guidelines, and if good compliance was declared or plasmatic levels were in range.

Results: We identified 226 patients, 61% female, median age 84.04 years, IQR 77.9-88.6. Admission therapy: 53% OACT (32% VKA, 21%

DOAC), 1% LAAO, 32% antiplatelet or low molecular weight heparin (LMWH), 14% no therapy. Seventy% of stroke were classified as cardioembolic. At discharge, OACT was recommended to 85% of patients that on admission were on antiplatelets or did not take any therapy. Survival at follow-up resulted significantly higher in patients on DOAC compared to those on antiplatelets or LMWH ($p<0.001$) after adjustment for age by Cox regression. OACT resulted adequate in 52.1% (44 VKA, 18 DOAC), non-adequate in 37.8% (28 VKA, 17 DOAC), uncertain in 10.1% (12 DOAC). Fifty-seven% of patients on adequate OACT presented a RS(70%VKA, 30%DOAC). Recommended therapy at discharge in RS group: -DOAC: 2 maintained with their therapy, 2 were shifted to VKA, 5 to another DOAC and 3 to non-specified OACT. -VKA: 7 maintained with VKA, 5 were shifted to DOAC, 7 to non-specified OACT and 2 unknown.

Discussion: Fourty-six% did not take OACT on admission despite lack of contraindications. OACT was not adequately assumed in 37,8%. More than 50% of patients on adequate OACT presented a RS.

Conclusions: Adequate OACT may be insufficient to prevent AF-related embolism and subsequent therapeutic decisions are empirical. Specific LAA morphologies are associated with higher thrombosis risk [3] potentially resistant to OACT. LAAO as add-on therapy to OACT could be an option worthy to be explored.

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## PRIMITIVE ANGIITIS OF THE CENTRAL NERVOUS SYSTEM: KALEIDOSCOPIC PRESENTATION, DIAGNOSIS AND TREATMENT

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Background: Primitive angiitis of the central nervous system (PACNS) represents a diagnostic challenge for its rarity and presentation [1].

Materials and Methods: On November 2020, a 50-year-old man arrived at the emergency room for loss of consciousness and generalized tonic-clonic movements preceded by paresthesia of the left upper limb. Neurological examination was unremarkable. A brain-CT revealed a lesion in the right upper parietal cortico-subcortical area without mass effect. At contrast MRI: showed a moderately increased diffusion, with an irregular graphic impregnation with a gyriform morphology following the cortical pattern with hypoperfusion at the subcortical level and an inconstant increase in microvascular permeability in cortical area. The lesion was classified as ischemia in subacute evolutionary phase. Patient's cardiovascular risk factors: hypertension, grade II obesity, past smoking habits, and alcohol abuse. After a thoroughly research of ischemic stroke cause only a permanent patent foramen ovale(PFO), severe after Valsalva maneuver, was found. He had no deep vein thrombosis in legs and in pelvis, nor pro-thrombotic diathesis. Percutaneous PFO closure was proposed by Heart&Brain Team; the intervention was postponed for patient's choice.

Results: On February 2021 he developed left lateral hemianopsia, difficulty in left-hand coordination, and left leg hypoesthesia. MRI showed an increased lesion volume and metabolic disease/vasculitis/neoplasm were hypothesised. Perfusione and spectroscopy brain MRI revealed deep hypoperfusion of the lesion, with irregular increase in cortical microvascular permeability, elevation of Choline peak, lowering of N-Acetyl-Aspartate and a double inverted peak in Lactate indicative of hypoxia Total body PET ruled out neoplasm and systemic signs of inflammation. Serological and urinary screening excluded metabolic disease. He further deteriorated on walking and balance, so invasive investigations were carried out: -lumbar puncture: no cellular or protein increase; -brain biopsy: inflammatory infiltrate mainly mononuclear, with immunophenotype T (CD3 ++; CD20, CD79a +/-, CD30 +/-) which thickened in the perivascular and vascular walls; a histiocyte-macrophage infiltrate (CD68 +) was also documented.

Conclusions: PACNS was diagnosed. The whole diagnostic process took about 1 year. The patient was treated with high-dose intravenous steroids and cyclophosphamide without benefit. Anti CD20 therapy was then begun.

Discussion: Onset with seizure without neurological signs in the presence of cerebral lesion should rise the suspect of "atypical" ischemia or something else. When suspecting a small vessel PACNS a cerebral biopsy and consecutively appropriate therapy should not be delayed. The attributable role of PFO is still challenging in clinical practice.

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## MYLK GENE MUTATION IN FUSIFORM BASILAR ARTERY ANEURYSM: TWO CASE REPORTS

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Introduction: Vertebrobasilar fusiform aneurysms have low incidence and male predominance [1], but only few studies focus on the genetic pathogenesis. MYLK gene mutation is already known in patients with aortic aneurysm, but we have no evidence about its role in vertebrobasilar fusiform aneurysm. We present two patients with fusiform basilar artery aneurysm and two different MYLK gene variants. Patients showed a prevalent compressive effect on brainstem and ischemic complications due to the perforating arteries occlusion by an intra-aneurysmatic thrombosis; none of them had the rupture of the aneurysm.

Cases 1: A 50 years-old man, with hypertension and dyslipidemia, was admitted with a posterior circulation TIA, and MRI imaging showed

a partially thrombosed fusiform basilar aneurysm. During the seven years of follow-up, he showed progressive worsening of neurological symptoms mainly due to the aneurysm growth with a brainstem compressive effect. Thus, antiplatelet therapy was started, together with cycles of steroid therapy, with only partial clinical benefits. Genetic exam revealed heterozygous MYLK variant (c.1348_1356delinsTCT,p.(Glu450_Thr452delinsSer)). Further studies showed thoracic aortic dilatation, without any other aneurysm. No other family member had vascular diseases.

Case 2: A 52 years-old man with hypertension, dyslipidemia, and obesity, was admitted for a partially thrombosed fusiform, basilar aneurysm discovered after a brainstem ischemic stroke. After multiple ischemic relapses during antiplatelet therapy, an anticoagulant therapy was started. The patient showed a clinical stability for over three years of follow-up, but neuroimaging showed a progressive growth of the intra-aneurysmatic thrombosis. Genetic study showed two rare heterozygous mutations: MYLK gene (c.4336G>A,p.(Glu1446Lys)), and LOX one (c.840C>A,p.(Ser280Arg)). Abdominal Angio-MR showed an aortic sub-renal ectasia, but no other systemic aneurysm. About his family, the mother died after hemorrhagic stroke due to an intracranial aneurysm rupture, and a sister, who refused genetic tests, had an aortic ectasia.

Discussion: MYLK gene mutation has never been described in patients with intracranial aneurysm. These two patients have basilar artery aneurysm and two different MYLK gene variants of uncertain significance (Class 3 ACMG). Both aneurysms are fusiform, like what is described for aortic ones. Furthermore, the second patient presents a probably pathogenic LOX gene mutation (Class 4 ACMG), but the interaction between these two gene variants is unknown. As for the treatment, we decided to apply two different conservative medical treatments based on the different clinical presentation.

Conclusion: The aim of these two case reports is underlying the possible association between MYLK gene mutation and basilar artery fusiform aneurysm.

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## EARLY LOADING DOSE OF DUAL ANTIPLATELET TREATMENT IN ACUTE ISCHEMIC STROKE ASSOCIATED WITH TANDEM LESIONS

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Introduction: Acute antiplatelet treatment in tandem lesions treated with intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) including acute carotid stenting (CAS) is challenging as a careful balance between the risk for parenchymal hematoma (PH) and stent thrombosis is needed.

Aim: To investigate the effects of early (within 12 hours) loading dose of Aspirin and Clopidogrel (A+C) after IVT and EVT plus CAS.

Methods: A retrospective analysis from a single center was performed. The main outcome was occurrence of PH. Secondary outcomes included rate of stent thrombosis, mortality, and independence at 90 days.

Results: The study included 71 patients. All patients received IVT and EVT plus CAS and 500 mg Aspirin. 7 patients did not receive any Clopidogrel treatment: 2 because of early stent thrombosis and 5 due to early PH. In the 64 patients receiving adjunctive Clopidogrel, both timing of treatment (early versus late) and dosing (300 mg versus 75 mg) did not affect the rate of PH (4.4% versus 8.3% versus 13.8% respectively [p NS]). Lower pre-Clopidogrel ASPECTS was the only significant predictor of PH (OR 0.333, 95% CI 0.148 – 0.753), and ASPECTS <8 predicted the development of PH (sensitivity 78%, specificity 73%). Stent occlusion occurred less frequently in patients treated with early loading dose (0% versus 8.5%). Rate of mortality and independence did not differ.

Conclusions: Administration of a loading dose of A+C within 12 hours after IVT and EVT plus CAS in tandem lesions resulted safe in terms of hemorrhagic transformation and effective in preventing stent thrombosis.

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## SELECTIVE USE OF BRAIN MRI IN SYMPTOMATIC PATIENTS CANDIDATES FOR CAROTID ENDARTERECTOMY: INSIGHTS FROM SAN GIOVANNI DI DIO HOSPITAL, FLORENCE

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Objectives: Symptomatic patients with carotid stenosis >50% require accurate clinical and instrumental assessments to evaluate the indication for early revascularization. Since, there is an increasing demand for emergency MRI due to new thrombolysis guidelines, it is crucial to define an appropriate use of brain MRI to ensure patients receive the most effective treatment while optimizing the allocation of economic resources. We analysed the application of brain MRI in a series of patients eligible for early carotid endarterectomy (CEA) in order to investigate the impact of brain MRI on the treatment decision and its effect on the timing of the intervention.

Methods: We conducted a retrospective observational study on consecutive symptomatic patients presenting carotid stenosis >50%. They were admitted to the Stroke Unit of San Giovanni di Dio Hospital between January 2016 and April 2021. The patients were divided in two groups: one group underwent early CEA following a multidisciplinary assessment, while the other group did not undergo the procedure. Furthermore, within each group, we further distinguished between patients who underwent brain MRI and those who did not.

Results: Out of the 218 patients included in the study, 179 patients underwent early CEA, while 39 patients did not undergo the procedure.

Among the patients treated, MRI was performed in 26 (14.5%). The time from symptom onset to CEA was measured to be 6.56 ± 4.51 days in the group that underwent MRI, while in the group that did not undergo MRI, it was 4.79 ± 3.64 days (p = 0.07). Likewise, in the MRI group, the interval from hospital admission to CEA was found to be 4.19 ± 2.88 days, whereas in the group that did not undergo MRI, it was 2.62 ± 2.02 days (p = 0.01). Among the patients who did not undergo early CEA, MRI was performed in 43.6% of cases. In 94.1% of those cases, the MRI results influenced the treatment decision.

Conclusions: The data indicate that the selective use of brain MRI in patients eligible for early CEA has a significant impact on the therapeutic decision in the majority of cases. This highlights the usefulness of MRI in the preoperative diagnostic workup. Although MRI slightly extended the average duration of hospitalization, it did not lead to a significant increase in the interval between symptom onset and CEA beyond the optimal threshold.

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## A NOVEL NOTCH3 MUTATION CAUSING A NON-CYSTEINE CHANGE ASSOCIATED WITH CEREBRAL ARTERIOPATHY WITH SUBCORTICAL INFARCT AND LEUKOENCEPHALOPATHY (CADASIL)


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Objective: To report a rare cause of CADASIL with a transversion in exon 18 of NOTCH 3 gene causing a non-cysteine change and its implication.

Design/Methods: We screened a patient with headache, vascular leukoencephalopathy and history of stroke for NOTCH3 mutations. Following informed consent, total genomic DNA was extracted from peripheral blood leukocytes using standard procedures, polymerase chain reaction (PCR) was performed with primers (comprising intron–exon boundaries) specific for exons 2–24 of the NOTCH3 gene and sequencing of these purified PCR products was performed.

Results: A 39-year old female patient with a history of stroke, three years before, hypertension, hypercholesterolemia, migraine, atonic seizures and ischemic cardiomyopathy, was admitted to hospital for the onset of asthenia, postural instability, dizziness, nausea and headache. CT scan revealed a colloid cyst of the third ventricle and the two previous ischemic lesions in left fontal and right parietal lobe. Neurological examination revealed only left-side hemiparesis, result of previous stroke, and a movement disorder characterized by dystonic features of the hands. Her emotions were noticeably unstable and neuropsychological assessment revealed no cognitive impairment. The results of ultrasound of carotid artery, electrocardiography and echocardiography, electroencephalography and Transcranial Doppler sonography (TCD) and were normal. Brain MRI showed in correspondence of the III ventricle, in the median area a 7 mm colloid cyst and multiple symmetric white matter hyperintensities in correspondence of the deep white matter and the two lesion in left frontal and right parietal lobe to be referred to gliotic outcomes. Brain magnetic resonance angiography was normal. A skin biopsy was refused by the patient. Considering the clinical symptoms, the MRI features and the CADASIL Scale Score the diagnosis of CADASIL was suspected. Genetic sequencing revealed a novel mutation, c.2918C>A. This transversion in exon 18 cause a probably pathogenetic (class 4) aminoacid change in position 973 (p.His973Pro). Genetic analysis was declined by the sister of the proband. The 973 Histidine is highly conserved during evolution as demonstrated by a phylogenetic analysis of NOTCH3 performed on BLASTP. Multiple sequence alignment with this conserved 973 Histidine were reported in in different species out of 100 orthologs vertebrate sequences analysed.

Conclusions: CADASIL with a point mutation in exon 18 of NOTCH 3 gene causing a non-cysteine change may present with milder disease and MRI phenotypes.

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## ISOLATED INSULAR STROKE: TOPOGRAPHY IS THE ANSWER FOR GOOD OUTCOME AND CARDIAC INVOLVEMENT


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Objective: To describe relevant features of pure insular stroke, focusing on cardiovascular factors.

Materials: Data were retrospectively collected from medical charts and consisted of demographic and baseline clinical characteristics, comorbidities, electrocardiograms, echocardiograms, stroke topography and etiology, reperfusive treatments, and outcome measures.

Methods: We identified 15 isolated insular ischemic strokes, visually assessed by a board-certified Neuroradiologist, occurred between January 1 st 2020, and December 31st 2021. Stroke etiology was defined according to TOAST classification. Outcome measures included NIHSS and mRS at discharge, in-hospital mortality, major neurological improvement at discharge and 3-months mRS.

Results: Five patients had history of atrial fibrillation (AF), while, in four cases, AF was newly detected. Other kinds of newly detected arrhythmias were found in eight patients. Three patients showed severe left atrial dilatation, while three other patients showed mildly reduced left ventricular ejection fraction. 80% of patients showed left insular involvement with middle cerebral artery (MCA) occlusion. Cardioembolism was the most frequent etiology. Regarding onset symptoms and signs, language disorders were most frequently

observed, followed by motor and somatosensory deficits. Newly detected cardiovascular alterations were found in 66,7% of cases, being the prevalent atypical presentation. Bridging therapy (rtPA + MT) was performed in most cases. Median NIHSS at discharge was 0 (baseline 11) and median mRS was 2 (baseline 0), while 3-months mRS was 0. Most of patients had major neurological improvement at discharge and good outcome at 3-months follow-up.

Discussion: Our findings showes that cardioembolism is the main pathological mechanism for insular stroke, in contrast to a recent review where cryptogenetic etiology appears to be the main one [1]. Cardiac alterations were frequently discovered during the acute phase, as the insula is known to play a key role in autonomic control [2]. The majority of our patients were discharged with slight disability and no disability was found at 3-months follow-up: thus, in line with previous studies, pure insular strokes seem to have a favorable outcome [3].

Conclusions: Our data suggest the possibility for isolated insular strokes patients to completely recover after acute ischemic stroke, notwithstanding the pivotal role of the insula in cerebral connections and the frequent association with MCA occlusion. Cardioembolism and cardiac arrhythmias must be taken into considerations. To our knowledge, this is the largest case series of pure insular stroke and might be useful for future systematic reviews.

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## PREDICTORS OF FUNCTIONAL OUTCOME IMPROVEMENT FROM THREE TO TWELVE MONTHS AFTER INTRACEREBRAL HEMORRHAGE

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Objective: To describe the recovery trajectories of patients with primary spontaneous intracerebral hemorrhage (ICH) patients from 90 days to 1 year after the index event and to investigate predictors of functional outcome improvement.

Materials & methods: Retrospective analysis of patients admitted to six European Stroke Centers for supratentorial ICH. Functional outcome was measured with the modified Ranking Scale (mRS) at 90 days and 1 year. Predictors of functional outcome improvement were explored with binary logistic regression, adjusted for known prognostic factors and variables with $p<0.1$ in univariate analysis.

Results: A total of 703 patients were included (median age 77, 56% males) of whom 245 (34,9%) died within three months. Among survivors, 28,6% had an improvement of mRS from 90 days to 1 year, 17% had a worsening of mRS and 54,4% had a stable functional status. Age (Odds Ratio (OR) per 1 year increase, 0,980; 95% Confidence Interval (CI), 0,963-0,996, p=0,016) and pre-stroke disability (OR per 1 point mRS increase at baseline, 0,764; 95% CI, 0,625-0,934, p=0,009) were associated with lower odds of functional improvement. Conversely, patients with deep hemorrhages were more likely to experience long-term mRS improvement (OR, 1,725; 95% CI, 1,100-2,705, p=0,018). Of note, traditional acute phase predictors like ICH volume, Glasgow Coma Scale score and ventricular hemorrhage presence were not associated with long-term changes in functional outcome.

Discussion: ICH is a disabling condition and most survivors have great morbidity and mortality during the acute phase. Most ICH trials assessed outcomes at 3 months, but recent evidence has shown that recovery trajectories may continue up to 1 year after ICH [1]. Our findings support this evidence and indirectly confirms the need for full medical support in the acute phase. [2]

Conclusions: Functional outcome recovery is common beyond 90 days from acute ICH. Our findings might inform future trials and improve prognostication in clinical practice.

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## MULTIPLE STROKES IN A PATIENT WITH EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS: A CASE REPORT

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Eosinophilic granulomatosis with polyangiitis (EGPA) is a small and medium-vessels vasculitis with systemic involvement, such as the respiratory tracts, skin, heart and kidney. Although neurologic manifestations of EGPA are reported, they are limited to peripheral neuropathy, and central nervous system (CNS) manifestations are poorly described. This case report aims to describe CNS involvement in EGPA in a patient with several confounders in her medical history. A 65-years-old woman with history of asthma, atrial fibrillation (AF), chronic ischemic heart disease, polycythemia vera, dyslipidemia, and hypertension was admitted due to sudden onset of chest pain accompanied by nausea. Blood tests revealed elevated cardiac enzymes and an ECG indicated ST-segment depression. Transthoracic echocardiography appeared normal. Coronary angiography didn't reveal occlusions. Systemic revascularization was not recommended due to recent anticoagulant use. Approximately 36 hours after symptom onset, the patient suddenly appeared drowsy and exhibited confabulations. A brain MRI performed 3 hours after neurological onset revealed multiple areas of microvascular tissue distress with hyperintensity in

diffusion weight imagine (DWI): subcortically in bilateral thalamus, corpus callosum, perirolandic, occipital and cortically in cerebral and cerebellar hemispheres. Neurological examination showed right limb plegia and Bouchard nodules on both hands. The routine blood tests showed hypereosinophilia (4.000/µl), elevated C-reactive protein (50.4 mg/dl) and high hemoglobin levels. Thrombophilia screening yielded negative results. Serum tests were negative for p-ANCA. Electroencephalogram (EEG) showed diffuse slowing consistent with multiple brain lesions. Electroneuromyography did not reveal peripheral neuropathy. Doppler imaging ruled out significant stenosis in the epiaortic vessels. The diagnosis of EGPA was considered given the history of asthma, extravascular eosinophilia and clinical and laboratory features. Immunosuppressive therapy was started with prednisolone for 5 days, but the patient's general conditions didn't improve. A follow-up brain MRI showed a reduction in lesion load in DWI, but with some persisting areas, indicating ischemic lesions. In response to the incomplete response to treatment, mycophenolate and rituximab were added. Two weeks later, the patient significantly improved her consciousness and muscular strength. She started rehabilitation. This clinical case highlights the possible differential diagnosis of multifocal brain lesions due to an inflammatory (vasculitis) or ischemic etiology. The presence of AF initially led to misleading suspicions, but the combination of clinical and laboratory features attributable to EGPA, allowed for a correct diagnosis and treatment. Moreover, compared to the literature, the widespread and multiple spread of the disease in CNS involvement of EGPA necessitated the use of a combined second-line therapy.

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## ACUTE ISCHEMIC STROKE ASSOCIATED WITH LEFT VENTRICULAR THROMBUS: A SINGLE CENTER EXPERIENCE

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Background: Left ventricular thrombus (LVT) is a known complication in patients with myocardial infarction (MI), primarily in anterior MI [1]. LVT is a rare cause of cardioembolic ischemic stroke (IS) and may remain unrecognized, as "embolic stroke of undetermined source (ESUS)"[2]. Transthoracic echocardiography (TTE) is the first investigation for the detection of LVT, and adding intravenous contrast increases its sensitivity. Cardiac magnetic resonance imaging (MRI) has a high sensitivity and specificity for thrombus delineation. Guidelines recommend treatment with vitamin K antagonists (AVK) for a period of a minimum of 3 to 6 months up to one year [3].

Patients and Methods: At the Stroke Unit of the 'G. Martino' University Hospital of Messina, from 2014 to 2022, out of 2792 patients with acute IS, LVT was reported in 15 patients (mean age = 65.8). 12 patients were discharged with a diagnosis of "cardioembolic IS", with transthoracic echocardiograph LVT detection. 3 patients were discharged with a diagnosis of ESUS and underwent cardio-MRI.

Results: The cardiological assessment with TTE showed diffuse hypo-akinesias and reduced left ventricular ejection fraction (LVEF<50%) in all patients. 13 patients (86%) had an ischemic stroke due to occlusion of a large vessel of the anterior circle, the remaining had bilateral ischemic lesions of the anterior circulation. 8 underwent mechanical thrombectomy, 3 thrombolysis and 4 bridging. 8 patients had hemorrhagic transformation of infarcted brain tissue, 2 of whom did not undergo reperfusion procedures. In 9 patients the TTE found LVT; in 3 patients the TTE showed LVT risk factors, so they performed cardio-MRI with finding of mural thrombosis.

Discussion: In patients untreated with AVK, the rate of stroke or systemic embolization due to LVT is about 15% (2). In particular, while the newly formed thrombus may be highly mobile and protruding into the ventricular cavity, the older thrombus tends to have smooth cavitary surface and typically more static and can be hardly seen at the TTE [2]. Whether there is a high clinical suspect of LVT thrombosis, due to a history of anterior MI or TTE findings (diffuse hypo-akinesia and LVEF<50%), cardio-MRI remains the gold standard examination for LVT detection. This examination should be performed when other methods, such as TTE, are not adequate for diagnostic outcomes.

Conclusions: LVT is a rare cause of cardioembolic IS. In patients with history of MI or presence of TTE risk factors LVT should be suspected in order to follow correct diagnostic/therapeutic procedures.

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## A CASE OF A PATIENT WITH ACUTE BULBO-MEDULLARY ISCHEMIC STROKE AND SUDDEN QUADRIPLEGIA IMPROVED AFTER INTRAVENOUS THROMBOLYSIS

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Introduction: Acute quadriplegia may be the clinical manifestation of potentially life-threatening disorders [1]. If it is caused by a vascular pathology, its early identification became crucial for treatment and prognosis.

Case Presentation: A 64-year-old patient, with a history of heavy smoking, arterial hypertension, dyslipidemia, and cervical spine stenosis (surgically treated five years earlier), was admitted for a sudden onset of anarthria and quadriplegia. In addition, he showed drowsiness, hypoesthesia and right Babinski sign with NIHSS score of 24. Brain CT scan was inconclusive while cervical and brain MRI showed on Diffusion Weighted Imaging (DWI), a hyperintense lesion in the left median-paramedian bulbo- medullary junction at the level of the pyramid decussation. Intravenous thrombolysis was rapidly administered according to ESO criteria [2]. During hospitalization, other causes of sudden quadriplegia were excluded by laboratory examinations. Electrophysiology and electroencephalography were also performed. Because of a lung cancer incidentally found, paraneoplastic encephalitis was excluded because of absence of cytoplasmic and surface

onconeural markers. The neurological pattern progressively improved; the patient was discharged with an NIHSS score of 3 after two weeks.

Conclusions: Acute quadriplegia can be caused by a large variety of central or peripheral nervous system diseases. In case of vascular accidents, a timely intervention is crucial. In this anecdotal case of bulbo- medullary ischemia, a thrombolytic treatment was effective and safe, improving patient clinical condition.

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## EFFICACY AND SAFETY OF THROMBOLYSIS FOR ACUTE ISCHEMIC STROKE PERI-PROCEDURAL TO CORONARY ANGIOGRAPHY IN PATIENTS UNDERGOING ANTICOAGULATION WITH UNFRACTIONATED HEPARIN AFTER ANTAGONIZATION WITH PROTAMINE SULPHATE: A CASE REPORT AND REVIEW OF THE LITERATURE

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Objectives: Acute cerebrovascular events could be serious, although rare, complications of diagnostic and interventional angiographic procedures, especially coronary angiographies [1]. Usually, these procedures are performed while the patient is undergoing anticoagulation with UFH, which, with the consequent elongation of aPTT, would exclude this subgroup of patients from thrombolytic treatment. We aim to reinforce the idea that intravenous thrombolysis can be safe and effective in treating patients with acute cerebrovascular events following coronary angiographies while on anticoagulation with Unfractionated Heparin (UFH), after adequate antagonization of UFH action with Protamine sulphate.

Materials: We reported the case of a patient who developed acute focal neurological deficits after a coronary angiography performed due to an unstable angina that was treated effectively and safely with intravenous thrombolysis after antagonization of UFH action with Protamine sulphate administration.

Methods: We performed a Pubmed search using the following MeSH terms "(Thrombolysis), (Unfractionated Heparin), (Coronary Angiography) AND (Protamine)", looking for articles reporting cases of patients who developed acute cerebrovascular deficits periprocedural to coronary angiography while on anticoagulation with UFH who underwent intravenous thrombolysis after Protamine sulphate administration.

Results: We reported the case of a patient undergoing coronary angiography for unstable angina on anticoagulation with UFH who, at the end of the procedure, developed left upper limb drift, dysarthria and drowsiness. NCCT was negative (ASPECT score 10) but CTA demonstrated superior cerebellar artery occlusion, thus the patient was not eligible for mechanical thrombectomy. The aPTT on admission to the Stroke Unit was 100.7 s. 50 mg of i.v. Protamine sulphate was administered, with rapid normalization of aPTT (24.5 s) and subsequent prompt initiation of thrombolytic treatment within 4.5 h since symptoms onset. There was an improvement in neurological symptoms, with no evidence of haemorrhagic transformation of the left cerebellar ischemic lesion pointed out by the follow-up NCCT.

Discussion: The case we presented, taken together with the preliminary body of evidence found in the literature [2,3], supports the efficacy and safety of intravenous thrombolysis in patients anticoagulated with UFH after adequate antagonization with Protamine sulphate, especially in the setting of periprocedural acute cerebrovascular events secondary to coronary angiography.

Conclusions: Intravenous thrombolysis after reversal of UFH anticoagulation therapy with Protamine sulphate may be safe and effective in treating ischemic stroke patients and it can increase the number of patients eligible for intravenous thrombolysis.

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## THE ROLE OF IPSILATERAL AND CONTROLATERAL CAROTID STENOSIS ON THE OUTCOME OF REPERFUSION TREATMENT FOR ISCHEMIC STROKE

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Objectives: Carotid stenosis is considered a major risk factor for acute ischemic stroke (AIS). Ipsilateral carotid stenosis (ICS) and contralateral carotid stenosis (CCS) play a different role on AIS severity and prognosis, but few data are available about their impact on interventional therapies efficacy. Aim of this study was to evaluate the impact of ICS and CCS on the efficacy of intravenous thrombolysis (IT), mechanical thrombectomy (MT) or both and of antiplatelet therapy (AT). Moreover, we evaluated the different incidence of major complications (deaths and hemorrhagic infarction) among patients treated by different approaches.

Methods: We enrolled all the consecutive patients admitted for AIS to the Stroke Unit of Azienda Ospedaliero-Universitaria delle Marche and submitted to IT, MT, IT+MT or AT. We established the presence of a significant ICS or CCS ($\geq$ 70%) by ultrasound examination or brain angio-CT or MRI. We collected clinical and instrumental information about our patients and employed as the main outcome measure the delta National Institutes of Health (NIH) Stroke Scale from the symptoms 'onset to the discharge.

Results: We finally enrolled 460 subjects, of which 86 with significant ICS and 38 with CCS. We observed a significant linear trend of delta(NIH) between carotid stenosis categories for patients undergoing IT (p=0,011), MT (p=0,046) and MT+IT, but we did not observe any significant trend among untreated subjects. Delta(NIH) was significantly higher among patients undergoing to any procedure (any procedure: 6[3] versus no procedure: 1[2]; p<0,0001). Actively treated patients showed a more frequent incidence of hemorrhagic infarction during hospitalization (any procedure: 28,5% versus no procedure: 6,9%; p<0,0001), while no significant differences were found in in-hospital death (any procedure: 6,90% versus no procedure: 3,40%; p=0,098).

Discussion: ICS and CCS act in different ways on cerebral hemodynamic, both by microembolization and by collateral circles effectiveness. Their presence influence in a significant way the outcome of AIS patients treated by interventional therapies. The importance of an early diagnosis to start the best medical therapy seems to be central in the prevention of AIS and should be suggested especially in individuals at higher vascular risk.

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## TIMING OF ANTITHROMBOTIC SECONDARY PREVENTION IN ISCHEMIC STROKE PATIENTS WITH INTRA CRANIAL HEMORRHAGE AFTER THROMBOLYSIS AND THROMBECTOMY


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Objectives: Hemorrhagic transformation of infarcted tissue (HT) is commonly observed after intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) in ischemic stroke patients. HT may delay the start of secondary stroke prevention and be associated with increased early stroke recurrence. We aimed to assess whether the presence and severity of intracranial hemorrhage after reperfusion treatment are associated with a delayed start of secondary stroke prevention therapy and to evaluate differences in stroke recurrence within three months.

Materials: We conducted a retrospective matched-control dual-center study collecting data of consecutive patients with ischemic stroke receiving IVT and/or EVT at Fondazione Policlinico Universitario A. Gemelli IRCCS in Rome and at Karolinska University Hospital in Stockholm in Sweden. We classified post-treatment ICH on CT within 36 hours as petechial hemorrhagic infarction (HI), parenchymal hematoma (PH), remote parenchymal hematoma (rPH), subarachnoid hemorrhage (SAH) and intraventricular hemorrhage (IVH) and grouped HI and minor SAH as "minor HT" and PH, rPH, major SAH, and IVH as "major HT".

Methods: Primary outcome was the time between revascularization and the start of any secondary prevention therapy; secondary outcomes were recurrent ischemic and hemorrhagic stroke and death within three months. A logistic regression model was fitted for the patient status (hemorrhagic vs. non-hemorrhagic). Additional analysis was performed using propensity score matching (PSM) to control for selection bias and baseline differences.

Results: The logistic regression model showed a statistically significant delay (median 28 vs 24 hours) in the start of antithrombotics in HT patients. Similar results were observed after PSM. We compared no-, minor- and major-HT patients after PSM and found that both no- and minor-HT patients had similar secondary prevention timings (26 vs 24 hours) and rates of stroke recurrence. In contrast, patients with major HT started antithrombotics later (median time 39 hours) or not at all (21.6%), but stroke recurrence was similar.

Discussion: Minor HT did not delay the start of antithrombotics or anticoagulants compared to no HT, with no significant difference in safety outcomes. Major HT patients remain a clinical challenge with a delayed or lacking start of treatment. In this group we did not see a higher rate of ischemic recurrence, although maybe masked by the elevated early mortality.

Conclusions: In conclusion, HT influences the timing of secondary prevention in ischemic stroke patients undergoing reperfusion treatments. Patients with only petechial or minor subarachnoid hemorrhage may start antithrombotic therapy equally early as those with no hemorrhage with similar safety.

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# CLINICAL NEUROPHYSIOLOGY AND BASIC NEUROSCIENCE

## NEUROMODULATION OF CHRONIC PAIN IN FIBROMYALGIC PATIENTS: A NEUROPHYSIOLOGICAL STUDY


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Objective: Fibromyalgia is a pathology characterized by widespread chronic pain, fatigue, and psychological symptoms, which affects patients' quality of life. Non-pharmacological treatments, such us non-invasive neuromodulation technique [1] and exercise therapy [2], seem to reduce perceived pain and therefore improve patients' quality of life.

Our study aims at verifying the effect of direct current stimulation, with or without concomitant exercise therapy, on chronic pain in fibromyalgic patients and assess its neurophysiological effects.

Materials: Outcome variables, such us questionnaires on pain (BPI, VAS) and quality of life (SF12, HADS), electroencephalography (EEG) and Laser Evoked Potentials (LEP), will be evaluated before the beginning of each treatment (T0), at one week (T1), at the end of the treatment (three weeks, T2), and again after three months from the start (T3).

Methods: Patients were randomised into three groups: (A) treatment with direct current administered three times a week for three weeks, in sessions of 20 minutes at an intensity of 2 mA; (B) treatment with computer-based training, three times a week for three weeks; and (C) combination of direct current stimulation and computer-based training, alternated during the week, for three weeks. Direct current stimulation was applied on the scalp over somatosensory area (cathode) and on the spinal cord over the 10th vertebra (anode).

Results: Reduction in the scores of the pain assessment scales emerged in all groups. By analyzing the LEP data, we found an increase in the nociceptive threshold and a decrease in the amplitude of N2/P2 responses in T1, T2 and T3 in groups C and A. By analyzing the electrical cortical activity, an increase in the absolute power of the alpha-band rhythm was recorded (8-13 Hz) in both T1 and T2 in group C.
Discussion: Data obtained show a decrease of pain after non-invasive treatment applied, related to significant modification of neurophysiologic parameters studied. This information suggests an involvement of nervous system on genesis and maintenance of chronic pain in fibromyalgic patients.

Conclusions: Non-invasive neuromodulation techniques and exercise therapy are demonstrated as promising therapeutic tools in the management of chronic pain in patients with fibromyalgia.
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## HAPPINESS: THE INGREDIENT FOR A HEALTHY LIFE. A PIONEERING AP-PROACH BY DR HUNTER "PATCH" ADAMS


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When talking about the power of happiness, a name comes readily to mind: Hunter "Patch" Adams, the American physician who has devoted his life to making people happy and who has made humor and happiness his reason for living. "Patch" Adams became famous worldwide thanks to a comedy-drama based on his life. As he himself states in his famous book titled "Gesundheit! Bringing Good Health to You, the Medical System, and Society through Physician Service, Complementary Therapies, Humor, and Happiness": "Humor is an solution to all ills. I consider the fun as essential as love. The principal thing, when you question individuals what they appreciate regarding life, is the fun they have, whether it is dancing, gardening, golf, or writing books. Life is a miracle and it is so wonderful to be alive that I ask why anyone wastes a minute! Laughter is the greatest medicine!".
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## NOVEL PLEKHG5 MUTATION AS A MODEL OF NON-INTERDEPENDENT COEXISTENCE OF AXONAL AND DEMYELINATING FEATURES IN HEREDITARY POLYNEUROPATHY: BEYOND THE ELECTROPHYSIOLOGICAL DICHOTOMY


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Aim: To describe the clinical and electrophysiological pattern of novel PLEKHG5 neuropathy as an example of pure mixed neuropathy.

Introduction: The characterization of neuropathies as "axonal" or "demyelinating" could be reductive in many cases. Among acquired neuropathies, this concept was overcame by the electrophysiological and pathophysiological characterization of node and paranodopathy. Genetic neuropathies also offer a valid contribution, demonstrating how axonal vs demyelinating dichotomy could be sometimes too reductive. We describe the case of an hereditary sensory-motor neuropathy due to a mutation of PLEKHG5 gene, in which dysmyelinating and axonal damage recognize different, not primitively interdependent, pathophysiological mechanisms.

Case Report: Our 38y.o. patient, of Afghan nationality, born from a consanguineous couple, harbored biallelic mutation c2293C>T(Gln 765)in exon 20 of PLEKHG5 showed ,at neurological examination, hypotrophy of shoulder and pelvic girdle muscles, both distal and proximal hyposthenia, bilateral drop foot without sensory involvement. ENG showed marked reduction of cMAPs from peroneal and axillary nerves and amplitude at lower limits of the normative values from median and ulnar nerves. Conduction velocities (CV) were widely reduced, even in nerves with preserved cMAP amplitude; F waves latencies were prolonged and no conduction blocks were detected. A mild, subclinical and widespread reduction in SAPs was detected. Needle EMG showed spontaneous denervating potentials and giant, polyphasic MUAPs polyphasic, with decreased recruitment in proximal and tibial muscles.

Discussion: PLEKHG5 mutations are associated with different clinical phenotypes including distal hereditary motor neuropathies (dHMN) and intermediate Charcot-Marie-Tooth disease (CMT). The product of this gene regulates autophagy of synaptic vesicles in axon terminal of motoneurons. Our electrophysiological data could have suggested a predominant axonal involvement, relegating this form among axonal neuropathies, according to the classical definition. However, this could not have explained the widespread slowing of CV and the prolonged F wave latency even in not severely involved nerves and

therefore not explainable by the loss of large diameter fibres as in intermediate CMT. Moreover, the clinical and electrophysiological pattern would not be typical of a length-dependent hereditary axonal polyneuropathy and not even suggestive of motor neuron disease because of the sensory involvement. These data are, instead, consistent with a further, different pathomechanisms according to which PLEKHG5 inactivation leads to a axon/Schwann cell units disease characterized by myelin infoldings in peripheral nerves.

Conclusion: PLEKHG5 mutation causes a polyneuropathy with phenotype ranging from MND and intermediate CMT. The uniqueness of this case is the coexistence of both phenotypes in the same patient due to a novel mutation not previously described in literature. Only an accurate electrophysiological examination, aimed to a precise description and not to a mere attempt of classification, can guide the clinician and the geneticist to the most targeted and coherent etiopathogenetic research.

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## KINEMATIC ANALYSIS OF HAND DEXTERITY IN HEALTHY SUBJECTS


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Objectives: Manual dexterity, a crucial motor function evaluated through the coin rotation task [1-3], has not been quantitatively studied using objective kinematic analysis. Here we aimed to conduct a kinematic analysis of hand dexterity in a sample of healthy human subjects.

Materials: Fifteen healthy young right-handed participants (6 females, mean age±standard deviation - SD 30.4±4.1) were enrolled. Handedness was assessed using the Edinburgh Handedness Inventory, and all participants had a score > 70. Kinematic analysis of a coin rotation task was performed using an optoelectronic system (SMART motion system, BTS, Milan, Italy). Reflective markers were placed on the coin to track its position during the task.

Methods: Participants performed the coin rotation task for 15 seconds under four separate conditions: using the dominant and non-dominant hands and rotating in both clockwise and counterclockwise directions. Motion analysis was conducted using specialized software (SMART Analyzer, BTS Engineering, Italy). we measured the total number of rotations executed, movement rhythm, as assessed by the coefficient of variation (CV) of the inter-cycle intervals, and the peak velocity achieved. Data were analyzed using two-way analysis of variance (ANOVA) with the factors of 'hand dominance' (dominant and non-dominant) and 'rotation direction' (clockwise and counterclockwise). Statistical significance was determined at $P < 0.05$.

Results: Although no significant differences were found for the total number of movements performed (mean ± SD: 6.4 ± 0.9), significant effects were observed for the 'hand dominance' factor in terms of both the CV [F(1, 14)=13.859, P=0.002] and movement velocity [F(1, 14)=7.076, P=0.018]. Notably, the non-dominant hand consistently exhibited higher CV values and lower movement velocities, indicative of poorer motor performance. Moreover, neither the rotation direction factor nor the interaction between factors showed significance for both CV and movement velocity, indicating that the direction in which the movement was performed did not differentiate between the dominant and non-dominant sides.

Discussions: This study represents the first attempt to provide objective quantification of a commonly used movement for assessing manual dexterity. The objective data obtained from this study could potentially provide indirect insights into the cerebral areas involved in the execution of manual dexterity movements and praxis functions.

Conclusions: The proposed methodology holds promising implications for research studies in healthy subjects and in neurological conditions, e.g., it can aid in the assessment, monitoring, and treatment evaluation of manual dexterity impairments in Parkinson's disease and other movement disorders, as well as in pyramidal and cerebellar diseases.

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## TRANCRANIAL MAGNETIC STIMULATION IN MITOCHONDRIAL NEUROGASTROINTESTINAL ENCEPHALOPATHY (MNGIE)


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Background: Mitochondrial neurogastrointestinal encephalopathy [1] (MNGIE) is an extremly rare disorder due to recessive mutations in the thymidine phosphorylase gene. Clinical manifestations include gastrointestinal dysmotility, diffuse asymptomatic leukoencephalopathy, severe demyelinating polyneuropathy. This study aimed to explore, for the first time in a patient with MNGIE, cortical spinal involvement/conduction time and excitability with single pulse transcranial magnetic stimulation (TMS).

Methods: A 40 year old man with molecular diagnosis of MNGIE underwent to neurophysiological investigation a with single pulse TMS [2]. We studied motor evoked potentials in the first dorsal interosseous muscle bilaterally. Motor evoked potential variables were assessed following the guidelines of the IFCN. We measured the following variables: relaxed motor threshold (rT); central motor conduction time (CMCT) during maximum efforts of the target muscle was calculated as cortical MEP latency (CTX) − radicular MEP latency -1ms and length of the central silent period. A round coil at the vertex was used. We repeated TMS Study after ten months. The control group consisted of 38 participants (age range, 22–65 years)

Results: Motor threshold was bilaterally higher as compared with controls (right FDI rT 65; left FDI rT 66 left; mean control group 51+8.6). CMCT was bilaterally prolonged (right FDI 11 ms, left FDI 10 ms; mean control group 6.5 + 0.8 ms) while central silent period was normal (right FDI 175,8 + 11,3; left FDI 201,3 + 10,6; mean control group 185 + 20). After 10 months CMCT did not changed

while CSP length slightly increased (right FDI 183,6 + 11,3; left FDI 221,1 + 11,6).

Conclusions: Transcranial magnetic stimulation disclosed in this patient with MNGIE for the first time a significant involvement of the central motor conduction time while intra-cortical inhibitory phenomenon at least for the GABA-B mechanisms were preserved [3]. TMS could be a useful tool for understand this rare disorder.

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## THE ROLE OF MUNIX AS A NOVEL ELECTROPHYSIOLOGICAL BIOMARKER FOR EVALUATING SEVERITY, MONITORING PROGRESSION AND PREDICTING PROGNOSIS IN ICU-ACQUIRED WEAKNESS

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Objectives: Intensive Care Unit Acquired Weakness (ICUAW) is a debilitating condition that significantly impacts patients' survival and quality of life [1], with long-term effects on morbidity and mortality rates [2]. However, the lack of substantial prognostic biomarkers hinders our understanding and management of ICUAW, particularly in the Intensive Rehabilitation Unit (IRU). The objective of this study was to investigate the potential of the Motor Unit Number Index (MUNIX), a non-invasive neurophysiological technique that efficiently estimates the number of functional motor units by recording surface electromyography (EMG) signals during voluntary muscle contractions at varying force levels [3], as a valuable biomarker for ICUAW management and predicting patient outcomes.

Material and Methods: In this longitudinal prospective study, 88 ICUAW patients, diagnosed using a combination of EMG and electroneurography criteria, underwent MUNIX measurements at admission in IRU (T0). We correlated MUNIX values with ICUAW severity, quantified using the MRC sum-score. At discharge (T1), a subset of 20 patients underwent a repeated neurophysiological examination and an assessment of gait and balance residual abilities (Performance Oriented Mobility Assessment, POMA). Multivariate logistic regression was used to evaluate the association of clinical and neurophysiological variables at T0 with functional recovery (modified Barthel Index) at T1.

Results: Statistical analysis revealed a significant negative correlation between MUNIX and MRC sum-scores ($r = -0.68$, $p < 0.001$) at T0. Logistic regression analysis showed that that MUNIX was one of the most indicative of good functional recovery among all the parameters collected at T0 (each one-unit increase in MUNIX was associated with 2.4 times higher odds of good functional recovery at T1 95% CI: 2.2 - 2.8, $p < 0.01$). Finally, for the subset of patients with follow-up neurophysiological measurements, Pearson's analysis demonstrated a significant correlation ($r = 0.72$, $p < 0.01$) between the change in MUNIX from T0 to T1 and the balance abilities as measured by POMA at T1.

Discussion: The findings suggest that MUNIX could serve as a supplementary biomarker for ICUAW severity in conjunction with EMG techniques at T0. Furthermore, MUNIX measurements and their changes over time could be used to monitor disease progression and predict successful rehabilitation outcomes at T1.

Conclusions: In conclusion, our findings propose MUNIX as a promising, reliable, and non-invasive tool for assessing ICUAW severity and tracking disease progression in IRU. The integration of MUNIX in clinical practice could substantially contribute to optimizing prognosis and improving patients' quality-of-life following ICU discharge.

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## PERIODIC DISCHARGES (PDS) IN PATIENTS WITH BRAIN TUMOR PATHOLOGY: CLINICAL AND ELECTROPHYSIOLOGICAL FEATURES

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Objectives: Periodic discharges (PDs) represent an EEG pattern commonly found in association with focal cerebral lesions, particularly brain tumors (BT). The clinical interpretation of PDs is controversial as well as their pathophysiological origin. The aim of this study is to describe the prevalence and characteristics of PDs in patients with BT, focusing on their association with epilepsy diagnosis and status epilepticus (SE).

Materials and methods: Adult patients suffering from BT who underwent a video-EEG recording were retrospectively selected from the Neurology Clinic of "G. d'Annunzio" University of Chieti-Pescara from January 2016 to January 2023. Demographics, clinical features, as well as tumor characteristics, and radiological findings, were collected. Video-EEG data were reviewed to identify patients with PDs. Diagnosis of epilepsy and SE were made according to ILAE criteria.

Results: 175 patients (115 primitive BT, mean age 61.3; 60 metastatic BT, mean age 70.1) were enrolled. Thirteen patients (7.4%) showed PDs at video-EEG, of whom 12 with primitive BT. Patients with PDs presented lateralized PDs (LPDs) in most cases (84.6%), with a mean frequency of 1.25 Hz and temporal lobe localization in 76.9%, concordant with the tumor lesion side in 66.7% of the cases. Nine patients suffered from epilepsy, whereas SE was described only in three patients. Comparing primary BT with and without PDs, patients with PDs presented more often a parieto-occipital lesion localization (p=0.01) and high-grade histology (p=0.01). No differences were observed according to sex, age, lesion dimension, and lateralization.

Conclusions: PDs can be more frequently observed in high-grade primary BT with parieto-occipital localization instead of metastatic BT. In addition, PDs are highly associated with epilepsy diagnosis but hardly ever can represent an ictal pattern.

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## SINGLE-FIBER ELECTROMYOGRAPHY (SFEMG) IN PATIENTS WITH SUSPECTED OCULAR MYASTHENIA: A COMPARISON STUDY BETWEEN VOLUNTARY VS. STIMULATED TECHNIQUE

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Objective: Single-fiber electromyography with voluntary activation (SFEMG-v) is one of the main electrophysiologic techniques used for the diagnosis of neuromuscular junction disorders. However SFEMG-v may be poorly tolerated for its extensive duration or for the difficulty of maintaining constant voluntary contraction. The SFEMG with near-nerve stimulation (SFEMG-s) may have some advantages, though there is lack of evidence regarding its diagnostic accuracy. In particular, no studies are available comparing the two methods in a population of patients with and without myasthenia. The aim of this study was to compare the results of these two techniques in a cohort of patients with suspected ocular myasthenia using reference values obtained in a population of age- and sex-matched healthy subjects.

Material and Methods: This study involved 33 patients with suspected ocular myasthenia (mean age 63 years, 9F) and 14 healthy subjects (mean age 52 years, 5F). All patients underwent an electrophysiological assessment consisting of repetitive nerve stimulation, SFEMG-v and SFEMG-s by using a concentric needle electrode. We tested the right orbicularis oculis in all subjects. Diagnosis of ocular myasthenia or ptosis and/or diplopia of other etiology was made based on extensive clinical, laboratory and instrumental investigations including assessment of treatment response to steroid and/or pyridostigmine and search for AchR-Ab.

Results: Ocular myasthenia was diagnosed in 18 of 33 patients without considering the results of SFEMG investigation. In most patients the results matched between SFEMG-v and SFEMG-s; however, in 3 of 33 patients (all with ocular myasthenia) the tests results were inconsistent since only SFEMG-s resulted positive. Sensitivity was 66,7% and 83,3% for SFEMG-v and SFEMG-s respectively, while both techniques had a specificity of 80%. No statistical differences were observed at the chi-square test between the two techniques. Area under the curve (AUC) was 0.73 for SFEMG-v and 0.82 for SFEMG-s.

Discussion and Conclusions: This is the first study to assess diagnostic accuracy of vSFEMG vs stSFEMG for diagnosis of ocular myasthenia. Both SFEMG-v and SFEMG-s had good accuracy and no statistical differences were observed in sensitivity and specificity values between the two methods. It is noteworthy that sensitivity and specificity values of both tests were suboptimal for diagnosing ocular myasthenia. Test repetition over time could be helpful in doubtful cases.

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## ECULIZUMAB AS FAST-ACTING RESCUE THERAPY IN A MYASTHENIA GRAVIS PATIENT WITH WORSENING SYMPTOMS WHILE ON TREATMENT WITH EFGARTIGIMOD: A CASE REPORT

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Objectives: Two novel FDA and EMA approved agents are available for treatment of refractory generalized Myasthenia Gravis (gMG): Eculizumab, an anti-C5 monoclonal antibody, and Efgartigimod, an antibody fragment targeting the FcRn. We describe a case of a patient who suffered a gMG relapse while on treatment with Efgartigimod, that was promptly rescued with Eculizumab treatment.

Materials and Methods: A 46 years old woman was diagnosed with anti-AChR positive gMG in 2012. She underwent thymectomy for thymic hyperplasia and started symptomatic treatment with pyridostigmine. She then started prednisone and azathioprine. IVIg was used with little benefit. She developed many side effects from chronic prednisone use: osteopenia, hypercortisolism, overweight. In December 2022 she started intravenous treatment with Efgartigimod (10 mg/kg weekly for four consecutive weeks for each cycle). At the time she took 75 mg/die azathioprine, 10 mg/die prednisone and 300mg/die pyridostigmine. Her MG-ADL and qMG score at baseline were 5 and 16, respectively. She started Efgartigimod infusions and clinical evaluations on a weekly basis.

Results and Discussion: Soon after the first week, her MG-ADL score dropped to 1, while her qMG was 11 after the first treatment cycle (4 administrations). This suggested a small reduction of prednisone to 5 mg/die and pyridostigmine to 240 mg/die. Her scores remained stable during the next months, during which she practiced two cycles (each consisting of 4 weeks of treatment followed by 4 weeks of clinical monitoring without drug administration). During the third cycle (18 weeks after starting treatment) her symptoms began to worsen, she reported an MG-ADL score of 9, and a measured QMG score of 20. For these symptoms she had to stop working. We immediately discontinued treatment with Efgartigimod and started Eculizumab as a rescue and long-term therapy (900 mg iv weekly for the first 4 weeks, followed by 1200 mg from the fifth week and every two weeks). After the first week, her MG-ADL dropped to 5 and at the beginning of the maintenance phase (fifth week) her MG-ADL and QMG score were 1 and 14, with great symptom relief and improvement in quality of life.

Conclusions: As far as we know, this is one of the first case reports of Eculizumab as a rescue therapy in a patient not responding to Efgartigimod. Eculizumab showed a fast and sustained action improving clinical measures of gMG.

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## DISCLOSING CENTRAL AND PERIPHERAL EXCITABILITY IN RESTLESS LEGS SYNDROME

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Background and Aims: Restless legs syndrome (RLS) is a neurological sensory-motor disorder causing an urge to move the legs due to an uncomfortable sensation occurring at rest. The underlying pathophysiology of RLS has not been elucidated yet. Previous studies showed decreased intracortical inhibition, enhanced spinal excitability and peripheral Ih channel dysfunction using heterogeneous methods, therefore leading to conflicting results [1]. In this study we investigated cortical, spinal and nerve excitability parameters simultaneously for the first time.

Material and Methods: We recruited 40 patients (PT-TOT) and 20 age-matched controls (HCs), subdividing the patients' group in patients on medication (PT-ON) and patients off medication (PT-OFF). We studied cortical excitability using threshold-tracking transcranial magnetic stimulation (TT-TMS) [2], recording the following parameters from the abductor pollicis brevis (APB): rMT, Short-Interval Intracortical Inhibition (SICI), Short-Interval Intracortical Facilitation (SICF), Long-Interval Intracortical Inhibition (LICI) and Intracortical Facilitation (ICF). Spinal cord excitability was assessed by recording F-waves, H-reflexes and long latency reflexes (LLRs) from APB and flexor carpi radialis (FCR). Nerve excitability testing (NET) was performed using the extended TRONDNF protocol, recording from the APB.

Results: TT-TMS showed a statistically significant decreased SICI in PT-TOT compared to HCs at numerous inter-stimulus intervals (ISIs), with 2.5 ms (12.99±2.06 vs 21.4±2.25%, $p<0.05$) and 3.5 ms (2.23±1.84% vs 7.92±1.58%, $p<0.05$) being the most affected ISIs; this difference was even more marked between PT-ON and HCs, with SICI reduction spanning throughout the whole 1-7 ms ISIs interval range (average: 2.82±2.03% vs 8.2±1.07%, $p<0.05$). We furthermore observed an increased SICF at 1.9 ms between PT-ON and HCs (-5.15% vs -0.4%, $p<0.05$) and a statistically significant increase in APB-LLRII (92 μV vs 58.5 μV, $p<0.05$) and FCR-LLRIII amplitude (14 μV vs 7 μV, $p<0.05$) between the same two groups. We found no changes in NET parameters. The cohorts displayed no age or sex differences.

Discussion: Decreased SICI is a widespread phenomenon, not confined only to the motor cortex of the leg; consistent with previous findings, this reflects reduced intracortical inhibition possibly due to dysfunctional subcortical projections. Increase in SICF is a novel finding, furtherly reinforcing the concept of augmented intracortical facilitation. The increase in LLRs amplitude points towards spinal hyperexcitability, possibly due to weakened supra-spinal descending inhibitory projections, thus providing a possible explanation to the uncomfortable sensation experienced by the patients [3].

Conclusions: Our findings aim towards decreased cortical inhibition coupled with increased cortical facilitation and enhanced spinal excitability in RLS pathophysiology, with no clear PNS alterations.

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## FOOD-BORNE BOTULISM. WHEN NEUROPHYSIOLOGY CAN ADD A TIP: A CASE REPORT

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Objectives: We describe the case of a man with early diagnosed food-borne botulism, treated with antitoxin serum, with normal magnetic brain imaging (MRI), unremarkable blood examinations, and normal electrodiagnostic conduction studies, except for the absence of the sympathetic skin response (SSR).

Materials and Methods: A 64-year old man accessed our Emergency Department (ED) on 11th January, 2023. He had unremarkable history, except for eating a precooked canned vegetable soup of industrial origin, on 07th January. After 2 days, he had gastrointestinal discomfort and diarrhea, vomiting, mild headache, asthenia, but he did not seek medical attention. On 11th January, he accessed the ED complaining of blurred vision and photofobia. On 12th January, he had diplopia and dysphonia, followed by internal and external ophthalmoplegia, dysarthria, dysphagia, and dry mouth. An urgent brain MRI excluded any inflammatory, vascular or neoplastic brainstem lesion. Urgent cerebrospinal fluid analysis was performed, and antiganglioside and antineuron antibodies were normal. Food-borne botulism was suspected, and during the night the patient received antitoxin serum (BAT Botulism Antitoxin Heptavalent-A, B, C, D, E, F, G; equine) after approval of Pavia CAV (Centro Anti Veleni), arrived from Bologna National Storage Center. Laboratory diagnostic confirmation was obtained after five days, by testing clinical specimens (toxin B-producing Clostridium was found in the stool sample by the PCR test) and leftover food (toxin B-producing Clostridium was found in a soup sample by microbiological examination, PCR and mouse bioassay) by Istituto Zooprofilattico Sperimentale delle Venezie activated by the Local Department of Hygiene and Public Health. Electrophysiological study performed the day after hospital admission revealed normal sensory and motor conduction, with reduced amplitude of the compound muscle action potentials (CMAPs), and no decremental response at electrical repetitive stimulation at 3 Hz, neither facilitation at 20Hz. The SSR study was pathological, and it remained absent for two months, until the complete clinical recovery.

Discussion and Conclusions: Differential diagnosis of food-borne botulism include Miller-Fischer variant of Guillaine–Barré syndrome, myasthenia gravis, Eaton–Lambert syndrome, brainstem lesions, tick paralysis, and shellfish or tetrodotoxin poisoning [1]. Clinical suspicion of foodborne botulism must be considered early, because of the urgency of rapid treatment with antitoxin to reduce neuro-denervation. Considering the latency of laboratory results, an accurate clinical history, together with neurophysiological studies, may be crucial for early diagnosis.

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## BELL'S PALSY: NEW PERSPECTIVES FROM NEUROPHYSIOLOGY AND NERVE ULTRASOUND

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Background and Aims: Bell's palsy is the most common cause of acute peripheral facial palsy. Although the etiology of the disorder is unknown, inflammation and oedema of the facial nerve probably play a key role in the pathogenetic process. Most patients recover within a few months, while up to a third have a residual functional deficit with the presence of facial muscle weakness or synkinesis [1]. Despite the fact that electrodiagnostic tests are widely used for the evaluation of facial nerve paralysis, data on the predictive value of these tests are conflicting. In recent years, nerve ultrasound has gained attention as a valuable tool for the diagnosis of peripheral nervous system diseases [2]. This clinical, neurophysiological and nerve ultrasound longitudinal study is aimed at assessing the utility of facial nerve ultrasound as a supportive tool for the diagnosis and assessment of Bell's palsy.

Methods: We prospectively enrolled 34 consecutive patients with Bell's palsy. All patients underwent clinical examination, neurophysiological testing (including facial nerve conduction study) and HRUS evaluations after 10-15 days (T0), one month (T1) and three months (T2) the onset of Bell's palsy. Patients who did not experience a complete recovery within three months were also evaluated after six months (T3). We have then compared the accuracy of HRUS with that of facial nerve conduction study in predicting the incomplete clinical recovery at three and six months.

Results: At T0 the facial nerve diameter, as assessed with HRUS, was larger on the affected side than on the normal side, particularly in patients with incomplete recovery at T1, T2 and T3. Nevertheless, ROC curve analysis showed that the facial nerve diameter at T0 had a lower predicting value than the facial nerve conduction study for an incomplete clinical recovery at three (T2) and six (T3) months.

Discussion and Conclusion: In the acute phase of Bell's palsy HRUS shows abnormally increased facial nerve diameter. The observed nerve enlargement may be due to inflammation-induced swelling of the nerve probably spreading from the geniculate ganglion [3]. Neverthless, the predicting value of this technique for incomplete clinical recovery at three and six months is lower than that of the nerve conduction study.

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## CARE PATHWAYS FOR INDIVIDUALS WITH ANOXIC DISORDERS OF CONSCIOUSNESS: AN INTERSOCIETY CONSENSUS CONFERENCE, CAPIADOC

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Introduction and aims: After a severe anoxic brain injury, comatose patients can evolve toward prolonged Disorders of Consciousness (pDoC; 1). Anoxic aetiology is considered to have worse outcome than traumatic brain injury, and based on solid predictors of poor outcome, this often leads to withdrawn of life-sustaining therapy in the acute phase. In this perspective, few data are available about care pathways for survivors with post-anoxic coma and pDoC. [1] To address these issues, 9 Italian Scientific Societies shared their expertise for providing a Consensus on diagnostic and prognostic procedures, still debated in literature.

Methods: Twelve working groups, involving 22 multidisciplinary professionals from the 9 scientific societies, implemented a systematic literature review focused on 12 PICO questions addressing the acute (n=6) and the post-acute (n=6) phases. The quality of evidence of the included studies was evaluated using the Oxford Centre for Evidence-Based Medicine Levels of Evidence. In March 2023, a Jury involving representative members of the Italian scientific societies and 2 patients' family associations weigh up working groups' reports for elaborating conclusive recommendations.

Results: A total of 47 out of 1,217 screened papers have been included. Each working group produced a report on the literature review, strengths, and limits of evidence for each PICO. For each PICO, 2-4 Jury recommendations were provided based on the evidence levels of eligible articles and expert opinion.

Discussion: The general and common suggestion was for multimodal patient assessment combining validated clinical scales, targeted neurophysiological assessment, and, when available, neuroimaging to improve diagnosis and prognosis and guide individualized treatment [2]. A strong recommendation was to use standardized and validated diagnostic criteria (e.g., Salzburg criteria for non-convulsive status epilepticus) and standardized terminology for neurophysiological analysis (e.g., ACNS 2021 terminology for EEG) [3]. Because of the limited evidence available on patients with anoxic aetiology, the Jury suggested developing multicentre longitudinal studies to ascertain the diagnostic and prognostic value of advanced tools (e.g., functional neuroimaging) to identify patients with "covert awareness".

Conclusions: Recommendations from this Consensus Conference will guide clinicians in the management of post-anoxic coma and pDoC from the acute to chronic phase, and hopefully could serve as a starting point for an international consensus on diagnostic and prognostic procedures for such complex patients.

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## INHIBITORY CORTICAL CONTROL IN HEALTHY SUBJECTS: MODULATION OF BETA AND GAMMA OSCILLATIONS IN FRONTAL CORTICAL AREAS

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Objectives: The inhibition of an ongoing response is a key component of executive control implying the voluntary suppression of inappropriate behaviours [1]. Physiological mechanisms underlying this response are based on an integrated cortical network, including the inferior frontal gyrus (IFG) and the dorsal premotor cortex (PMd) [2]. Inhibition of unwilling actions can be experimentally probed through a standardised paradigm, the Stop Signal Task (SST), that requires subjects to start a movement as quickly as possible when a Go Signal is presented and to refrain from it if suddenly a Stop Signal appears during the reaction time (RT). This protocol allows for the assessment of the inhibitory ongoing response, reflected by the Stop Signal Reaction Times (SSRT). Recently, it has been demonstrated in healthy subjects (HS) that the activation of these cortical areas during specific behaviours is reflected by modulations of beta-/gamma- oscillations [3]. These oscillations can be experimentally and noninvasively modulated by transcranial alternating current stimulation (tACS) protocols. The aim of this study is to explore the role of cortical beta-/gamma- oscillations in the physiology of inhibitory human behaviours through SST protocol performed during specific tACS paradigms, in HS.

Materials and Methods: Six HS performed the SST during three different tACS protocols (β-, γ- and sham-tACS) randomly delivered over the IFG and PMd, bilaterally, over two different days. The coordinates of right and left IFG and PMd were assessed through neuronavigation. During the SST paradigm we quantified RT and SSRT.

Results: Preliminary results suggest that beta- and gamma- tACS differently modulate action inhibition in HS. A two-way repeated measures Anova revealed a significant interaction among the factors Area (IFG; PMd) and tACS(β; γ). Post-hoc comparisons pointed out a significant difference in γ-tACS modulation among the two areas (p=.03); gamma-tACS applied over the IFG decreased RTs, while the stimulation of the PMd increased RTs. Furthermore, gamma-tACS increased SSRTs when applied over both IFG and PMd.

Discussion and conclusion: We demonstrated that beta- and gamma-tACS can modulate cortical oscillations underlying physiological mechanisms of inhibitory control behaviours, in frontal cortical areas, in HS. These preliminary results provide the background for future applications in neurological disorders characterised by deficit of inhibitory control, such as Parkinson's Disease.

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## EEG AND BRAIN MRI ALTERATIONS IN TRANSIENT GLOBAL AMNESIA: DO TIME AND GENDER MATTER?

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Objectives: The aim of the study is to evaluate the prevalence and characteristics of EEG and Brain MRI findings in patients with transient global amnesia (TGA).

Materials and Methods: In this single-center observational retrospective study, we examined adult inpatients consecutively admitted to the Neurological Clinic of Policlinico Tor Vergata from 2013 to 2023 with TGA diagnosed according to Hodges and Warlow criteria [1]. Only patients who underwent both EEG recording and brain MRI were included. Data were collected on demographics, past medical history, results of diagnostic investigations, and TGA recurrence.

Results: 69 patients (41 females, 28 males, mean age 62.38±9.20 years) fulfilled the inclusion criteria. Mean duration of TGA symptoms was 5.46±6.14 hours. Medical history of hypertension was detected in 36%. Ten out of 69 patients (14.49%) experienced a recurrence of TGA [2]. EEG abnormalities were found in 47/69(68.1%) patients, mainly bilateral (left 38.3%, 51% bilateral, 10% right, p =0.002). Focal slowing was observed in 23/69 (33.3%) and interictal epileptiform abnormalities (spikes, sharp waves) in 24/69 (34.8%). Mean latency of EEG recordings from TGA was significantly shorter in recordings with epileptiform abnormalities than the normal EEG group (47±22.63 vs 61.86±36.6 hours, p=0.013). Brain MRI showed DWI positive lesions in hippocampal/parahippocampal region in 16/69 patients (23.2%), with a statistically significant left prevalence (left 11/16, bilateral 4/16, right 1/16, p=0.007). The time interval between the attack and brain MRI was significantly shorter in the DWI positive group than normal MRI (82±27.66 vs 101.43±45.54 hours, p<0.05). We did not observe significant differences between patients with normal EEG and epileptiform abnormalities and between MRI-DWI positive and negative groups, regarding age, past medical history of hypertension, event duration and recurrence of TGA, except gender since epileptiform alterations were significantly more frequent in females than males (19/41, 46.3%, vs 5/28, 17.86%, p<0.05). No significant correlation was found between DWI positivity and EEG alteration [3], nor a significant association between lateralization of abnormalities.

Conclusions: The present study confirms the importance of timing as the time interval between TGA attack and diagnostic investigations correlates with the rate of EEG and MR-DWI findings. A left dominance of DWI lesions was found, as reported in previous studies, but no lateralization of EEG abnormalities, with no significant association between MRI and EEG findings. Furthermore, our data demonstrated a significant correlation between gender and paroxysmal EEG abnormalities, suggesting that women may have a different underlying etiology for TGA, which has so far not been clarified.

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## NEUROCHEMICAL DATA ON THE PERIVASCULAR NEURON: A NEGLECTED NEURON TYPE OF THE BLOOD BRAIN BARRIER

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The blood brain barrier (BBB) is the morphofunctional structure involved in the control of molecular transport mechanisms between the blood and the central nervous system (CNS). Moreover, the BBB protect the CNS from injurious agents and modulates selectively the passage of pharmacological agents. Furthermore, a structural damage of the BBB in neurologic and psychiatric disorders, has been demonstrated. The BBB is composed by a monolayer of endothelial cells, incompletely covered by pericytes surrounded by an extracellular matrix sheathed by end-feet astrocyte processes. The end-feet astrocytes are the mainly target of neuronal processes. Currently, the neuronal elements involved in the control of the BBB and the neuronal role in the neurovascular unit it is not completely know. Morphofunctional studies demonstrate the existence of perivascular neuronal processes involved in the modulation of the BBB and, only few studies evidenced in several regions of the CNS the presence of neuronal cell bodies in close relationship with the wall of microvessels. Therefore, the goal of this study of chemical neuroanatomy by means of an immunohistochemical approach is to investigate on the presence of monoaminergic and peptidergic perivascular neuronal elements in the human cerebellum. The study was carried out on autoptic fragments of human cerebellum fixed in an aldehyde picric acid solution, embedded in paraffin, cut into 5µm sections and subjected to light microscopic immunohistochemistry with rabbit polyclonal antibodies for serotonin (5-HT), dopamine transporter (DAT), dopamine type 2 receptor (DRD2), neurotensin (NT), neurotensin receptor type 1 (NTR1). The immunoreaction revealed in the molecular layer, in the three zones of the granular layer of the cerebellar cortex, in the dentate nucleus the presence of different neuronal cell bodies and processes in close relationship with the wall of microvessels immunoreactive for NT and NTR1, DAT, DRD2, 5-HT. Although, these results provides further insights, we suggest that in the human cerebellum exist different subpopulations of perivascular neurons may be considered a new specific neuron type of the neurovascular unit involved in the permeability control mechanisms of the BBB.

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## NEUROTENSINERGIC NEURONS IN THE HUMAN CEREBELLAR CORTEX: A STUDY OF CHEMICAL NEUROANATOMY

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Neurotensin (NT) is a neuropeptide distributed in the central and peripheral nervous systems (CNS and PNS). NT is involved to hypotension, hyperglycemia, hypothermia, antinociception, intestinal motility, secretion. In the CNS, NT is involved in neurotransmission/neuromodulation mechanisms of the dopaminergic system [1]. Studies evidenced a role of NT in dopamine-related disorders (e.g. Parkinson's disease and schizophrenia) [1]. The cerebellum is not considered a neurotensinergic area, and not are available data on the presence of neurotensinergic neurons. Currently, only few neurotensinergic extrinsic fibers, and the NT receptor subtypes NTR2 and NTR3 has been detected. Therefore, the aim of this study, was to evaluate in the human cerebellar cortex by means of an immunohistochemical approach, the existence and the distribution of a neurotensinergic neuronal subpopulation. The study was carried out on fragments of postmortem human cerebellar cortex 36-48 h after death. Each fragment was fixed in an aldehyde and picric acid solution, embedded in paraffin, cut into 5 µm sections, and subjected to light microscopy immunohistochemical procedures using rabbit and goat polyclonal antibodies respectively against NT and NTR1. For positive controls were used fragments of rat intestine subjected to the same experimental procedure. In the cerebellar cortex, NT and NTR1 immunoreactivity were detected in neuronal cell bodies and processes of all the layers. The NT and NTR1 immunoreactivity were observed in the molecular layer, in stellate and basket neurons; in the Purkinje neuron layer, in a subpopulation of Purkinje neurons; in the granular layer, in a subpopulation of granules and Golgi neurons and in some non-traditional large neurons (e.g. candelabrum, synarmotic, perivascular neurons) [2]. NTR1 immunoreactivity was also observed in form of fine 'puncta' (putative axon terminals) in the neuropil and in close relationship to the wall of microvessels. The present study of chemical neuroanatomy demonstrate the existence of a neurotensinergic neuronal system in the human cerebellar cortex, which could be involved in neurotransmission/neuromodulation mechanisms of intrinsic circuits, in microvascular innervation, and in cerebellar cortico-nuclear projective circuits. In addition, we plan to carry out further studies to evaluate in the cerebellum the presence of NT-dopamine co-transmission mechanisms, and its possible role in cerebellar neuronal circuits related to dopaminergic disorders, such as Parkinson's disease, schizophrenia and autism spectrum disorders.

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## MOTOR CORTICAL CORRELATES OF PAIRED ASSOCIATIVE STIMULATION INDUCED PLASTICITY: A TMS-EEG STUDY

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Paired associative stimulation (PAS) is a non-invasive brain stimulation technique that modulates synaptic plasticity in the human motor cortex (M1) [1,2]. The PAS paradigm effectively induces a fast-developing, enduring and stimulus-specific enhancement in corticomotor excitability [2,3]. Since previous studies have primarily used motor evoked potentials (MEPs) as an outcome measure, cortical correlates of PAS-induced plasticity remain unknown.

Aims: This observational study aimed to investigate cortical correlates of a standard PAS-induced plasticity in the primary motor cortex by using a combined TMS-EEG approach in a cohort of eighteen healthy subjects. To this aim, we recorded MEPs and TEPs before and after a PAS intervention, as well as the TEPs evoked during the PAS protocol. To better characterize the relationship between PAS-induced corticospinal facilitation and cortical changes we also investigated possible relationships between MEPs and TEPs measures.

Methods: We determined for all patients the resting motor threshold and the stimulator intensity sufficient to evoke a peak-to-peak MEP amplitude of 1mV in the relaxed FDI at the optimal position of the coil to constantly elicit the largest MEPs in the right resting FDI. PAS intervention was performed by pairing right ulnar nerve stimulation with TMS on left M1 with an interstimulus interval of 25 ms. We collected MEPs before (T0) and at 5 (T1), 15 (T2), and 30 (T3) minutes after PAS. At T0 (pre-PAS) and T2 (post-PAS) we also collected real and sham TEPs by delivering, in two separate blocks, one-hundred real TMS pulses and one-hundred sham TMS pulses, during EEG recording. Finally, EEG was continuously recorded during PAS intervention to record TEPs elicited by the paired stimulation.

Results: In addition to the expected long-lasting facilitatory modulation of MEPs amplitude, PAS intervention also significantly increased transcranial magnetic stimulation evoked potentials (TEPs) P30 and P60 amplitude. No significant correlation between the magnitude of PAS-induced changes in TEP components and MEP amplitude were observed. However, the linear regression analysis revealed that the combined changes in P30 and P60 component amplitudes significantly predicted the MEP facilitation after PAS.

Conclusions: The findings of our study offer novel insight into the neurophysiological changes associated with PAS-induced plasticity at M1 cortical level and suggest a complex relationship between TEPs and MEPs changes following PAS.

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## A NEW APPROACH TO THE EVALUATION OF SMALL NERVE FIBERS

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Diagnosing small fiber neuropathy (SFN) remains a challenge due to the relevant limitations of current tests. Recently, a surface electrode for small fiber-selective stimulation was developed. Its specificity relies on an interdigitated micropattern with the conductive leads spaced 150 micrometers (150IDE) and alternately connected to opposite stimulator poles; this cathode-anode distance generates an electric field with a maximum skin depth of 100 micrometers, thus selectively activating the intraepidermal nerve endings. It allows the assessment of the nociceptive system through Nociceptive Evoked Potentials (NEPs) recorded from the scalp. We hereby propose a protocol for SFN diagnosis and monitoring that integrates Sudoscan and 150IDE-NEPs. We enrolled outpatients affected by Charcot-Marie-Tooth disease type 1A (CMT1A) and hereditary transthyretin amyloidosis (hATTR), including hATTR pre-symptomatic carriers. Healthy controls matched by age and sex were also studied with 150IDE-NEPs and Sudoscan. Patients with different neuropathies or skin diseases/lesions which may affect the 150IDE-NEPs were excluded. The medical history was collected and dysautonomia symptoms were reported and quantified using Compound Autonomic Dysfunction Test (CADT) and Composite Autonomic Symptom Scale-31 (COMPASS-31). Neurological examination, electroneurography, Sudoscan, and 150IDE-NEPs test were performed. We investigated eight subjects with CMT1A, 4 males and 4 females, with a mean age of 42 years (range 22-55), six patients with hATTR, 4 males and 2 females, with a mean age of 77 years (range 72-83) and with an average disease duration of 8 years, two presymptomatic Phe64Leu TTR mutation carriers, both females, one aged 54 years, and the other aged 48 years. The fast Aδ fibers had a behavior similar to that of the Aβ fibers in people affected by CMT1A, with an increase in latency or absence of the 150IDE-NEPs. All CMT1A patients had normal Sudoscan results. High interpatient variability was detected in hATTR, possibly due to the different TTR variants. The 150IDE-NEPs results were also mismatched with the Sudoscan findings. All the healthy controls and the two presymptomatic Phe64Leu TTR mutation carriers had normal Sudoscan and normal 150IDE-NEPs. Since the 150IDE allows a low-cost evaluation of small fibers using standard electromyographic material, it is important to confirm its reliability in early SFN detection. SFN diagnosis could have therapeutic implications, for example by identifying early conversion to symptomatic disease in hATTR carriers. Enrollment of more patients is needed to confirm the reliability of the method and a comparison with skin biopsy would be helpful.

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## EVALUATION OF PLASMATIC AND CELLULAR REDOX STATE PARAMETERS IN PATIENTS AFFECTED BY AMYOTROPHIC LATERAL SCLEROSIS

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Background: Oxidative stress, alteration of mitochondrial function, and changes in the neurovascular unit (NVU) could play a role in Amyotrophic Lateral Sclerosis (ALS). Nowadays, no therapy can change ALS course, suggesting the need to test new approaches to slow down disease progression. Acetyl-L-carnitine (ALCAR) has neurotrophic and protective effects, which could be beneficial in ALS [1,2].

Objectives: This study aimed to analyze: 1) the plasma redox system and nitric oxide (NO) in ALS; 2) the plasma effects on peroxidation/mitochondrial function in human umbilical cord-derived endothelial vascular cells (HUVEC) and astrocytes; 3) ALCAR effects on the redox state of ALS patients.

Materials and Methods: We included 32 newly diagnosed ALS patients and five healthy controls. Each patient underwent a clinical evaluation combined with a blood sample, which was used to analyze the aforementioned parameters at diagnosis (T0). After starting ALCAR (T0), the same investigations were repeated at three months (T1) and six months (T2).

Results: In the plasma of ALS patients at T0, an increase in TBARS and a reduction in GSH and NO were found compared to controls. In HUVEC/astrocytes, treated with plasma of 10 ALS patients, mitoROS increased, whereas cell viability and mitochondrial membrane potential decreased. Plasma analyses were repeated at T1 and T2 and showed an improvement in the redox state in all patients involved. No statistically significant correlation was found between clinico-demographic features (e.g., age, sex, site of onset, ALSFRS-R, FVC%, and BMI at baseline) and plasmatic values of TBARS, GSH, and NO at baseline and over time. Interestingly, we found higher levels of TBARS in fast progressor patients compared to slow progressors at T1 (p-value: 0.02). Discussion/Conclusions: Our results show that oxidative stress and NVU play a central role in ALS and suggest that plasma molecules could be involved in the disease pathogenesis. Our data suggest that NVU members may be a possible pharmacological target of ALCAR, which could be protective in ALS. Indeed, ALCAR was able to improve the redox state of ALS patients. TBARS and GSH levels were in fact, respectively, reduced and increased at 3 months after ALCAR start administration, compared to T0. This improvement was confirmed after 6 months. Moreover, ALCAR would act as a protective factor on mitochondrial function of NVU members. Indeed, our results revealed a decrease mitoROS production and a decrease damage in HUVEC and astrocytes.

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## FLASH-EVOKED HIGH-FREQUENCY EEG OSCILLATIONS IN MIGRAINE WITH AND WITHOUT AURA

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Aim of the study: Scalp-recorded, flash-evoked, high-frequency EEG oscillations (F-HFOs) can be easily extracted from flash visual evoked potentials (F-VEPs) and may represent a convenient measure of visual cortical excitability, as they are markedly enhanced in photosensitive epilepsy. Since migraine patients are also characterized by some degree of altered cortical excitability, aim of the present study is to assess F-HFOs in migraine with (MA) and without aura (MO).

Materials and Methods: 91 migraine patients were consecutively recruited, of which 54 with MO and 37 with MA. 51 healthy subjects (HS), matched for demographic features, acted as controls. F-VEPs were recorded from occipital electrodes in the interictal phase (after dark adaptation, 80 white flashes were delivered through a xenon lamp). F-HFOs were extracted through appropriate filtering (Autosignal ver 1.7, Fourier filtering and reconstruction, in the frequency band of 75-175 Hz, with a latency of 20-110 ms after the flash stimulus, example shown in fig. 1). Time-frequency domain spectrum analysis was subsequently performed. ANOVA was applied for statistical analysis.

Results: F-HFOs showed two consistent spectral peaks (around 85 and 125 Hz) in all three groups. The power of the first peak was significantly enhanced ($p<0.05$) in patients with migraine (MO+MA) compared to HS. However, patients with MA failed to show a significant difference compared to HS ($p>0.05$). The second peak was unaffected.

Discussion and Conclusions: Increased F-HFO spectral power may reflect enhanced visual cortex excitability in migraineurs in the interictal phase. Aura is not associated with an increased excitability as detected by F-HFOs. Other factors, such as the frequency of migraine attacks and central sensitization, might be relevant in affecting F-HFOs.

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## EPILEPTIFORM PATTERNS PREDICTING UNFAVORABLE OUTCOME IN POSTANOXIC PATIENTS: A MATTER OF TIME?

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Historically, epileptiform malignant EEG patterns (EMPs) have been considered to anticipate an unfavorable outcome, but an increasing amount of evidence suggests that they are not always or invariably associated with poor prognosis. We evaluated the prognostic significance of an EMP onset in two different timeframes in comatose patients after cardiac arrest (CA): early-EMPs and late-EMPs, respectively. We included all comatose post-CA survivors admitted to our intensive care unit (ICU) between 2016 and 2018 who underwent at least two 30-minute EEGs, collected at T0 (12-36h after CA) and T1 (36-72h after CA). All EEGs recordings were re-analyzed following the 2021 ACNS terminology by two senior EEG specialists, blinded to outcome. Malignant EEGs with abundant sporadic spikes/sharp waves, rhythmic and periodic patterns, or electrographic seizure/ status epilepticus, were included in the EMP definition. The primary outcome was the cerebral performance category (CPC) score at 6 months, dichotomized as good (CPC 1-2) or poor (CPC 3-5) outcome. A total of 58 patients and 116 EEG recording were included in the study. Poor outcome was seen in 28 (48%) patients. In contrast to late-EMPs, early-EMPs were associated with a poor outcome ($p = 0.037$), persisting after multiple regression analysis. Moreover, a multivariate binomial model coupling the timing of EMP onset with other EEG predictors such as T1 reactivity and T1 normal voltage background can predict outcome in the presence of an otherwise non-specific malignant EEG pattern with quite high specificity (82%) and moderate sensitivity (77%). The prognostic significance of EMPs seems strongly time-dependent and only their early-onset may be associated with an unfavorable outcome. The time of onset of EMP combined with other EEG features could aid in defining prognosis in patients with intermediate EEG patterns.

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## INVESTIGATING INTERHEMISPHERIC CONNECTIONS BETWEEN PRIMARY SOMATOSENSORY AREAS USING PAIRED MEDIAN NERVE STIMULATION AND HIGH-FREQUENCY OSCILLATION ANALYSIS

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Interhemispheric interactions between the motor cortices are well-established, but evidence regarding interhemispheric connections in other modalities, such as the somatosensory system, remains elusive. This study aimed to investigate and characterize possible interhemispheric connections between the primary sensory areas by studying the responses elicited by bilateral peripheral stimuli delivered with timing dependent on the latencies of each subject's N20. Median nerve somatosensory-evoked potentials (SEPs) were recorded from both median nerves in 15 healthy right-handed subjects using a paired median nerve somatosensory evoked potential (PMNSEP) protocol. The N20-latencies of both hemispheres were evaluated using single median nerve stimulations, and modified interstimulus intervals (mISIs) were computed to elicit SEPs between the two hemispheres at specific N20-latency intervals (5, 10, 20, and 40 ms). The short-latency SEP components (P14/N20 and N20/P25) were analyzed and normalized for each condition. The results revealed significant differences in normalized amplitudes between mISIs, indicating an mISI effect for both N20 components. Post-hoc tests further confirmed specific differences between different mISIs. These findings provide insights into the interhemispheric connections between primary sensory areas and highlight the potential role of interhemispheric interactions in somatosensory processing. Further investigations are warranted to gain a comprehensive understanding of these connections and their functional implications in sensory perception and information processing.

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## THETA-ALTERNATING CURRENT STIMULATION MODULATES CEREBELLAR-RELATED MOTOR FUNCTIONS AND CEREBELLO-CORTICAL CONNECTIVITY

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Objectives: To evaluate through a double-blind, randomized study, whether transcranial alternating current stimulation (tACS) delivered at θ and γ frequency over the cerebellum modulates upper limb performance and the cerebellum-primary motor cortex (M1) connectivity in healthy subjects.

Materials: We enrolled 15 healthy young subjects. An optoelectronic kinematic system was used to record cerebellar-dependent motor tasks, including rhythmic finger-tapping (FT) [1], and two arm-reaching movements that differed in terms of complexity: reaching-to-grasp (RG) and reaching-to-point an object (RP) [2]. tACS was delivered over the cerebellum through a BrainSTIM (E.M.S.) at θ and γ frequency [3]. Sham-tACS was used as a control condition. Cerebellum-(M1) connectivity was tested using transcranial magnetic stimulation (TMS) for the assessment of the cerebellar-brain inhibition (CBI).

Methods: Participants underwent a single experimental session. We first recorded the three behavioural tasks performed during tACS in the three different stimulation conditions: i) θ-tACS; ii) γ-tACS; iii) sham-tACS. Then, we evaluated the CBI during θ-, γ-, and sham-tACS. The stimulation condition order for both kinematic and TMS assessments was random, and both participants and researchers were blinded to stimulation conditions (double-blind study design). Repeated-measures (rm)ANOVAs were adopted to test the possible tACS effects on each kinematic and TMS variable. Correlation analysis was also performed.

Results: θ-tACS modulated movement rhythm during the FT task, i.e., it incremented rhythm irregularity as compared to sham- ($p=0.02$) and γ-tACS ($p<0.01$). θ-tACS also modified the RP task, as it increased the duration of both the entire movement and the approach-to-the-target phase as compared to sham- ($p=0.02$ and 0.01) and γ-tACS ($p=0.05$ and $p=0.04$). Finally, CBI was more effective (i.e., greater inhibition) during θ-tACS than sham- and γ-tACS (both $ps<0.001$). The effect of θ-tACS on movement rhythm in the FT task correlated with CBI changes, that is, the greater the movement rhythm deterioration, the greater the CBI strengthening during θ-tACS.

Discussion: We here demonstrated that tACS delivered at a cerebellar resonant frequency, i.e., θ frequency, modulates fine finger and arm movements. This modulation may relay on the cerebellar inhibitory output onto M1.

Conclusions: Our results may be interpreted for a better understanding of the physiological mechanisms of motor control in healthy humans. Also, our data offers new cues to design innovative, non-invasive neuromodulation protocols to shape cerebellar–cerebral functions.

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## ECULIZUMAB IN REFRACTORY MYASTHENIA GRAVIS: A SINGLE CENTER ONE YEAR EXPERIENCE

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Objective: To report the results of One-year single center experience regarding Refractory Ab AchR Myasthenia gravis (rMG) patients treated with Eculizumab.

Materials and Methods: Among 500 MG patients followed at our division, 12 AchR refractory MG patients with unstable clinical condition were selected.

Results: Almost all patients have shown a progressive clinical improvement according with approved clinical scales (MG-ADL - QMG). At one year follow-up the average steroid dose has been reduced and, in some cases, the immunosuppressive treatment stopped. No serious adverse effects emerged.

Discussion and conclusions: Eculizumab is proving safe and effective in treating Ab-AChR rMG patients.
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## THE LOSS OF BRAIN FINGERPRINT IN PARKINSON'S DISEASE PREDICTS THE MOTOR IMPAIRMENT: A MAGNETOENCEPHALOGRAPHIC STUDY


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Aims: Extracting subject-specific information from the human brain can enhance tailored therapeutic approaches in neurodegenerative diseases. The clinical connectome fingerprint (CCF) has proven valuable in differentiating brain patterns in healthy individuals and those with neurodegenerative diseases [1, 2]. However, its potential to reveal meaningful information about the individual clinical status in Parkinson's Disease (PD) remains largely unknown. Therefore, we analyzed magnetoencephalography (MEG) data of PD patients within the CCF framework, hypothesizing that PD individuals would display reduced fingerprint compared to HC, which might predict motor clinical impairment.

Materials: We recruited 47 PD patients (off medication) and 47 healthy controls (HC). Brain signals were recorded through a magnetoencephalography system. Clinical motor scores were obtained using the Unified Parkinson's Disease Rating Scale (UPDRS-III).

Methods: MEG signals were preprocessed, source-reconstructed, and transformed into frequency-specific functional connectomes (FCs) using phase linearity. FCs were cross-correlated within each group to construct identifiability matrices representing the similarity between FCs. Two parameters were extracted: I-self, representing the similarity between two FCs of the same individual, and I-others, representing the similarity between different individuals. Additionally, the FC of each patient was compared to those of HC, yielding an I-clinical score. Permutation tests were used to compare scores between groups. Multilinear regression was applied to assess the predictive ability of I-clinical for UPDRS-III.

Results: PD patients exhibited lower I-self values ($p = 0.01$) and lower I-others values ($p < 0.001$) compared to HC in beta band. Disease duration ($p = 0.01$, $\beta = 0.4$) and I-clinical ($p < 0.001$, $\beta = -0.48$) resulted to be significant predictors, and the model predicted ~45% of the variance of the UPDRS-III. Finally, I-clinical was significantly correlated (negatively) with the UPDRS-III score ($r = -0.48$, $p < 0.001$).

Discussion: The CCF analysis revealed significant findings in the beta band, known to be altered in PD. The low differentiation found in PD patients suggested impaired large-scale brain dynamics. Furthermore, the relationship between PD-HC brain similarity (i.e., the I-clinical) and the motor score, showed that the greater the similarity between a patient's FC and those of HC, the milder their motor impairment.

Conclusions: Brain fingerprinting allowed us to analyze the specific brain connectivity patterns of each patient, highlighting its potential for guiding tailored therapies in PD [3].
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## SMALL FIBERS ASSESSMENT BY THERMAL QUANTITATIVE SENSORY TESTING IN PATIENTS WITH IGM PARAPROTEIN-RELATED NEUROPATHY


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Objectives: IgM paraprotein-related neuropathies, also including anti-MAG associated neuropathy, are a wide and heterogeneous group of peripheral nerve diseases. Pain is frequently reported by the patients, and it usually gets worse during disease's progression also being poorly responsive to treatment. The aim of this study was to assess the involvement of small fibers by using thermal Quantitative Sensory Testing (QST) in a group of patients with IgM paraprotein-related neuropathies, also to highlight whether differences between patients with anti-MAG and non anti-MAG associated neuropathy may exist.

Material: Twenty-four patients with IgM paraprotein-related neuropathies have been enrolled in the study. Sensory functions and pain

sensations were assessed by means of clinical evaluation, clinical scales and interview. Small fibers function was evaluated by thermal QST.

Methods: All patients underwent a clinical interview, assessing demographic and clinical data, and neurological examination. Warm, cold and heat pain thresholds (WDT, CDT, HPT) were evaluated on the right thenar eminence and on the right foot dorsum using the reaction-time independent QST method of levels.

Results: Fifteen patients resulted positive for the presence of anti-MAG antibodies whereas the remaining nine patients were negative. Pain was reported in the 40% and 33% of MAG-positive and MAG-negative patients respectively. WDT and CDT resulted frequently abnormal though statistically significant differences were not detected between groups. Indeed, at least one thermal threshold was altered in 66% and 78% of MAG-positive and MAG-negative patients respectively. HPT was abnormally increased in the hand and/or the foot respectively in 20% and 27% of MAG-positive patients. In the MAG-negative group HPT was elevated in only one patient in the hand.

Discussion: Abnormalities of WDT, CDT and HPT observed in our patients are compatible with a small fibers impairment in patients with IgM paraprotein-related neuropathies, both with and without anti-MAG antibodies. Interestingly, the alterations mainly involved the WDT and CDT, which are considered to be mainly mediated by the C fibers. Indeed, especially in the MAG-negative group, non-length dependent alterations in the HPT, which is mainly mediated by A-delta fibers, were less frequently observed.

Conclusions: Thermal thresholds, mainly dependent on C unmyelinated fibers, were altered in most patients with or without MAG positivity, which is in line with the hypothesis of a peripheral small fibers impairment. Finding that HPT, which is mainly mediated by Aδ fibers (myelinated), was less frequently altered in both patients group is an unexpected finding, especially in patients with MAG positivity where peripheral myelin is primarily involved.

## USEFULL OF EVOKED MOTOR POTENTIAL IN EARLY STAGE OF GUILLIAN BARRÉ SYNDROME'S DIAGNOSIS

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Goals: Benefits of evoked motor potential (MEP) to confirm the clinical suspicion of Guillian Barré syndrome's early stage and its variants, when the traditional instrumental signs are absent, as albumino-cytological dissociation and demyelinating on nerves conduction studies.

Materials: The patient presents acute onset of signs and symptoms compatible to Guillian Barré syndrome, which stock-like numbness, complete loss of reflex, diffuse muscle weakness but asymmetrical (worse on the right of superior limb), dysarthria. The medical history reports an infection of upper respiratory tract, one week previously. It is performed hematochemical tests blood test with research of antibodies against nerves, head CT with angioCT, MRI of the brain and spine with gadolinium, rachycentesis and neurophysiological studies.

Methods: By neurophysiological point of view, blink reflex study, electroneurography, electromyography and evoked motor potentials to all four limbs are done. The patient receives treatment with one cycle of intravenous Immunoglobulin.

Results: Imaging tests are within normal limits. The Lumbar puncture does not show typical albumino-cytological dissociation. The electromyography is not significative as well as blink reflex and nerves conduction studies; in particular, there are not signs of demyelination and the F waves of four limb are symmetrical and regular for persistence and minimal latency. The study of evoked motor potentials are recorded in two ways: with magnetic stimulation both transcranical both transcervical. If transcervical stimulating is normal, the transcranical study highlights alteration of M responses because to reduction of amplitude with chronodispersion signs and delay of absolute latencies and central conduction time, especially on superior right limb. By blood test, it is decteted the presence of specific antibody IgG type against GQ1b protein.

Discussion: The transcranical MEP's positivity, compared with the normal results of transcervical MEP, means that the dysimmune process is localized on that small part of nervous system between the horn cell and the outflow of fibers nerve by conjugation foramens. This site is difficult to study with the only F wave for reason of spatial dispersion. Furthermore, considerating acute onset, cranic nerve involvement with Ab anti GQ1b positive and, mainly, after treatment, the reversible conduction failure with complete recovery (absence of temporal dispersion or conduction block), it is possible to suspect a proximal nodopathy. So, MEP can detect significant abnormalities in early stage of these diseases when the other routine tests can be negative.

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## CLINICAL NEUROPSYCHOLOGY AND COGNITIVE BEHAVIORAL NEUROLOGY

## COGNITIVE RESERVE IS ASSOCIATED WITH QUALITY-OF-LIFE CHANGES IN NEWLY DIAGNOSED PEOPLE WITH MULTIPLE SCLEROSIS: AN EXPLORATORY AND LONGITUDINAL STUDY

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Objectives: The protective effect of cognitive reserve (CR) on cognition in Multiple Sclerosis (MS) has been confirmed in multiple studies [1,2]. It is not clear, however, whether high CR may also counteract a decline of quality-of-life (QoL) over time in recently diagnosed people with MS (pwMS), as demonstrated in studies on older healthy adults [3]. Therefore, the aim of the study was to evaluate the effect of CR on changes in QoL at three years after the onset.

Materials and Methods: Fifty-five newly diagnosed pwMS (women = 58.2%) underwent a neurological and neuropsychological evaluation at baseline (T0; at least 1 month after the onset) and follow-up (T1; at least 3 years from T0). At both time points the evaluation included: Symbol Digit Modalities Test (SDMT), Multiple Sclerosis Quality of Life-54 (MSQoL-54), Beck Depression Inventory II (BDI-II), State-Trait Anxiety Inventory (STAI-Y) to evaluate cognitive status, QoL, depressive and anxiety symptomatology, respectively. A repeated measures MANCOVA with Bonferroni correction for multiple comparison was performed. Within-subject factor was time (T0 vs T1),

between-subject factor was CR (categorized in high [>13 years], medium [13 years] and low [<13 years] CR), whereas the dependent variables were each subscore of MSQoL-54. Covariates of the model included: sex, disease duration, EDSS, BDI-II, STAI-Y and SDMT.

Results: The MANCOVA revealed no significant main effects of CR or time on MSQoL-54 scores; however, an interaction effect between CR and time was found (Wilks' $\Lambda = .22$, $F(32,48) = 1.721$, $p = .043$, partial $\eta 2 = .534$). Univariate analysis showed that the CR*time interaction was significant for social function ($p = .029$), sexual function ($p = .011$), satisfaction with sexual function ($p = .009$) and overall QoL ($p = .021$), meaning that only pwMS with low CR showed a decline of these MSQoL-54 subscales at T1 evaluation.

Discussion: CR may be a protective factor of QoL decline in newly diagnosed pwMS; low CR seems to be associated with a worse perception of their social and sexual functioning and to a more negative evaluation of one's overall QoL levels at T1.

Conclusions: These findings may support the hypothesis that CR may reflect the individual's resilience not only to physical and cognitive damage, but also to changes on perception of social and sexual wellness. Future studies may further investigate this issue by including more proxies of CR and other psychological variables (e.g., coping strategies).

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## DEPRESSIVE SYMPTOMS AND ATRIAL FIBRILLATION: CLINICAL, NEUROIMAGING AND COGNITIVE ASSOCIATIONS IN A COHORT OF OLDER PATIENTS WITH ATRIAL FIBRILLATION ON ANTICOAGULANTS. STRAT-AF 2 STUDY

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Aims: Depression is frequently encountered in older people, represents a risk factor in many cardiovascular diseases, including atrial fibrillation (AF), and finally affects overall prognosis. The term Vascular Depression indicates the possible associations between depressive symptoms and cerebrovascular diseases. Cerebral small vessel disease plays an important role. Our aims were to: 1) investigate the presence of psychiatric disorders, depressive symptoms and quality of life in older patients with AF on anticoagulants for primary and secondary prevention of ischemic stroke; 2) explore which clinical, cognitive, functional and neuroimaging factors were associated with psychiatric disorders and depressive symptoms.

Methods: Strat-AF2 is a single center, longitudinal, observational study evaluating older (≥65 years) patients with AF on anticoagulants. Patients were assessed at baseline by means of a comprehensive standardized protocol (clinical, functional and cognitive data), and brain MRI and/or CT. SVD lesions were visually assessed according to validated scales. Depressive symptoms were evaluated by the Geriatric Depression Scale (GDS).

Results: Out of the 182 patients enrolled (mean age 78.3±8.7 years, males 58%), 88 (48%) had a history of psychiatric disorders. Compared to patients without psychiatric disorders, those with presented a short-lasting AF (138.9±118.1 vs. 102.3±89.7 months, respectively, p=.023), more gait disorders (33% vs. 50%, p=.020), more sedentary lifestyle (48% vs. 63%, p=.047), worse global cognitive efficiency (mean MoCA score 22.5±4.3 vs. 21.2±3.8, p=.040), more memory complaints (37% vs. 62%, p<.001) and higher GDS score (2.5±2.3 vs. 5.3±3.3, p<.001). Forty-three subjects (24%) had mild to severe depressive symptoms according to GDS scores. Higher depressive symptoms were associated with: female sex (rpb=.301), lower education (r=-.291), living alone (rpb=-.260), sedentary lifestyle (rpb=-.224), worse global cognitive efficiency (r=-.249), disability (ADL r=-.246; IADL r=.239), history of psychiatric disorders (rpb=.448), memory complaints (rpb=.256) and worse of quality of life (r=-.296). Regarding neuroimaging, depressive symptoms (GDS scores) were associated with white matter hyperintensities [Fazekas (r=.281) and Scheltens scales (r=.328)].

Discussion: In our cohort of older patients with AF on anticoagulants, history of psychiatric disorders and depressive symptoms seem quite frequent and associated with several environmental, cognitive and behavioral factors that could be the target of prevention and treatment strategies. White matter hyperintensities seem to confirm the vascular depression hypothesis.

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## ALTERATIONS OF SPONTANEOUS SPEECH IN PRIMARY PROGRESSIVE APHASIA VARIANTS: A NEUROPSYCHOLOGICAL AND BRAIN MRI STUDY

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Objectives: The aims of the study were: 1) to identify which features of spontaneous speech most effectively distinguish PPA variants (non-fluent/agrammatical [nfvPPA], semantic [svPPA], and logopenic [lvPPA]) from healthy controls (HC) and each other; 2) to determine whether the

speech measures associated to each variant are related to gray matter (GM) density of specific language brain circuits.

Materials: 95 patients with a diagnosis of PPA (40 nfvPPA, 35 svPPA, and 20 lvPPA) and 25 HC underwent a neuropsychological assessment, the audio-recorded 'Picnic Scene' test from the Western Aphasia Battery, and a brain MRI.

Methods: Stepwise regression models detected the best speech parameters able to distinguish the groups. Multiple regressions were performed between GM volumes and global z-scores of each 'best model' resulting from the Stepwise Regression analysis.

Results: The best model differentiating PPA patients and HC included: false starts, mean production rate, mean frequency, and length of sentences for lvPPA (R2=0.731); production rate and self-corrected sequences for nfvPPA (R2=0.665); mean frequency of produced nouns for svPPA (R2=0.466). In lvPPA, nfvPPA and svPPA, z-scores of each 'best-model' variables were positively associated with the GM density of left postcentral, inferior frontal, and inferior temporal gyri, respectively. The best model to distinguish: lvPPA from nfvPPA cases included incomplete and subordinate sentences (R2=0.295); lvPPA from svPPA included naming and repetition, proportion of sentences and verbs (R2=0.646); nfvPPA from svPPA included naming, repetition, number of produced verbs and sentences, and production rate (R2=0.757).

Discussion: In this study we provided quantitative measures of speech by considering a very large sample of PPA patients. The Stepwise regression models highlight the best speech variables associated to each variant. In the comparisons among PPA variants, the best models were reached when distinguishing svPPA cases from each other variant, mainly when also standard language tests were included in the model. The accuracy in distinguishing lvPPA and nfvPPA cases is still low; however, the proposed models could benefit from including other biomarkers, such as the brain MRI measures.

Conclusions: The speech variables that we identified and that were related to specific GM circuits, may be used in the clinical practice for patients' differential diagnosis, prognosis, and planning pharmacological and non-pharmacological interventions.

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## PSYCHOMETRIC PROPERTIES AND CLINICAL CORRELATES OF THE FRONTAL BEHAVIOUR INVENTORY IN PROGRESSIVE SUPRANUCLEAR PALSY: DATA FROM THE PSP-NET

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Objectives: Behavioural symptoms, such as apathy, disinhibition, dysphoria and anxiety are frequent complains in progressive supranuclear palsy (PSP) [1]. Specific scales evaluating neuropsychiatric disturbances in PSP are lacking. The Frontal Behaviour Inventory (FBI) is widely used to evaluate behavioural issues in dementia. Aims of the present study were to (I) report the psychometric properties of the FBI in PSP and (II) describe the clinical correlates of behavioural symptoms in PSP patients.

Design, Setting and Participants: PSP patients diagnosed according to the Movement Disorder Society Criteria underwent a clinical interview, a motor evaluation, cognitive and behaviour testing. Data were collected from several centres throughout Italy within the PSP-NET supported by Fondazione LIMPE.

Results: Two-hundred and eight subjects, with mean (± DS) age of 63.90 ± 12.25 years and mean (± DS) education of 9.82 ± 3.98, were screened for the present study. One-hundred-twenty-two were men (67,80%) and 59 were women (32,60%). The internal consistency was high (Cronbach's alpha = 0.868) and corrected item-total correlation was > 0.40 for the majority of items. Principal component analysis revealed that five factors with the highest eigenvalues accounted for 54.92% of the total variance. Behavioural aspects measured with FBI associated with less education and more aggressive and apathetic symptoms.

Conclusion: The FBI is a reliable tool for the assessment of behavioural symptoms in PSP. Higher behavioural symptoms scores may represent a marker of prevalence of aggressive and apathetic aspects in PSP. The lack of items exploring depressive symptoms in the FBI may justify the low total variance displayed by factor analysis.

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## THE EVOLUTION OF SPEECH IMPAIRMENT IN PRIMARY PROGRESSIVE APHASIA

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Objectives: To identify which features of spontaneous speech are the most affected overtime in the different primary progressive aphasia (PPA) variants (non-fluent/agrammatical [nfvPPA], semantic [svPPA], and logopenic [lvPPA]).

Materials: Thirty-four patients with a biomarker-based supported diagnosis of PPA (10 nfvPPA, 17 svPPA, and 7 lvPPA) and 25 healthy controls underwent a neuropsychological assessment which included the audio-recorded 'Picnic Scene' test from the Western Aphasia Battery. Patients underwent the same visit at the follow-up within a period between 6 and 24 months.

Methods: At baseline, sociodemographic and speech features (in terms of speech production rate, speech fluency, syntax production, and lexical content) were compared between groups. Linear mixed effect models, which accounted for age, sex, education, and time between visits, investigated significant speech changes overtime within each PPA group and between groups.

Results: At baseline, patients and healthy controls were similar for age, sex and education. PPA cases performed worse than healthy controls in almost all speech parameters. Patients were similar among each other in terms of age, sex, education, and disease severity. At baseline, compared to the other groups, nfvPPA cases showed the most severe speech profile with a reduced performance in speech and syntax production. Compared to the other groups, lvPPA cases showed more

fluency interruptions, such as false starts and full pauses, while svPPA patients produced more verbs than nouns and adopted a high-frequency lexicon. Overtime, nfvPPA patients did no show significant further speech changes; lvPPA cases showed a significant reduced production rate; and svPPA cases produced more semantic errors.

Discussion: In this study, we provided quantitative measures of speech at baseline and speech changes overtime in each variant of PPA. The three PPA variants showed different speech trajectories: at baseline, nfvPPA cases presented severe speech disturbances that were not anymore quantifiable overtime; lvPPA accumulated speech production difficulties which were similar to those presented by nfvPPA cases at baseline; and svPPA cases revealed a focal decline involving lexical content and semantic knowledge only.

Conclusions: The speech variables that we identified as the most affected at baseline and overtime by each PPA variant may be used in the clinical practice for increasing knowledge on disease progression, patients' prognosis and for planning speech language therapy interventions. Funding. European Research Council (StG-2016_714388_NeuroTRACK); Foundation Research on Alzheimer Disease.

## BPSD-SINDEM SCALE, A NEW TOOL TO ASSESS BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA: ITALIAN VALIDATION AND ASSOCIATION WITH PHARMACOLOGICAL TREATMENTS

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Objectives: Behavioral and psychological symptoms of Dementia (BPSD) are part of disease course and associated with a high burden for patients and caregivers. Tools assessing BPSD do not usually cover the complete range of BPSD and are based only on caregivers' perception. Our objective was to validate a new scale for BPSD including both clinician and caregivers' observations, and caregivers' perception of their own coping abilities.

Materials: The BPSD SINDEM study group developed a tool to assess BPSD comprising three 17-item parts: two questionnaires completed by the caregiver assessing respectively the BPSD extent (a global concept tied to both frequency and severity) and caregiver's coping abilities, and an observational scale completed by clinicians. 208 patients from four Italian CDCD were included. NPI, CDR, MMSE, ADL, IADL, and CIRS were also administered.

Method: The scale correlation was tested by Person's coefficients between BPSD-SINDEM subscales. For each BPSD-SINDEM subscale we ran linear models to identify possible predictors of scale scores.

Results: The BPSD-SINDEM extent questionnaires (caregiver and observational) were positively correlated ($r = 0.34$, $p < 0.001$). A diagnosis of Lewy Body or Fronto-temporal dementia and the usage of antidepressants and antipsychotics were predictive of higher BPSD-SINDEM extent scale scores. Increased BPSD extent was also predicted by higher fluoxetine and olanzapine equivalent doses. We found that usage of benzodiazepines was predictive of higher score at the caregivers' coping questionnaire. As far as BPSD-SINDEM observational scale is concerned, only the use of antidepressants, but not their dose, was a predictor of higher scores.

Discussion: The correlation between BPSD-SINDEM extent and the observational scales indicates that the BPSD burden perceived by caregivers is at least in part mirrored by clinicians' direct observation. Therefore, the BPSD SINDEM scale could be indeed a reliable tool to assess BPSD. BPSD burden was predicted by antidepressants and antipsychotics use and the BPSD extent in the observational scale was consistently predicted by antidepressant use, supporting a strong association between BPSD severity and pharmacological treatments. Interestingly, caregivers coping was associated with benzodiazepines use, possibly mediated by the idea to have a tool to personally manage BPSD (above all sleep disturbances).

Conclusions: The BPSD-SINDEM-scale can be an innovative instrument for BPSD assessment, considering both clinician's observation and caregivers' perception. The results from this new scale are consistently associated with pharmacological treatments. These findings suggest that the BPSD-SINDEM-scale can represent a valid tool to better manage these distressful symptoms in the clinical context.

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## IMPROVING THE DETECTION OF SUBJECTIVE COGNITIVE DECLINE USING NOVEL NEUROPSYCHOLOGICAL TEST PARADIGMS

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Background: Subjective Cognitive Decline (SCD) is defined as a self-experienced persistent decline in cognition relative to previous levels of functioning, in the context of normal performance on standard neuropsychological tests and preserved activities of daily living. A consistent body of evidence indicates that SCD represents a risk factor for cognitive decline and dementia, in that it is associated with higher rate of conversion to MCI and AD as compared to the general population and with an improved likelihood of positive biomarkers and neurodegeneration consistent with AD pathology. Since traditional neuropsychological tests for the evaluation of cognitive impairment have remained largely unchanged for decades, identifying novel cognitive measures that are sensitive enough to objectively detect the subtle cognitive decline associated with AD pathology has become even more crucial for identifying individuals at risk, monitoring disease progression, and ascertaining treatment efficacy.

Objectives: In this light, here we investigated the diagnostic accuracy of novel neuropsychological testing paradigms (which have been proposed as potentially challenging tools for the identification of preclinical AD) in capturing the subtle cognitive changes leading to SCD but not objectively detected by traditional tests.

Methods: The performances of 28 patients with SCD and 28 age and education-matched healthy individuals with no worries of cognitive decline (healthy controls, HC) was compared on demanding tasks that investigated, respectively, associative memory, memory binding, spatial pattern separation processes and semantic memory. The diagnostic power and accuracy parameters of these tests in classifying cognitive status (SCD vs. HC) were calculated. Moreover, possible relationships

between experimental tests and SCD-related worries were investigated using a novel self-report questionnaire designed to assess subjects' global experience of memory decline and the impact of these memory concerns in daily life.

Results: No significant between-group difference was found on the standard neuropsychological tests. Conversely, the performance of patients with SCD and HC differed significantly on specific indexes derived from experimental tasks assessing face–name associative memory and spatial pattern separation. Moreover, these measures correctly classified group membership with good overall accuracy (up to 86%) and were significantly associated with the rate of self-perceived memory functioning.

Conclusions: Our findings suggest that specific measures derived from demanding cognitive paradigms could be sensitive neuropsychological indexes for detecting the subtle cognitive impairment associated with SCD. These observations could be useful for further refining cognitive assessment aimed at early detection of AD.

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## ALONG THE ALZHEIMER'S DISEASE CONTINUUM: EMPATHY IMPAIRMENT IN SUBJECTIVE COGNITIVE DECLINE AND MILD COGNITIVE IMPAIRMENT

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Objectives: Empathy is the ability to understand and to feel what others feel [1]. The aims of our study were to assess empathy deficit along Alzheimer's Disease (AD) continuum, and to explore if changes in empathy might be an early red-flag of AD pathology.

Material and Methods: Forty-five SCD, 83 MCI and 80 AD demented (AD-d) patients underwent evaluation of empathy in both cognitive and affective domains by means of Informer-rated Interpersonal Reactivity Index (perspective taking, PT, and fantasy, FT, for cognitive empathy; empathic concern, EC, and personal distress, PD, for affective empathy) before (T0) and after (T1) cognitive symptoms' onset. Ekman 60 Faces (EK-60F) Test was administered to investigate emotion recognition ability. Twenty-two SCD, 53 MCI and 80 AD underwent CSF biomarker analysis and/or amyloid-PET and were classified as carriers of AD pathology (AP+) when A+/T+ (regardless of N), or non-carriers (AP-) when they were A- (regardless of T and N), or A+/T-/N-, or A+/T-/N+ according to A/T(N) system.

Results: PD-T1 scores were lower in SCD than in MCI (20.13±5.55 vs 24.03±5.76, p=0.002) and AD-d (25.82±5.77, p<0.001). Δ-PD (T0-T1) was significantly lower in AD-d as compared to SCD (-8.17±6.87 vs -2.50±3.08, p<0.001) and to MCI (-5.13±5.21, p=0.003), while Δ-PT (T0-T1) was higher in AD-d than in SCD (5.12±6.11 vs 0.50±3.50, p<0.001) and MCI (2.05±4.71, p=0.001). In SCD Δ-PD (T0-T1) was lower AP+ than in AP- patients (-7.75±2.63 vs -1.81±2.16, p<0.001). In a multivariate linear regression analysis, AP status was the only variable that significantly influenced Δ-PD (T0-T1) (B=-2.96 [95% CI -5.68:-0.24], p=0.033). In MCI and in AD-d, PT scores decreased T0-T1 (MCI z=-3.82, p<0.001, AD-d z=-6.37, p<0.001). PD scores increased T0-T1 in SCD (z=-4.27, p=0.001), MCI (z=-7.06, p<0.001) and AD-d (z=-7.14, p<0.001). AD-d patients showed lower scores in recognition of all facial emotions than MCI and SCD (p<0.001). No differences were detected in EK-60F scores between SCD and MCI, except for lower scores in recognition of fear in MCI than in SCD (3.08±2.38 vs5.11±2.66, p<0.001).

Discussion: A significant decrease of PT seems to start at MCI stage [2]. On the other hand, we confirm that a significant increase in PD starts from SCD stage [3] and seems to be influenced by the presence of an underlying AD pathology alone.

Conclusions: Empathy is impaired in AD and seems to change along the AD continuum. Changes in personal distress might be a predictive feature of a cognitive decline driven by AD pathology.

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## DON'T TOUCH THE FLANKER! A KINEMATIC ANALYSIS OF EYE-HAND MOVEMENTS IN PATIENTS WITH AMNESTIC MCI DUE TO AD

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Objectives: Although severe movement disorders are traditionally considered pathognomonic of an advanced stage of Alzheimer's disease (AD), patients with MCI (PwMCI) seem to exhibit a certain degree of visuomotor perturbations, resulting in slower, less accurate, and less coordinated in performing eye-hand movements than healthy controls [1]. Such visuomotor difficulties would become more pronounced under high cognitively demanding conditions [2]. All the few studies assessing kinematics of reaching movements in MCI have been conducted under poorly ecological conditions (in the absence of visual distractors). Here, we attempted to compensate for this gap.

Materials and Methods: Eleven patients with amnestic MCI due to AD (5 females; M age=72.36 years, SD=7.09; M education=12.55 years, SD=4.32), 10 healthy older adults (HOA, 4 females; M age=66.70 years, SD=5.35; M education=12.40 years, SD=4.19), and 11 healthy young adults (HYA, 5 females; M age=29.92 years, SD=3.20; M education=18.08 years, SD=0.90) participated in this experiment. All were right-handed. The apparatus consisted of a

digitizer and a non-inking electronic stylus. The stimuli were two vertically-aligned dots (starting and target dot). The axis covering the inter-dot distance (200 mm), referred to as reaching axis (RA), could be flanked by a visual distractor, i.e., a small black square (the flanker), arranged to the left at a distance of 1, 3 or 5 mm, with the flanker side midpoint matching the RA midpoint. Participants were instructed to execute, at a natural speed, right-handed movements to reach the target. Movements could be performed with or without the flanker (40 randomized trials). If present, participants were instructed not to "touch" the flanker.

Results: Bonferroni's adjusted mixed design was used. Trajectories significantly deviated away from the flanker location ($F(3,75) = 11.568$, $p<0.001$), with lateral deviations amplitude being a function of the flanker proximity, i.e., the closer the flanker was to the RA, the greater the rightward deviation of trajectories. When the flanker was 1 mm away, a greater constant lateral deviation was recorded in PwMCI (M diff=0.985, $p<0.001$). Also, patients demonstrated reduced movement consistency regardless of the experimental manipulation ($F(2,25) = 4.887$, $p<0.05$). Both HOA and PwMCI were slower in the "flanked" than in control trials, while HYA reached the target dots with the same average speed across all trials.

Discussion: Our findings are in line with the growing prevalent view that a multidimensional assessment involving both cognitive and motor domains should be taken into account for profiling the clinical picture of individuals with suspected MCI-AD.

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## SUPRAMODAL EXECUTIVE ANOSOGNOSIA IN PATIENTS WITH AMNESTIC MCI DUE TO AD

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Objectives: Despite the seemingly established assumption that the prevalence of anosognosia increases as Alzheimer's disease (AD) worsens, recent evidence has suggested that patients with Mild Cognitive Impairment (PwMCI) may demonstrate poor awareness of their memory deficits. Indeed, the presence of memory complaints/concerns is no longer considered a mandatory prerequisite for amnestic MCI diagnosis [1]. Therefore, the detection of anosognosia has important clinical implications. While studies using offline methods (patient-informant discrepancy) converge on the view that mnemonic anosognosia is commonly encountered in MCI, conflicting findings arise from studies assessing metamemory monitoring [2]. Accordingly, we further investigated executive anosognosia in PwMCI.

Materials and Methods: Sixteen patients with a clinical and etiological diagnosis of amnestic MCI due to AD (9 females; M age=72.06 years, SD=6.32; M education=10.06 years, SD=4.88) and 19 healthy controls (HCs, 10 females; M age=68.11 years, SD=5.81; M education=12.05 years, SD=5.24) took part in this experiment. We administered two isomorphic tasks based on either verbal or visuospatial material according to Galeone et al. [3]. Participants were asked to predict their memory performance over three trials, before (pre-study prediction) and after (post-study prediction) the encoding session. Specifically, they were instructed to rate how many words from a 10-word list, and how many of five spatial positions from a 6x6 random matrix configuration, they would have memorized, respectively.

Results: A Bonferroni-adjusted 2x3x3 mixed factorial design (2 groups vs. 3 trials vs. response type, i.e., pre-study, post-study, recall) was applied. In the verbal task, all participants overestimated their memory performance at both pre- (M diff=1.351, $p<0.001$) and post-study (M diff=0.961, $p<0.001$). While overestimation of HCs was quite negligible (M diff=0.868, $p<0.05$), PwMCI claimed to remember about 1.5 more words than they actually did ($p<0.001$). In the visuospatial task, all participants revised upward their predictions after viewing the spatial matrices (M diff=0.353, $p=0.04$), exhibiting a sort of overconfidence bias. However, PwMCI demonstrated a higher degree of overestimation (M diff=1.813, $p<0.001$) than HCs (M diff=0.772, $p=0.002$). Interestingly, PwMCI substantially revised upward their predictions in the third/last attempt, which is a potential marker of executive anosognosia.

Discussion: PwMCI due to AD may suffer from supramodal executive anosognosia, i.e., unaffected by the type of material to be encoded. Results from this study may support the change of course of international guidelines in the direction of removing the "categorical imperative" of subjective memory complaints/concerns from the criteria used to make diagnosis of amnestic MCI.

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## MONOAMINERGIC NETWORK ABNORMALITIES EXPLAIN FATIGUE IN PEDIATRIC MULTIPLE SCLEROSIS

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Objectives: Although fatigue is frequently observed in pediatric multiple sclerosis (pedMS), little is known about its pathological substrates in these patients. The aim of this study is to investigate monoaminergic network abnormalities in pedMS patients according to their fatigue status through a positron emission tomography (PET)-based constrained independent component analysis (ICA) on resting state (RS) functional MRI (fMRI).

Material and Methods: Fifty-five right-handed pedMS and 23 matched pediatric healthy controls (HC) underwent neurological,

fatigue, depression and RS fMRI assessment. Patients were classified as fatigued (F) or non-fatigued (nF) according to their fatigue severity scale (FSS) score. Patterns of dopamine-, noradrenaline- and serotonin-related RS functional connectivity (FC) were derived by ICA, constrained to PET atlases for dopamine, norepinephrine and serotonin transporters, obtained in HCs' brain.

Results: None of pedMS patients had depression and fifteen of them were F. Compared to nF pedMS patients and HC, F pedMS patients showed decreased dopamine-related RS FC in the right postcentral gyrus. In addition, F pedMS patients showed decreased dopamine-related RS FC in the left insula vs HC and increased dopamine-related RS FC in the left middle temporal gyrus and cerebellar lobule VI vs nF pedMS. In the noradrenaline-related network, F pedMS patients showed decreased RS FC in the left superior parietal lobule and increased RS FC in the right thalamus compared to HC and nF pedMS. In addition, F pedMS patients showed decreased RS FC in the right calcarine cortex and increased RS FC in the right middle frontal gyrus vs HC. Finally, in the serotonin-related network, F pedMS patients showed decreased RS FC in the right angular gyrus and increased RS FC in the right postcentral gyrus vs nF MS patients and HC.

Discussion: PedMS patients with fatigue showed diffuse dysregulation in the monoaminergic networks of sensorimotor areas, such as the primary sensorimotor cortex, as well as of cortico-subcortical circuits, including thalamus and cerebellum, which are part of the sensorimotor network and are central to motor planning and execution.

Conclusions: Our findings may provide a pathological marker for fatigue and putative targets for its treatment in pedMS population.

## DEVELOPMENT OF DEPRESSIVE SYMPTOMS AND RESTING STATE FUNCTIONAL CONNECTIVITY MODIFICATIONS IN MONOAMINERGIC NETWORKS IN MULTIPLE SCLEROSIS

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Objectives: Growing pieces of evidence suggest that depression in multiple sclerosis (MS) patients might have a neurobiological basis rather than being a mere consequence of disability accumulation. Here, we investigated whether the development of depressive symptoms in MS was associated with changes of resting state functional connectivity (RS FC) within monoaminergic networks.

Materials and Methods: Forty-nine MS patients and 27 healthy controls (HC) underwent clinical and 3.0 T RS functional MRI assessment at baseline and after a median follow-up of 1.6 years (interquartile range=1.0-2.1 years). Depressive symptoms were evaluated using the Montgomery-Asberg Depression Scale (MADRS). MS patients were included if their baseline MADRS was <9 (i.e., no depression). Monoaminergic network-related RS FC was derived by independent component analysis, constrained to PET atlases for dopamine, noradrenaline and serotonin transporters.

Results: Fourteen (29%) MS patients developed depressive (D) symptoms at follow-up, while 35 (71%) remained not depressed (ND). At baseline, MS patients showed decreased RS FC vs HC in all three PET-guided monoaminergic networks in frontal, cingulate and cerebellar cortices, and increased RS FC in parieto-occipital regions. HC showed no significant RS FC changes over time, while ND-MS patients showed limited RS FC changes over time. Conversely, D-MS patients showed a widespread RS FC decrease over time in the PET-guided dopamine network, mainly in orbitofrontal, middle occipital, anterior cingulate and precuneal cortices (all significant at time-by-group interaction analysis), and in calcarine/lingual cortices. They also presented decreased RS FC over time in parahippocampal and occipital regions of the PET-guided noradrenaline network. In MS patients, increased MADRS scores over time correlated with decreased RS FC in the right precuneus ($r=-0.65$, $p<0.001$) of the dopamine network and in parahippocampal gyrus ($r=-0.61$, $p<0.001$) of the noradrenaline network.

Discussion: The results showed that MS patients who developed depressive symptoms exhibited significant decreased RS FC in multiple regions within the PET-guided dopamine and noradrenaline networks. These findings highlight the potential neurobiological basis of depression in MS and emphasize the importance of considering the underlying neural mechanisms when addressing depressive symptoms in MS patients.

Conclusions: RS FC alterations within the monoaminergic networks may contribute to the development of depression in MS.

## GERSTMANN SYNDROME WITH ACUTE, SUBACUTE, AND INSIDIOUS ONSET. A SYSTEMATIC REVIEW AND INDIVIDUAL PATIENT DATA ANALYSIS

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Gerstmann syndrome (GS) is a rare neurological condition featuring agraphia, acalculia, finger agnosia, and left-right disorientation. Many pathological conditions, such as focal brain injuries (e.g., stroke, trauma, or tumors) and neurodegenerative diseases, can lead to GS. In this systematic review, we compared the features of GS cases with acute, subacute, and insidious onset. Eighty-eight patients were selected (M 63.6%, mean onset age: 55.2±15.8). Acute onset was the most common presentation of GS (40.9%), followed by the insidious one (39.8%), while the subacute cases were less frequent (19.3%). Of the 36 acute cases of GS, 44.4 % were caused by ischemic strokes, 41.6 % by brain hemorrhages, 5.5 % by brain tumors, and 8.3% by other conditions. Among the 17 subacute cases, 47.0% were associated with brain tumors, 17.6% with encephalitis, and 35.3% with other conditions. Of the 35 cases with insidious progression, 62.8 % were due to neurodegenerative disorders, 14.3% to brain tumors, 2.8 % to encephalitis, and 20.0% to other conditions. Interestingly, patients with subacute onset of GS were younger (49±18,2 yo) than the other two groups (acute onset: 58,9± 14,6 yo; insidious onset: 55,4±15,2). Furthermore, the three categories showed differences in clinical features and concomitant cognitive and non-cognitive symptoms, possibly due to different compensatory mechanisms ensuing in subacute and insidious progressions. Finally, we analyzed and compared the differences among etiological subgroups (vascular, neurodegenerative, tumor-related) to highlight distinctive features.

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## COGNITIVE FUNCTION IN NON-RELAPSING MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY ASSOCIATED DISEASE (MOGAD): A CASE SERIES

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Background: MOGAD is an inflammatory antibody-mediated disease, affecting both white and grey matter of CNS. It is more frequent in children and young adults. The clinical course can be either monophasic or relapsing, often with complete recovery. To date, only few studies explored cognitive functions in patients with MOGAD. Patients with relapsing MOGAD have recently been reported to have impaired reasoning skills and overall response time, compared to healthy controls. Aims: To assess cognitive performance in a small cohort of six patients with non-relapsing MOGAD.

Materials and Methods: Six patients with non-relapsing MOGAD were included (4F:2M, mean age 29.6 years). We assessed cognitive functions with the Rao's Brief Repeatable Battery and the Stroop test after at least twelve months from recovery (follow-up=28.3±16.9 months). All test results were adjusted for age, sex and education and converted to Z scores. Patients who failed two tests or more (Z score <-1.5) were defined cognitively impaired (CI).

Results: As clinical manifestation at onset, three patients had acute disseminated encephalomyelitis (ADEM), one had cortical encephalitis with seizures, and two had optic neuritis. Clinical recovery occurred in all patients (mean EDSS at follow-up 1.5). After the first event, no patient experienced relapses, without any further treatment. Improvement in lesions volume on MRI during follow-up occurred in all cases, without new lesions. Cognitive assessment did not reveal CI patients. Discussion: Differently from patients with relapsing MOGAD, in our non-relapsing cohort no patients failed any cognitive tests. These data could suggest that the relapsing course could be a risk factor for the development of long-term cognitive impairment in patients with MOGAD.

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## FRAILTY IN ATRIAL FIBRILLATION: IMPACT OF SOCIODEMOGRAPHIC AND COGNITION IN A COHORT OF OLDER PATIENTS ON ORAL ANTICOAGULANTS: STRAT-AF 2 STUDY

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Background and Aims: Frailty is a condition of higher vulnerability to stressful stimuli, characterized by poor homeostatic resolution and reduced resistance to stressors representing one of the most problematic expressions of population aging. In patients with atrial fibrillation (AF), frailty is associated with increased stroke incidence, length of hospitalization, and mortality. In a cohort of older AF patients on oral anticoagulants (OAC), we evaluated: the prevalence of frailty and its association with sociodemographic, psychological, cognitive, clinical, functional, and motor dimensions.

Methods: Strat-AF 2 is an observational prospective study that enrolled patients with AF, age ≥65 years, on OAC. All patients were evaluated by means of a comprehensive standardized protocol, and frailty was assessed using the 5 criteria of the Fried phenotype: weight loss, grip strength, walking speed, exhaustion, and physical activity. Each patient was categorized as robust (no criterion), pre-frail (1-2 criteria), and frail (≥3 criteria).

Results: Out of the 171 enrolled patients (mean age 77.7±8.8, 41% females), 12 (7%) were classified as frail, 70 (41%) pre-frail, and 89 (52%) robust. Compared with robust and pre-frail patients, frail ones were significantly older (75.9±10.2, 78.9±6.2, 83.4±7.3, p=.003, respectively), less educated (10.5±4.5, 10.4±4.5, 5.9±1.7, p=.001), mostly women (28%, 49%, 92%, p=.001), and more frequently not married (18%, 27%, 50%, p=.037) and living alone (12%, 21%, 42%, p=.030). Frail patients presented also higher presence of depressive symptoms (Geriatric Depression Scale: 3.2±2.8, 3.9±3.1, 7.7±3.7, p=.001), psychiatric disorders (42%, 50%, 83%, p=.023), and cognitive impairment (40%, 51%, 83%, p=.015), compared to robust and pre-frail ones, as well as reduced cognitive efficiency in memory (Short Story: 14.5±4.9, 13.9±4.6, 9.6±3.5, p=.004) and executive functions (Stroop execution time: 24±20.3, 29.7±32.1, 60.7±40.2, p=.001). As expected, functional and motor status was worse in frail patients, while comorbidities and vascular risk factors were not different among the 3 phenotypes.

Discussion: In our cohort of older AF patients, frailty was mainly and strongly associated with unfavorable sociodemographic, psychological and cognitive characteristics, stressing the fact that frailty is a real multidimensional construct. Further studies are needed to explore the multifaceted nature of frailty syndrome beyond its physical dimension.

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## USEFULNESS OF PERSONALITY INVENTORY FOR DSM-5 IN SUBJECTS WITH MESIAL TEMPORAL LOBE EPILEPSY AND PSYCHOGENIC NONEPILEPTIC SEIZURES

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Aims: The 5th version of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) introduced a new dimensional, trait-based approach in the Section III to become an emerging model for personality disorders (PDs) [1]. In this work we assessed personality psychopathology through the instrument of personality Inventory for DSM-5 (PID-5) [1] in subjects with mesial temporal lobe epilepsy (MTLE), Psychogenic Nonepileptic Seizures (PNES) and healthy controls (HC).

Material: We consecutively enrolled 30 MTLE patients (female: 18/30; mean age: 43±14.3 years), 36 subjects affected by PNES (female: 25/36; mean age: 41±14.1 years) and 25 HC (female: 15/25; mean age: 32.7±10 years), matched for age and gender.

Methods: In all three groups, the neuropsychiatric evaluation provided Beck Depression Inventory-2 (BDI-2), estimating the severity of depressive symptoms; State-Trait Anxiety Inventory (STAI), measuring state (STAI-S) and trait (STAI-T) anxiety; Toronto Alexithymia Scale (TAS-20), testing alexithymia; PID-5 assessing the pathology model proposed in Criterion B of DSM-5 Section III. Differences among three groups were demonstrated through ANOVA and Kruskal–Wallis test by ranks for normally and not-normally distributed values, respectively.

Results: We found a statistically significant difference in the following PID-5 trait facets: i) Anxiousness ($p=0.014$), showing the PNES group higher values than HC ($p=0.014$); ii) Emotional lability ($p=0.023$), manifesting PNES greater values than HC ($p=0.006$); iii) Impulsivity ($p=0.007$), having PNES higher values than HC ($p=0.002$) and lower than MTLE ($p=0.046$); iv) Cognitive and perceptual dysregulation ($p=0.011$), with greater values in PNES ($p=0.016$) and MTLE ($p=0.005$) groups compared to HC; v) Perseveration ($p=0.037$), with greater values in PNES ($p=0.044$) and MTLE ($p=0.014$) subjects compared to HC. Moreover, we demonstrated a significant difference in Disinhibition PID-5 domain ($p=0.023$), having PNES higher values than HC ($p=0.023$). A statistical difference was proved in STAI-S ($p<0.001$), STAI-T ($p<0.001$) and BDI-2 ($p<0.001$) with higher values in PNES ($p<0.001$) and MTLE ($p<0.001$) groups compared to HC as well as in TAS-20 ($p=0.002$), with greater values in PNES subjects than MTLE ($p=0.001$).

Discussion: In our work, PNES subjects exhibited some personality traits considered as predictive of Borderline PD[1] using the latest tool for fulfil DSM-5 criterion B, as Disinhibition, Anxiousness, Emotional lability, and Impulsivity. Concomitantly, although not satisfying the criteria for a specific PD, MTLE patients manifested aspects of Perseveration and Cognitive and perceptual dysregulation.

Conclusions: Our results contribute to delineate personality profile in MTLE[2] and PNES[3] subjects, in whom assessment of pathological personality traits could have relevant clinical implication in diagnosis and therapeutic intervention.

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## EVALUATION OF CAREGIVERS BURDEN IN MULTIPLE SCLEROSIS

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Background: Patients with multiple sclerosis (pwMS) experience an accumulation of disability through a worsening of clinical conditions associated with relapses or through relapse-independent progression. Therefore, many patients need for greater assistance which in the most dramatic cases also concerns the activities of daily life such as dressing, feeding or washing [1].

Aims: To evaluate the impact of disability and disease severity on caregivers of pwMS.

Methods: 148 subjects, 74 patients and 74 caregivers were enrolled. The caregivers were evaluated through two questionnaires, the Hospital Anxiety and the Depression Scale (HADS) and Caregiver Burdy Inventory (CBI), in order to explore the physical and psychological burden of their cares to the patients. We collected demographic data and level of education for each caregiver, and severity of disability assessed by EDSS, disease duration, form of disease (relapsing-remitting (RR) or progressive) and treatment for each patient.

Results: We found that the caregivers of RR pwMS were more frequently male, while for progressive patient the caregivers resulted more often a woman. A higher level of education was found for caregivers of RR pwMS (median [IQR] 13 [12-16] vs 8 [8-13], $p=0.001$). Burden between caregivers of RR pwMS and progressive pwMS was higher in the second group both at HADS ($7.4 \pm 6.3$ vs $12.3 \pm 6.7$, $p<0.002$) and CBI ($8.5 \pm 10.4$ vs $22.4 \pm 16.8$, $p<0.0001$). In particular, caregivers of progressive patients spend much more on patient care as evaluated by Time-dependence burden in CBI (mean value ± SD was $9.9 \pm 6.6$ vs $2.9 \pm 4.5$ $p<0.0001$) and need more to rest.

Discussion and Conclusions: Our study showed that caregivers of pwMS experience high levels of anxiety and depression. In particular, caregivers of progressive patients spent much time on patients care and are a high risk of depression, anxiety and burnout.

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## COGNITIVE IMPAIRMENT IS ASSOCIATED WITH GAIT VARIABILITY AND FALL RISK IN AMYOTROPHIC LATERAL SCLEROSIS

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Background: In amyotrophic lateral sclerosis (ALS), gait abnormalities contribute to poor mobility and represent a relevant risk for falls. To

date, gait studies in ALS patients focused on the motor dimension of the disease, underestimating the cognitive aspects.

Materials and Methods: Using a wearable gait analysis device, we compared gait patterns in ambulatory ALS patients with Mild Cognitive Impairment (ALS MCI+; n=18), and without MCI (ALS MCI-; n=24), and healthy individuals (HS; n=16) under two conditions: (1) normal gait (single task), (2) walking while counting backward (dual task). Finally, we examined if the occurrence and number of falls in the three months following the baseline test were related to cognition.

Results and Discussion: In the single task condition, ALS patients, regardless of cognition, displayed higher gait variability than HS, especially for stance and swing time ($p< 0.001$). The dual task condition revealed additional differences in gait variability parameters between ALS MCI+ and ALS MCI- for cadence ($p=0.005$), stance time ($p=0.04$), swing time ($p=0.04$) and stability index ($p=0.02$). Moreover, ALS MCI+ showed a higher occurrence ($p=0.001$) and number of falls ($p<0.001$) at the follow-up. Regression analyses demonstrated that MCI condition predicted the occurrence of future falls ($\beta= 3.649$ $p= 0.01$) and, together with executive dysfunction, was associated with the number of falls (cognitive impairment: $\beta= 0.63$; $p<0.001$; executive dysfunction: $\beta= 0.39$; $p= 0.03$), regardless of motor impairment at clinical examination.

Conclusion: In ALS, MCI is associated with exaggerated gait variability and predicts the occurrence and number of short-term falls, independent of motor impairment.

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## "SOMEWHERE BETWEEN AN ACTUAL DISEASE AND A DISEASE": A GROUNDED THEORY STUDY ON COMPREHENDING FUNCTIONAL NEUROLOGICAL DISORDERS DIAGNOSIS IN AN ITALIAN HOSPITAL


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Aims: Functional neurological disorders (FNDs) refer to several conditions characterised by sensorimotor or cognitive symptoms. For long interpreted as psychogenic, FNDs are increasingly explained through complex models of the interrelation of biological, psychological and social factors. Studies suggest how uncertainty and discrepancies about the diagnosis and the appropriate treatments persist.

Materials: We designed a constructivist Grounded Theory (GT) study to explore the generative questions: "1- How are FNDs understood by health professionals (HPs) and patients and 2- how does that affect the care pathway?".

Methods: The study was conducted in the provincial hospital of Reggio Emilia in Northern Italy, part of the Local Health Authority (Azienda USL-IRCCS di Reggio Emilia). We recruited the participants from the Neurology Department. We performed an initial sampling and a theoretical sampling. Before the initial sampling, a kick-off meeting with all the neurologists recruiters was organised, then seven patients and seventeen HPs were interviewed. We conducted semi-structured interviews: we pre-planned the interview guides, one for patients and one for HP.

Results: Through conceptual data analysis, we generated a theoretical model to explore our questions along four phases: 1- the onset of the symptoms, 2- access to health services, 3- labelling the disease and 4- treatment proposal. We systematised the model into a core category: "negotiating the multiple ontologies of medical practice", and three sub-categories: i) defining the disease, ii) exposing reductionisms, iii) emergence of a pluralist vision.

Discussion: The care process of FNDs arose at the intersection of different ways to understand the problem. Various barriers to the effective delivery of care depended on the way the disease is thought of and defined based on a reductionist mindset that "flattens" it on the body or the mind. Both HPs and the patients felt the need for a more integrated understanding and management of FNDs.

Conclusions: We suggest that proper attention should be given to improve provider-patient communication to build a therapeutic alliance and provide HPs with training on the clinical and relational components of FNDs. Structured multi-professional care pathways must be developed based on integrated biopsychosocial etiological models.

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## THE CARE PATHWAYS BEYOND MEDICAL ASPECTS THAT ARE OFFERED TO PATIENTS DIAGNOSED WITH FUNCTIONAL NEUROLOGICAL DISORDER. A SCOPING REVIEW


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Aims: The interpretation of care pathways for non-medical issues of Functional Neurological Disorders (FNDs) is challenging. A comprehensive understanding of the illness, considering the interaction between psychological, social, and biological factors, should be promoted to better support non-medical treatment strategies for FNDs. We aimed to map the psycho-social, non-medical interventions targeting FNDs, identifying existing knowledge and major areas of interest.

Materials: We adopted the Scoping Review methodology to provide a comprehensive understanding of how to effectively support individuals with FNDs beyond physical complaints. The final review question

was: "What are the care pathways beyond medical aspects that are offered to patients diagnosed with Functional Neurological Disorder?".

Methods: PPC mnemonic tool (Population, Context, and Concept) was used to define a search strategy. Functional Neurological Disorder patients (Population) and non-medical interventions (Concept) terms were applied. We undertook a comprehensive literature search on electronic databases, plus hand-search, that encompassed a wide range of study designs, from randomized clinical trials to single case reports.

Results: Twenty-eight papers were included. Patients aged approximately 30-50 years old and 68.2% were females. Interventions were usually provided in person at healthcare facilities. Education on the illness, psychotherapy, and treatment adherence improvement were adopted as core intervention strategies to pursue (i) symptoms reduction, (ii) global health status improvement, and (iii) encourage patients' understanding and acceptance of the disorder. Multi-professional care pathways including neurologists, psychiatrists, physiotherapists, occupational therapists, and psychologists were encouraged.

Discussion: By exploring care pathways, a crucial point is to understand how professionals from various disciplines can provide holistic care that meets the patient's needs. Within healthcare facilities, neurological diagnosis is the first step; at this stage, education about the illness is provided to enable patients' understanding and minimize uncertainty. Next, psychiatric consultancy follows, and psychological support or psychotherapy is offered. Patients are then engaged in physiotherapy if motor functionality recovery is needed. Occupational therapy, though helpful to restore daily activities of the individual, is less common. The use of motivational interviewing has been lately evaluated to engage patients in group or individual psychotherapy.

Conclusions: FNDs symptoms can trigger clinically significant distress or impairment in social, occupational, or other important areas of functioning. (Psycho)education is documented as the first-line strategy to give patients a starring role in their own care. Insights about the mind-body connection is supposed to raise awareness of subjective dysfunctional emotional processing and negative appraisals about the disease, with the potential to improve treatment adherence.

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## PSYCHOANALYTIC PSYCHOTHERAPY UNCOVERS VERY HIGH PREVALENCE OF STRESSFUL LIFE EVENTS AT THE ORIGIN OF FUNCTIONAL NEUROLOGICAL DISORDERS

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Objectives: Despite high incidence of adverse life events in patients with functional neurological disorders (FNDs), a considerable proportion of patients report no traumatic events [1,2]. Some difficulties in assessing relevant personal life experiences through standardized evaluations may contribute to the observed variability [3]. We compared the frequency of remote and recent adverse life events assessed by a standardized psychological/psychometric approach and by a brief psychoanalytic intervention (BPI).

Materials and Methods: In 81 newly diagnosed FNDs patients a comprehensive psychological/psychometric assessment of mood, personality disorders, and adverse remote and recent life events was performed using standardized questionnaires (Life Stressor Checklist-R, LSCL-R). Each participant completed 5-8 sessions of psychoanalytic psychotherapy. Psychotherapists, who were blind to psychometric assessment, recorded relevant remote and recent adverse events. To compare the two evaluations, overall agreement, positive and negative percent agreement were calculated along with their 95% exact (Clopper-Pearson) confidence intervals (95% CI). The prevalence of adverse events assessed by the BPI in FNDs patients was compared with a group of 66 patients with organic neurological symptoms and psychological complaints requiring psychotherapy.

Results: Psychological/psychometric evaluation showed a high prevalence of depression (64.2%), state and trait anxiety (59.2% and 71.6% respectively) and personality disorders (10.5%) in patients with FNDs. A high prevalence of remote (54.3%) and recent (39.5%) adverse life events was evidenced, while no adverse events were reported by 33.3% of patients. The BPI identified significant traumatic/adverse life events in 88.9% of patients with FNDs. The BPI and the psychological/psychometric assessment (considered as a non-reference standard) showed a 68% overall agreement (95% exact-CI: 57%; 78%). Among patients reporting adverse events in the psychometric evaluation, the BPI confirmed the finding in a very high proportion of cases (positive percent agreement 93% [95% exact-CI: 82%; 98%]). Conversely the BPI identified a significant traumatic event in 81.5% of patients reporting no adverse life experiences in the psychometric/psychological assessment (negative percent agreement 18% [95% exact-CI: 6%; 38%]). Finally, the prevalence of traumatic events detected during the BPI was significantly higher in FNDs patients than in the control group (88.9% vs 62.1%, p=0.01).

Discussion and Conclusions: An individualized psychoanalytic approach may contribute to a comprehensive evaluation of predisposing or triggering factors in patients with FNDs, revealing a very high prevalence of adverse life experiences. These data could have important implications for the pathogenesis and the treatment of FNDs.

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## THE BRIEF REPEATABLE BATTERY OF NEUROPSYCHOLOGICAL TEST (BRB-N) VERSION A: UPDATE OF ITALIAN NORMATIVE DATA FROM THE ITALIAN NEUROIMAGING NETWORK INITIATIVE (INNI)

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Objectives: Cognitive impairment is a frequent manifestation of MS and significantly affects patients' quality of life. Accurate cognitive assessment is of utmost importance for treatment decisions and understanding disease progression. Several neuropsychological batteries are used in MS, including the Brief Repeatable Battery of Neuropsychological Tests (BRB-N), which includes two versions: A and version B for follow-ups; the Minimal Assessment of Cognitive Function in MS (MACFIMS), and the Brief International Cognitive Assessment for MS (BICAMS). Normative data for version A of the BRB-N in Italy were published in 2006 and are outdated. We aimed to revise and update the normative data for BRB-N version A in the Italian population and standardize demographic correction for BRB-N version A to align with other commonly used neuropsychological batteries in Italy, using consistent statistical methods.

Materials and Methods: 320 healthy subjects aged from 18 to 81 years (161 males and 159 females; mean age: 40.96, standard deviation [SD]= 14.25 years; mean education= 15.30, SD= 4.24 years) were recruited from four Italian sites affiliated with the Italian Neuroimaging Network Initiative (INNI). All participants underwent neuropsychological assessment using the BRB-N version A following standardized procedures. Demographic correction for each test of the BRB-N version A was calculated using a regression-based method relying on scaled scores. To normalize all tests' score distribution, raw scores of BRB-N tests were transformed into a scaled score metric (mean= 10, SD= 3) based on the fractional ranks of each test. Then, the resulting scaled scores were regressed on four demographic variables: centered age (agec = age – age mean), agec2, education level, and sex.

Results: No significant differences were found in age, education, and sex distribution among the four different sites (all $p \geq 0.33$). Regression analysis provided the normative data for calculating demographically adjusted z-scores for each BRB-N version A test.

Discussion: The use of a regression-based method and scaled scores ensures consistency with other commonly used neuropsychological batteries in Italy, namely MACFIMS and BICAMS. This study increases the reliability of neuropsychological testing in assessing cognitive functions of Italian MS patients using the BRB-N version A.

Conclusion: This study provides updated normative data for the BRB-N version A in the Italian population. Updated normative data improve the validity and reliability of neuropsychological testing, providing valuable insights for clinical and research applications. Funding: Partially supported by Fondazione Italiana Sclerosi Multipla (grant FISM2018/S/3), and financed or co-financed with the '5 per mille' public funding.

## AFFECTIVE AND COGNITIVE THEORY OF MIND NETWORKS IN YOUNG HEALTHY INDIVIDUALS

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Objectives: Among social cognition sub-domains, Theory of Mind (ToM) refers to the ability to infer others' beliefs (cognitive ToM) and to understand others' emotions (affective ToM). Despite the identification of several brain areas related to these skills, no definitive consensus has been reached as regards the underlying brain networks, and only a few neuroimaging studies investigated functional connectivity (FC) in non-clinical settings, especially in healthy adults at a young age (before 30 years), when brain circuits are still not affected by aging. We aim to identify core regions specifically and differentially involved in the two networks mediating cognitive and affective ToM in young healthy individuals, as well as to determine overlapping areas of FC.

Materials: 50 young healthy subjects (27 males and 23 females, age: 25.25±2.8, education: 15.5±2.7) underwent resting-state functional MRI (RS-fMRI) and a neuropsychological evaluation.

Methods: Based on a recent metanalysis on healthy middle-aged adults [1], two regions of interest were created as main nodes for affective and cognitive ToM, respectively: left medial prefrontal cortex (lmPFC) and right supramarginal gyrus (rSMG). A seed-based RS-FC analysis was performed between the two nodes, separately, and the rest of the brain.

Results: We observed that the lmPFC FC included an anterior and ventral network encompassing left supplementary motor area, left temporal pole, and, bilaterally, precentral gyrus and insula. On the other hand, the rSMG FC encompassed a more posterior and dorsolateral network including right precuneus, left inferior parietal gyrus and middle occipital gyrus, bilateral angular gyrus, and cerebellum crus I and II. Overlapping brain areas shared by both networks were inferior frontal gyrus, middle temporal gyrus, temporoparietal junction, and anterior cingulate cortex bilaterally.

Discussion: In line with existing literature, seed-based RS-FC analysis revealed two distinct, but interdependent ToM systems. Moreover, the involvement of the cerebellum, observed in cognitive ToM network, has been not frequently reported; however this finding is consistent with a growing body of research suggesting the cerebellar role in non-motor functions and, particularly, in social cognition.

Conclusions: By broadening our understanding of the functional circuitry responsible for ToM abilities in healthy individuals, these findings provide a model to evaluate the integrity of such networks also in a clinical scenario. This knowledge may serve to compare network deterioration across different neurodegenerative diseases, with a preferential application in the Frontotemporal Lobar Degeneration Spectrum of disorders.

Funding: European Research Council (StG-2016_714388_NeuroTRACK); Foundation Research on Alzheimer Disease.

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## DEGENERATIVE DISEASES

## PLASMA BETA-SYNUCLEIN IS A HIGHLY ACCURA TE BIOMARKER FOR THE DIAGNOSIS OF SPORADIC CREUTZFELDT-JAKOB DISEASE

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Background and aims: Beta-synuclein (beta-syn) is an emerging biofluid marker of synaptic damage in neurodegenerative diseases [1,2]. We have recently developed highly sensitive in-house immunoassays for measuring the marker in cerebrospinal fluid (CSF) and blood and reported increased concentrations in patients with prion disease compared to controls and subjects with other neurodegenerative diseases [1,2]. Here, we investigated the diagnostic value of beta-syn compared to that of classic surrogate markers in the context of rapidly progressive dementia (RPD), as well as beta-syn distribution and prognostic performance across sporadic Creutzfeldt-Jakob disease (sCJD) subtypes.

Methods: We analysed CSF and/or plasma beta-syn levels in 150 patients with sCJD, belonging to the most prevalent molecular subtypes [MM(V)1, VV2 and MV2K][3], and in 106 subjects with non-prion RPD. In the same groups, we measured CSF total tau protein (t-tau), CSF 14-3-3 protein, plasma tau and plasma neurofilament light chain protein (NfL). We assessed the diagnostic performance of all biomarkers and the possible associations between CSF/plasma beta-syn and survival in patients with sCJD.

Results: sCJD subjects demonstrated higher CSF and plasma beta-syn levels compared to non-prion RPD patients ($p<0.001$ for both). sCJD molecular subtypes showed different patterns of CSF and blood beta-syn. In the differential diagnosis between sCJD and non-prion RPD, CSF beta-syn outperformed 14-3-3 (AUC 0.95 vs. 0.89, $p=0.028$) but not t-tau (AUC 0.92, $p=0.212$). Moreover, the diagnostic value of plasma beta-syn (AUC 0.91) was superior to that of plasma tau (AUC 0.79, $p=0.001$) and plasma NfL (AUC 0.65, $p<0.001$) and not inferior to that of CSF markers (t-tau, $p=0.765$; 14-3-3, $p=0.447$; CSF beta-syn $p=0.135$). CSF and plasma beta-syn were significantly related to survival in sCJD after accounting for PRNP codon 129 genotype.

Discussion and conclusions: CSF beta-syn might be an alternative first-level diagnostic test in patients with RPD. Further, the comparable performance of plasma beta-syn to that of classic CSF surrogate markers suggests that beta-syn might represent the first highly accurate blood marker for the diagnosis of sCJD in vivo. Moreover, CSF and blood beta-syn might ameliorate stratification and prognostication of patients with sCJD.

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## COGNITIVE, BEHAVIOURAL AND MOTOR IMPAIRMENT: COMPARISON BETWEEN FRONTOTEMPORAL DEMENTIA, LEWY BODY DEMENTIA, ALZHEIMER'S DISEASE AND PROGRESSIVE SUPRANUCLEAR PALSY

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Introduction: Neurodegenerative disorders are a heterogeneous group of diseases that involve different anatomical systems, resulting in various clinical phenotypes. In addition to cognitive symptoms, behavioural and motor manifestations also play a crucial role in the diagnosis, having different impact on daily life of patients, leading to a gradual loss of functional independence.

Objective: The aim of this study is to describe motor, cognitive, and behavioural differences among different types of dementia.

Methods: Four groups of patients were used for the analysis: frontotemporal dementia (FTD spectrum), Lewy body dementia (LBD), progressive supranuclear palsy (PSP) and mild cognitive impairment/Alzheimer's disease (MCI/AD). An extensive battery of cognitive and behavioural tests was administered, including Montreal Cognitive Assessment (MOCA) scale and Neuropsychiatric Inventory (NPI) scale. The motor burden was calculated using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS III). Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL) and Schwab and England Activities of Daily Living Scale (S&E) were used to assess functional autonomy. The comparison between groups was performed using analysis of variance (ANOVA) and post hoc tests.

Results: Sixty-three patients were included in the study (24 FTD, 8 LBD, 11 MCI/AD, 20 PSP). The population was homogeneous in terms of age, disease duration and level of education. Significant differences of MDS-UPDRS III were found among the groups ($p<0.05$). Specifically, PSP patients exhibited the highest motor burden, while MCI/AD patients had the lowest. MOCA scores were lower in LBD compared to other types of dementia. All LBDs had a score below the median value of the MOCA, compared to 61.1% of FTDs, 40% of MCI/ADs and 26.7% of PSPs. No significant differences were observed among others neuropsychological tests. According to NPI scale, groups vary in their tendency to develop depression ($p<0.05$), with a higher prevalence observed in patients with FTD and PSP. ADL and IADL significantly differ among the groups ($p<0.05$), with PSPs exhibiting the lowest scores. The score on the S&E scale was higher in the MCI/AD group compared to LBD and PSP groups ($p<0.05$).

Discussion and Conclusion: As expected, PSP presented the greatest motor burden with the major impact on ADL and IADL. Global cognition assessed with the MOCA showed worse scores in LBD. Meanwhile, MCI/AD presented lower disease disability measured with S&E compared to other types of dementia. Finally, the behavioural burden assessed with NPI was greater in FTD spectrum and PSP.

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## ACCEPTANCE TO INVASIVE THERAPIES: IMPLEMENTATION OF LAW 219/2017 FOR AMYOTROPHIC LATERAL SCLEROSIS PATIENTS IN PALLIATIVE CARE

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Objectives: Our study evaluate Amyotrophic Lateral Sclerosis (ALS) patient acceptance to invasive therapies (PEG, Trachestomy) after admission to Palliative Care Unit, analyzing inpatient and outpatient medical records between January 2020 and March 2023 by multiprofessional team approach.

Material: Patients admitted to palliative care average 19.6/year. 90% of cases are sporadic, 10% are familial. The male to female

ratio is 2:1. Mean age of onset of enrolled patients is 64 years. On 2020, 87 patients were admitted and 22 patients died during the year; on 2021, 74 patients and 12 deceased; on 2022, 82 patients and 22 deceased; on 2023, 70 patients, 5 admissions.

Methods: Patients sign an informed consent regarding preference on advanced therapies, i.e. the PAC (Implementation Path of Certifiability), as well as express their wishes on the end of life (DAT Advance Treatment Provisions). Multidisciplinary meeting draw up a PAI (individual Assistance Project) determining patient needs at disease progression. Professional figures involved: 1 neurologist, 2 pulmonologists, 1 medical nutritionist, 1 speech therapist, 1 dietician, 1 health coordination manager, nursing staff.

Results: On 2020, there were 87 patients, 10 with PEG died on average after 8 months; 8 with tracheostomy died on average after 12 months; on 2021, 74 patients, 12 with PEG died and 10 with tracheostomy died on average after 10 months; on 2022, 82 , 10 with PEG died after 10 months, 6 with tracheostomy died after 8 months on average; on January February and March 2023, 70 patients including 13 with tracheostomy and 13 with PEG, 1 patient with naso-gastric tube. Patients who undergo invasive therapies have a median survival of 5 months. Non-invasive therapies have median survival of 3 months. Patients between 36 and 39 years are 2%; between 40 and 50 years are 12% and 20% accepted invasive therapies; patients aged between 51 and 60 years are 23%, 13% accepted invasive therapies; between 61 and 90 years are 63% and 6% accepted invasive therapies.

Discussion: We observed a 10% decline in adherence to invasive therapies over time and as age increases. We highlight greater acceptance of PEG compared with tracheostomy.

Conclusions: Patients must explicit their wills at the time of diagnosis. Decisions on medical treatments [1] in advanced stage and on end-of-life best quality of life must be based on respect for personal dignity and on self-determination.

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## MICROSTATES IN MULTIPLE SCLEROSIS: AN ELECTROPHYSIOLOGICAL SIGNATURE OF ALTERED HUBS FUNCTIONING?

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Objectives: Multiple sclerosis (MS) has variable disease course with disabling symptoms even in absence of a high lesional load. Resting-state (RS) fMRI studies have shown changes in the large-scale brain networks in MS. However, these rearrangements are still debated. In this study, we aimed to investigate the temporal dynamic of large-scale networks in RS-condition by high-density EEG (hdEEG) in relapsing-remitting MS (RRMS) patients compared with healthy subjects (HCs). We pointed to identify a specific set of microstates in both populations and to correlate their activity with clinical and neuropsychological parameters.

Materials and Methods: We enrolled 50 patients with RRMS and 24 HCs, matched for age and gender. All patients performed the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS); clinical details were also collected. Each participant underwent to hdEEG with 256-channels in RS-condition and we analyzed 15min. of free-artifact segments. Microstates analysis [1] consisted in a k-mean cluster analysis that permitted to identify the most representative topographical maps, which best explain the variance of the RS-hdEEG. Then, these maps were back-fitted on the artifact-free EEG and for each map was computed: mean duration, time coverage, frequency and the global explained variance (GEV). As reported in literature, these microstates were associate to well-known brain networks: auditory (Map-A), visual (Map-B), salience (Map-C/F), attention (Map-D), default mode networks (Map-C/E) [2,3]. Repeated measures two-way ANOVA was run to compare microstates parameters. Pearsons's correlation and stepwise multiple linear regression were performed between clinical and neuropsychological data; alpha=0.05.

Results: Six templates were found across all subjects. A significant increase of temporal dynamic of Map-A ($p<0.001$), B ($p<0.001$) and E ($p<0.001$) and decrease of Map-D ($p<0.001$) and F ($p<0.001$) were observed in patients than controls. The correlation analysis revealed a moderate significant correlation between disease duration and mean duration of Map A ($p<0.05$). A cognitive impairment was also detected in 8% of patients with MS and it was found a strong prediction of Symbol Digit Modalities Test (SDMT) score by the temporal activity of Map-A ($p=0.017$; 11.2%).

Discussion: These findings showed a peculiar increase/decrease pattern of the microstates' activation as also reported in RS functional connectivity studies. The association between SDMT and Map-A may suggest a possible marker of overt cognitive dysfunctions.

Conclusion: The hdEEG microstate analysis offers a new and advanced perspective of large-scale networks functioning in multiple sclerosis patients, indicating a possible electrophysiological signature of brain reorganization.

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## ENTRAINING BRAIN OSCILLATORY ACTIVITY AT ALPHA FREQUENCIES IN DEMENTIA WITH LEWY BODIES

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Objectives: Dementia with Lewy bodies (DLB) is characterized by a marked shift of electroencephalographic (EEG) power and dominant rhythm, from the alpha towards the theta frequency range. Transcranial alternate current stimulation (tACS) is a novel non-invasive brain stimulation technique that allows entrainment of cerebral oscillations at desired frequencies. The objective of the present study was to evaluate safety and efficacy of occipital alpha tACS in DLB patients.

Methods: We performed a double-blind, randomized, sham-controlled, cross-over clinical trial in 12 DLB patients. Patients were randomized to receive real (60 minutes of 3 mA peak-to-peak stimulation at 12 Hz) or sham stimulation over the occipital cortex (Oz according to the 10-20 international EEG system). Patients underwent clinical evaluation (clock-drawing test, trail-making test part A and B, the quantitative pentagon drawing test subitem), neurophysiological assessment (short-latency afferent inhibition to evaluate cholinergic circuits) and EEG recordings, at baseline and after real/sham stimulation.

Results: Occipital alpha tACS was safe and well tolerated in all patients. We observed a significant increase in clinical performance scores, in neurophysiological measures of cholinergic transmission and in occipital alpha power spectrum density after real stimulation but not sham stimulation.

Conclusions: Occipital tACS delivered at alpha frequencies may be a novel therapeutic approach in patients with DLB.

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## FROM VISION TO LANGUAGE: NEUROPSYCHOLOGICAL PROFILE IN A COHORT OF PATIENTS WITH POSTERIOR CORTICAL ATROPHY

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Aims: The aim of this study was to analyze the neuropsychological profile of a group of patients with Posterior Cortical Atrophy (PCA), a neurodegenerative syndrome characterized by progressive and relatively selective decline in higher visual processing and other posterior cortical functions, most commonly associated with the histopathological features of Alzheimer's disease (AD). Unlike typical AD, memory, insight and judgement are relatively preserved until latter stages of the disease but patients commonly report early language difficulties. However, some inconsistencies exist among the cognitive features described.

Materials and methods: Clinical features and neuropsychological profile of 20 subjects (13 females) aged between 49 and 71 years (58.8 ± 7.16) with PCA due to AD have been analyzed. Each patient underwent a battery of neuropsychological tests, brain MRI, brain PET with 18-FDG and alternatively amyloid-PET or research for AD biomarkers on CSF. The average time elapsed between reported onset and assessment was 19.80 ± 12.01 months.

Results: The most frequent symptoms reported were unspecified visual impairment (70%), difficulty in objects manipulation (40%), alexia (40%) and increased anxiety (75%). At the extended neurological and neuropsychological evaluation, all patients showed impairment in visual-perceptual and visual-spatial abilities and visuospatial memory, assessed with VOSP (Visual Object Spatial Perception) and Cubes Test respectively. Only one patient complained speech disturbances, but variable language impairment was detected in 70% of patients.

Discussion: Analyzing the neuropsychological profile of this cohort of patients, we found a considerable variability in the language profile. Specifically, in some patients an impairment of semantic verbal fluency was observed, while in others anomia, repetition deficits and difficulty in naming tasks were detected, in agreement with data in literature describing a logopenic phenotype in some groups of PCA. Moreover, an impairment of other cognitive domains, besides the visuospatial one, was observed from the onset. This feature may be explained, on the one hand, by a late diagnosis due to a belated neurological assessment, when an initial impairment of other cognitive domains has already occurred (advanced PCA) and, on the other hand, by supporting the hypothesis of degeneration of a common core network in all AD profiles.

Conclusion: Further studies are needed to characterize the progressive evolution of the neuropsychological profile of PCA, also in relation to the specific phenotype in the PCA spectrum at the onset, and to eventually schedule distinct management strategies for patients who may have different impairment of cognitive abilities over time.

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## CARDIOVASCULAR FACTORS DIRECTLY DRIVE NEURODEGENERATION BUT NOT COGNITIVE DECLINE IN ALZHEIMER'S DISEASE: A LONGITUDINAL STUDY

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Objectives: The heterogeneous course of Alzheimer's Disease (AD) is supported by its multifaceted etiology [1,2]. We first aimed at verifying the association of vascular risk factors with CSF markers of amyloid deposition (p-tau/Aβ42) and neurodegeneration (t-tau), accounting for other factors, namely sex, APOE, and blood-brain-barrier (BBB) integrity measured as Albumin Quotient (Qalb), and stratifying patients according to age-of-onset into early (< 65, EOAD), classic (65-75, COAD), or late (>75, LOAD). Then, we explored their effects on cognitive decline and their interplay with Qalb and neurodegeneration.

Methods: We enrolled 387 patients with a biomarker-based diagnosis of Mild-Cognitive-Impairment (MCI) due to AD. We computed a composite score for 8 vascular risk factors and transformed the output to a 0-to-1 continuous percentage (vascular score, VS). First, we regressed VS on p-tau/Aβ42 and on t-tau, accounting for sex, APOE and Qalb, and repeated the analysis in the subgroups. In a subset of 105 patients, we regressed sex, APOE, Qalb, VS and t-tau on ΔMMSE (negative changes in MMSE at 1 year follow-up) in a multivariate regression. Finally, we tested the indirect association between VS and cognitive decline, using a bias-corrected bootstrapped mediation model to c alculate the indirect effects of t-tau and Qalb as mediators.

Results: No association was found between VS and p-tau/Aβ42 in any group. Instead, we found a positive association with t-tau in the whole sample (β=0.173, p<.001), in EOAD (β=0.264, p=0.016) and LOAD (β=0.350, p<.001), but not in COAD (β=0.042, p=0.580). We also found a negative association of ΔMMSE with Qalb (β=−0.407, p=<.001) and t-tau (β=−0.270, p=0.004), but not with VS (β=−0.040, p=0.662). The mediation model confirmed the absence of global effects of VS on ΔMMSE, despite indirect negative repercussions on ΔMMSE mediated by Qalb (ADE: β=−1.097, p=0.406, ADME: β=−0.678,

p=0.027, total: β=−1.775, p=0.183), but a strong direct positive effect on t-tau, with Qalb acting as a partial negative mediator (ADE: β=293.98, p=0.001, ADME: β=−39.25, p=0.044, total: β=254.74, p=0.006).

Discussion: Vascular risk factors impact the progression of neurodegeneration differently depending on age-of-onset. Higher VS causes a global increase of t-tau, despite the finding of a relative inverse effect, mediated by the increase of BBB permeability. Albeit VS-induced increased t-tau has negative repercussions on ΔMMSE, we found no evidence of a direct role of VS on the progression of cognitive decline. Overall, these results highlight the need to carefully address the actual clinical impact of vascular risk factors in AD.

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## ABNORMAL PRESYNAPTIC DOPAMINERGIC IMAGING IN CORTICOBASAL SYNDROME WITH ALZHEIMER'S DISEASE ETIOLOGY: INSIGHTS FROM A CASE-SERIES

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Introduction: Corticobasal syndrome (CBS) is a heterogeneous condition with various underlying causes. Besides the most prevalent 4R-tauopathy, Alzheimer's disease (AD) accounts for at least 20% of cases [1]. Presynaptic dopaminergic imaging using SPECT or PET has been employed for differential diagnosis due to the clinical overlap among etiologies. However, recent anecdotal evidence has raised doubts about the traditional association of CBS-AD with normal striatal uptake, questioning the sensitivity of dopaminergic imaging in this condition [2]. This case-series describes four patients with CBS attributed to AD pathology, confirmed through cerebrospinal (CSF) or PET assessment, all exhibiting abnormal striatal uptake in presynaptic dopaminergic imaging.

Case-series: We describe four patients (2 females, age 74±9.8 years, MMSE 17.0±4.3), fulfilling the diagnostic criteria for possible or probable CBS(3) with evidence of underlying AD pathology. This was confirmed either through CSF biomarkers (three patients with pathological levels of both amyloid-β42/40 ratio and phosphorilated-Tau) or positive amyloid-PET (one patient) based on the AT(N) framework. The typical asymmetric cortical hypometabolism was consistent with CBS on [18F]FDG PET, extending to the lateral parietal, temporal, and posterior cingulate regions, additionally. Interestingly, they all exhibited abnormal presynaptic dopaminergic imaging (DaT-SPECT in three patients, [18F]Dopa PET in one patient) with the highest magnitude in the most affected hemisphere. No core or suggestive clinical features of a Lewy body disorder (LBD) were detected, except for parkinsonism, after thorough investigation at baseline and follow-up. Furthermore, one patient also had normal cardiac [123I]MIBG scintigraphy.

Discussion: These findings suggest potential disruption of dopaminergic pathway in AD cases presenting with CBS. Given the absence of suggestive features, it is unlikely that the patients in this case series are affected by an LBD, which seldom manifests clinically as CBS, yet it is associated with abnormal dopaminergic imaging and may coexist with AD pathology in nearly half of cases. It is possible that AD-related pathology spreading into the brainstem or striatum may affect the nigro-striatal pathway, leading to abnormal striatal uptake. The suboptimal accuracy of presynaptic dopaminergic imaging and the lack of standardized thresholds for result interpretation in CBS-AD, as well as the absence of validated biomarkers for 4R-tauopathy, further complicate this scenario. This underscores the need for further research to prevent misinterpretation of the underlying etiology of CBS and guide management strategies.

Conclusion: Caution is recommended when using dopaminergic imaging to differentiate between etiologies within the CBS spectrum, as abnormal findings may be associated with either 4R-tauopathy or AD pathology.

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## HEREDITARY SPASTIC PARAPLEGIA 5 (SPG5A) ASSOCIATED WITH LEGG CALVÈ PERTHES SYNDROME

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Case presentation: A 15 years-old patient presented to our clinic after a long history of orthopedic care for avascular necrosis of femur head (Legg-Calvè-Perthes syndrome), complaining in teenage years difficulty with running and coordination tasks in lower limbs. On history she had autoimmune thyroiditis with subclinical hyperthyroidism. Motor stages of development were normally achieved. At a first neurological examination neither weakness or hypotrophy was noted, whereas pyramidal signs and slight hypertonia were observed in lower limbs with bilateral Babinski. Impaired proprioception and vibration senses in lower limbs with sensory ataxia and positive Romberg sign were found. Her parents were not consanguineous. Her maternal grandmother complained walking impairment from young age, stable over the years. We present a case of autosomal recessive SPG5A hereditary spastic paraplegia (HSP) with an unusual association with Legg-Calvè-Perthes syndrome. Possible explanations of effects of abnormal circulating oxysterol levels on avascular necrosis of femur head are provided.

Materials/Methods: Brain and spine MRI, electromyography and somatosensory and motor evoked potentials (SSEP and MEP) were performed. At 18 years old she performed genetic testing with Next Generation Sequencing (NGS).

Results: NGS revealed two heterozygous point mutations in CYP7B1, the pathogenetic variant c.889A>G (p.Thr297Ala) and missense mutation c.1082G>A(Arg361Gln), classified as a VUS. Segregation studies on proband's parents confirmed combined heterozygosity in CYP7B1.Brain and spinal cord MRI excluded inflammatory abnormalities; no cerebellar or cervical cord atrophy were noted. SSEP and MEP were consistent with a pure form of HSP. Electromyography excluded concomitant neuropathies. After five years

of follow-up the proband is clinically stable and she doesn't require any walking aid.

Discussion and Conclusion: We describe a case of SPG5A with two missense mutations in CYP7B1. The c.889A>G variant determines an amino acid substitution in proximity to key binding residues and has already been extensively described in literature in patients with pure HSP [1], whereas c.1082G>A (Arg361Gln) has been only recently reported [2]. This is the first report of a pure HSP associated with Legg Calve Perthes syndrome. Risk factors for this condition are metabolic liver impairment, hypercholesterolemia, hypercoagulability, altered epiphyseal closure, and elevated steroid levels. CYP7B1 mutations can lead to some extent to all of these conditions, by causing decreased levels of cholesterol through the altered acidic pathway in the liver, which also leads to high levels of 27-hydroxysterol, a selective estrogen receptor modulator with multiple effects on cardiovascular system, cholesterol levels, and bone physiologic processes [3].

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## ASSOCIATION OF PLASMA GLIAL FIBRILLARY ACIDIC PROTEIN (GFAP) WITH AD BIOMARKERS

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Objectives: GFAP is a protein expressed by astrocytes in the CNS. Its levels increase in neurodegenerative diseases such as Alzheimer's disease (AD) in both Cerebro Spinal Fluid (CSF) and blood. Nevertheless, few studies explored plasma GFAP in prodromic and preclinical stages of AD. In our cross-sectional study we wanted to demonstrate how the plasma values of NFL and GFAP are able to show with high sensitivity and specificity the presence of Alzheimer's disease in early stages.

Materials and methods: We enrolled 40 patients (11 SCD, 21 MCI, 8 AD dementia). All patients underwent: comprehensive family and clinical history assessment, neurological examination, extensive neuropsychological investigation, ,18F-FDG-PET, CSF biomarkers analysis (Aβ1-42, Aβ1-42/1-40, p-tau, t-tau). Patients were rated according to the ATN system. Blood was collected for measurement of plasma GFAP and NfL concentration and for Apolipoprotein E (APOE) genotype analysis.

Results: SCD and MCI patients were rated based on AD biomarker results as follows: 16 (40.00%, 8 SCD and 8 MCI) had normal AD biomarkers (NB), four patients (10.00 %, 1 SCD and 3 MCI) were carriers of non Alzheimer's pathology (non-AD), 12 patients (30.00%, 2 SCD and 10 MCI) were considered as prodromal AD. All eight patients with clinical diagnosis of AD showed biomarkers consistent with AD and were defined as AD-d (AD-demented). LogGFAP was lower in NB compared to prodromal AD (p=0.003, d=1.463) and AD-d (p=0.002, d=1.695). LogNfL was lower in NB patients than in AD-d (p=0.011, d=1.474). GFAP showed an excellent accuracy in differentiating NB from prodromal AD (AUC=0.901, accuracy=85.71% [95% C.I.=72.75 : 98.67], sensitivity=66.67 [95% C.I.=49.21 : 84.13], specificity=100%) with a cut-off level of 198.13 pg/mL. NfL showed a fair accuracy (AUC=0.718, accuracy=70.37% [95% C.I.=53.46 : 87.28], sensitivity=75.00% [05% C.I.=58.96 : 91.04]), specificity=66.67 [95% C.I.=49.21 : 84.13]) in differentiating between NB and prodromal AD, with a cut-off value of 11.65 pg/mL.

Discussion and conclusions: GFAP showed good accuracy, more than NfL, in differentiating MCI and SCD patients with negative CSF biomarkers from prodromal AD patients. This underlines the possible use of GFAP as an indicator of disease in the very early stages of the disease.

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## SLEEP MICROSTRUCTURE IN PARKINSON'S DISEASE RELATED DEMENTIA: IS CYCLIC ALTERNATING PATTERN A NEUROPHYSIOLOGICAL MARKER OF NEURODEGENERATION?

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Objective: Sleep microstructure, specifically called cyclic alternating pattern or CAP, could be more informative than standard sleep stage scoring about neurophysiological alterations in neurodegenerative diseases. The main aim of this study was to evaluate CAP in PD patients with different degrees of cognitive impairment, in order to provide an objective measure of sleep microstructure alteration and evaluate possible associations with neurodegeneration progression.

Materials: Patients affected by PD with and without cognitive impairment were recruited at the Neurology Units of Hospital Auxologico Piancavallo of Verbania and C. Mondino Institute.

Methods: MCI or dementia diagnosis was based on recommended criteria of Movement Disorder Society task force (Litvan 2011). All

patients underwent an in-lab full-night Video-polysomnography (PSG). CAP scoring of each patient was revised by an evaluator of the Sleep Medicine Unit of Parma.

Results: We recruited 16 PDMCI patients, 16 PD dementia patients (PDD) and 16 PD without cognitive impairment (PD) as control group. All groups were comparable for age and sex. Concerning sleep macrostructure, REM sleep (% of TST) was significantly reduced in PDD compared to PDMCI and PD (p=0,002). CAP rate was significantly reduced in both PDD and PDMCI groups compared to PD and normative values, with a greater decrease in PDD compared to PDMCI and PD. The proportion of CAP A1, A2 and A3 phases were reduced in both PDD and PDMCI groups, and the same trend of reduction in PDD compared to PDMCI was found. Furthermore REM sleep time, CAP rate and related component A1, A2 and A3 phases correlated with both MMSEc and several neuropsychological tests.

Discussion: Despite the small sample size, sleep microstructure proved to add more information about neurodegeneration progression in PD related dementia. In particular, reduction of both A3 and REM sleep in PD related dementia patients is in accordance with Braak's hypothesis. In this view, combined sleep microstructure parameters and total REM sleep time seemed to better correlate with the degree of cognitive impairment.

Conclusion: Cycling alternating pattern could become a non-invasive and cost effective neurophysiological marker in neurodegenerative diseases.

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## A RARE CASE OF DIFFUSE BRAIN CALCIFICATIONS AND LEUKOENCEPHALOPATHY DUE TO BI-ALLELIC MUTATION IN FARSB


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Background: Aminoacyl-tRNA synthetases are essential for the initial stage of protein synthesis and for cellular survival by regulating cellular signalling and metabolism. Phenylalanyl-tRNA synthetase attaches phenylalanine to tRNA and is encoded by two genes: FARSA and FARSB. Biallelic variants in FARSA or FARSB have been implicated in exceedingly rare human diseases characterized by a broad and variable spectrum of multisystem dysfunctions [1,2].

Materials and Methods: A 55-year-old patient came to our attention regarding chronic refractory migraine and recurrent episodes of temporo-spatial disorientation. His medical history was relevant for chronic respiratory failure attributed to pulmonary emphysema and fibrosis with bullous dystrophy, complicated by pneumothorax; splenectomy due to splenic infarction resulting from a thrombosed splenic artery aneurysm. Physical examination revealed skeletal abnormalities, including pectus excavatum, thoracic hyperkyphosis, and dolichostenomelia. Unusual fat distribution was observed in the hips, buttocks, thighs, and forearms, along with cutaneous bullous dystrophy and subcutaneous micronodules. Neurological examination showed diffuse overresponsive osteotendinous reflexes with bilateral Hoffmann sign. A neuropsychological assessment revealed overall poor performance with ideational slowing. Brain MRI examination revealed diffuse and symmetrical calcifications predominantly in the basal nuclei and cerebellum, along with marked leukoencephalopathy. In suspicion of an autosomal recessive form (with unaffected parents and a sister who died suddenly at the age of 27, also with a history of pneumothorax), genetic evaluation was performed. A blood sample was taken for whole-exome sequencing combined with variant analysis within a panel of genes associated with brain calcification disorders.

Results: Two variants of uncertain significance, both in heterozygosity, were identified in the FARSB gene: c.1057C>G (p.Pro353Ala) and c.1394A>C (p.Asn465Thr). To date, no previous descriptions of these variants exist. They are not present in population database (GnomAd, ExAC) and they are predicted to be deleterious by different bioinformatics tools. Moreover, the clinical phenotype fits with the FARSB-related disorder, leading to the classification of these variants as likely causative of the proband's complex clinical presentation.

Discussion and Conclusions: Cerebral calcifications and leukoencephalopathy can have numerous underlying etiologies; however, they are infrequently observed as components of complex clinical presentations like the one described. The presence of concurrent pulmonary involvement, aneurysms, liver disease, skeletal abnormalities and abnormal fat distribution can serve as valuable guiding factors for clinicians. Achieving a precise diagnosis is crucial for therapeutic purposes: recent studies have indicated a partial therapeutic benefit from oral phenylalanine supplementation in individuals with FARSB mutations, particularly in conjunction with infections or fever [3].

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## PERSISTENT HYPERSOMNIA AND VERY SLOW PROGRESSION: AN ATYPICAL CASE OF SPORADIC CREUTZFELDT-JAKOB DISEASE


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Introduction: Sporadic Creutzfeldt-Jakob disease (sCJD) is a rare and fatal neurodegenerative disorder characterized by rapidly progressive dementia, myoclonus, visual disturbances, ataxia and pyramidal/extrapyramidal signs1. Atypical presentations can also occur,

posing diagnostic challenges2. We present a case of sCJD with unusually slow progression and hypersomnia as the predominant initial complaint.

Case presentation: A 72-year-old woman presented with a 30-month history of excessive daytime sleepiness, word finding difficulty, and mild forgetfulness. No prior neurological history was reported. Six months after symptom onset, neuropsychological examination revealed non-amnestic mild cognitive impairment and brain MRI showed areas of restricted diffusion in parietal-temporal cortex bilaterally, with left predominance. Additionally, brain 18F-FDG PET demonstrated hypometabolism of the left parietal cortex. However, EEG was unremarkable, while cerebrospinal fluid (CSF) analysis revealed only mildly increased protein, with negative 14-3-3 protein immunoblot. After abstaining from seeking medical attention for two years, the patient presented to our center due to progressive symptom worsening. Neurological examination revealed frequent word finding pauses, postural tremor, right-limb spasticity, and hypokinetic gait, while neuropsychological examination demonstrated moderate executive and memory impairment. Restricted diffusion was confirmed on repeat MRI, and periodic triphasic sharp-wave complexes were detected over the left centrotemporal region on EEG. A second lumbar puncture was performed: immunoblot for 14-3-3 protein was again negative, while CLEIA measurements of CSF biomarkers revealed slightly increased total tau (T-tau; 566 pg/ml), phosphorylated tau (P-tau181) within the normal range (47.2 pg/ml), and Aβ42 in the low part of the normal range (612 pg/mL). Real-time quaking-induced conversion (RT-QuIC) yielded a positive result. Based on the CDC criteria, a diagnosis of probable sCJD was made3. Analysis of the PRNP gene revealed methionine/valine heterozygosity at codon 129 without additional mutations. At two-month follow-up, symptoms remained unchanged.

Conclusions: While rapid neurodegeneration is the typical fingerprint of sCJD, slowly progressing cases are infrequently reported1. The protracted course of the present case is consistent with the evidence of only mild neuroaxonal degeneration, as inferred from the relatively modest elevation of T-tau, and the absence of negative prognostic markers such as myoclonus, visual disturbances, or positive 14-3-3 immunoblot1. Despite early MRI findings suggesting sCJD, the atypical clinical presentation and the slow worsening of symptoms could question the diagnosis. RT-QuIC, whose value in case confirmation has recently been highlighted in the diagnostic criteria for sCJD3, played a pivotal role in unmasking this atypical case, definitively leading the clinician to the correct diagnosis.

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## SPORADIC CREUTZFELDT–JAKOB DISEASE MANIFESTING AS FATAL SPORADIC INSOMNIA: A CASE REPORT


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Introduction: Human prion diseases are rapidly progressive neurodegenerative disorders caused by prion protein misfolding. Sporadic Creutzfeldt-Jakob disease (sCJD) is the most common form. It comprises six subtypes defined by the genotype at the polymorphic codon 129 in PRNP gene and by the type of prion protein accumulating in the brain. There is an important clinical and biomarkers variability among these subtypes, that is a major problem in diagnosing sCJD, especially the atypical variants.

Case Presentation: A 63-year-old man presented at our Memory Clinic complaining of cognitive impairment and mood disturbances. He reported for the previous 9 months sleep fragmentation, hobbies withdrawal, tendency to social isolation, anxiety and episodic agitation; there was also an alteration in sweating. Patient's family history was silent. He has already performed brain MRI, which was unremarkable and Cerebral FDG-PET which detected a widespread cortical and subcortical hypometabolism including both thalami. Initially he has been diagnosed with Alzheimer's Dementia and Donepezil has been introduced. Our first neurological examination showed postural instability and mild upper limbs postural tremor. MMSE score was 20/30. Neuropsychological tests revealed executive dysfunction with loss of verbal and motor initiative and memory impairment. FlorBetapir PET was negative. EEG showed a diffuse slowing. After two months on neurological examination pyramidal signs, ataxia and startle myoclonus were evident. Speech deteriorated rapidly along with overall cognitive performance, subsequently gait worsened with assistance needed for all daily activities. A subsequent MRI showed mild brainstem atrophy, EEG was unchanged. A dynamic EEG with polysomnography was performed, revealing an abnormal sleep structure with significant reduction in sleep spindles and K-complexes and absence of REM sleep. In CSF Tau protein was normal. Tests were also negative for autoimmune encephalitis and paraneoplastic antibodies. Real-time quaking induced conversion (RT-QuIC) assay in CSF was positive for the pathological prion protein. Genetic analysis revealed MM polymorphism in codon 129 in PRNP gene and no mutations were found in this gene. Patient was thus diagnosed with sCJD. His psychophysical conditions declined and patient's family discontinued contact with our Clinic. Patient's death occurred 21 months after disease onset at the patient's home, so it was not possible to determine the pathological subtype of prion protein.

Conclusion: Brain MRI, EEG and CSF Tau protein value were inconclusive. Clinical evaluation therefore remains fundamental in the diagnostic definition of sCJD. In our case clinical symptoms, disease progression, polysomnography and RT-QuIC were decisive for the confident pre-mortem diagnosis.

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## DIVERSE PRESENTATIONS OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY: A COMPARATIVE ANALYSIS OF TWO CASES


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Backgrounds: Progressive multifocal leukoencephalopathy (PML) is a rare and often fatal disease of the Central Nervous System caused by John Cunningham Virus (JCV), affecting immunocompromised individuals. Human immunodeficiency virus (HIV) infection, immunomodulator therapy, lymphoproliferative and autoimmune diseases are accounted as relevant risk factors [1].

Aims: We compared two confirmed cases of PML having different aetiology and clinical onset.

Case-1: A 78-year-old man came to our attention with speech and writing disturbances and short-term memory abnormalities lasting three months. In the previous three years, he suffered from Non-Hodgkin lymphoma which was in clinical remission after receiving Rituximab and Bendamustine treatment until 2022, when the disease relapsed, needing a second-line therapy with R-CHOP regimen (Rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisolone). Neurological examination upon admission revealed global aphasia, apraxia, asomatoagnosia with right hemispatial neglect, spastic muscular tone at the limbs and bilateral Babinski sign. Brain magnetic resonance imaging (MRI) showed hyperintense leukoencephalopathy on T2/Fluid Attenuated Inversion Recovery (FLAIR) weighted images and hypointense on T1 images, primarily involving the left hemisphere and both occipital hemispheres exhibiting the classical "barbell sign". The EEG revealed interhemispheric differences in global slowing, predominantly in the delta frequencies on the left hemisphere. Cerebrospinal fluid (CSF) analysis confirmed the diagnosis of PML with more than 12,000 copies of JCV-DNA.

Case-2. A 40-year-old man, without prior medical conditions, came to our attention with a four-months history of worsening diplopia and vertigo. At admission, neurological examination revealed nystagmus, diplopia in vertical and horizontal gaze, ataxia, bilateral telekinetic tremor and mild adiadochokinesia. Brain-MRI showed FLAIR hyperintensity of the left cerebellar lobe and cerebellar mesial peduncle. The CSF analysis showed more than 5000 copies of JCV-DNA, confirming a PML diagnosis. To investigate immunodeficiency aetiology, an extensive laboratory screening was performed, from which our patient resulted positive for HIV testing with a significant reduction of CD4+ T-cells. Therefore, he started Highly Active AntiRetroviral Therapy (HAART). After one month of therapy, we had a twofold increase in CD4+ T-cell levels and a reduction of HIV-DNA at three thousand copies. However, patient's ataxia and dysarthria worsened despite absence of immune-reconstitution inflammatory syndrome (IRIS) on follow-up MRI, which showed enlargement of previous lesions instead. We suggested the possibility of starting Pembrolizumab [2].

Conclusions: PML should be included in the diagnostic workup of patients showing subacute, nonspecific neurological manifestations given the increased likelihood of underlying predisposing causes that may influence treatment and prognosis.

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## CEREBELLAR ATAXIA AND COGNITIVE DEFICIT ASSOCIATED WITH A DE NOVO MUTATION IN THE NALCN GENE

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Objectives: Recessive mutations in Sodium Leak Channel, Nonselective (NALCN) gene predominantly cause hypotonia and severe intellectual disabilities like infantile neuroaxonal dystrophy, while dominant mutations cause contractures of limbs and face, hypotonia, and global developmental delay syndrome, or cognitive deficit, ataxia, and arthrogryposis. Mutations in NALCN gene usually cause severe phenotypes in childhood, while recently an adult case with milder phenotype has been described. Here we describe the second adult case with a de novo mutation in NALCN gene and cerebellar ataxia.

Materials and Methods: A 33-year-old young woman presented in early infancy language difficulty and mild intellectual disability; she learned walking quite normally with mild impairment in running; she was able to swim and go by bicycle. Since the age of 23 years, she has had progressive gait and balance impairment. At 26 years the neurological examination showed cerebellar gait ataxia without support, impossible on toes, on heels and in tandem; moderate limb dysmetria; hypodiadokinesia; mild upward ophthalmoparesis; oculomotor apraxia; slurred speech; facial grimaces; inappropriate laughing; moderate cognitive difficulty in several domains. In the successive years the clinical features were slowly progressive.

Results: Brain magnetic resonance imaging showed cerebellar atrophy and asymmetria in occipital skull. Brain positron emission tomography revealed cerebellar hypometabolism. Peripheral neurophysiological study was normal. Molecular analysis excluded spinocerebellar ataxia (SCA)1, 2, 3, 6, 7, 15/16, 17, 28, 36. An extended NGS panel for ataxia genes and, subsequently, a clinical exome sequencing detected a novel missense variant in NALCN gene (c.1514A>T) that is classified as likely pathogenetic according to bioinformatic analysis with predictive software. This variant in NALCN gene was confirmed by Sanger sequencing, was not found in the unaffected parents or in the sister and can be considered a de novo pathogenetic mutation.

Discussion and Conclusions: Our case confirms that mutations in NALCN gene can be associated with adult onset cerebellar ataxia with relatively mild clinical features, thus extending the clinical phenotypes of NALCN mutations.

## HEREDITARY HAEMORRHAGIC TELANGIECTASIA IN A PATIENT AFFECTED BY TURNER'S SYNDROME

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Objectives: Hereditary Haemorrhagic Telangiectasia (Hht) is a rare autosomal dominant disease, caused by vascular dysplasia leading to telangiectasias and arteriovenous malformations of skin, mucosa, and viscera, including lung, liver, and brain. The most frequent form of Hht (Type 1, Hht1) maps on chromosome 9q34 and is associated with heterozygous mutation in the gene encoding endoglin (Eng). Turner's Syndrome is characterized by complete or partial loss of an x chromosome in phenotypic females, clinically manifesting with short stature, primary ovarian insufficiency, neurocognitive abnormalities, hearing loss, and cardiovascular, renal, liver, and autoimmune diseases. The objective of our work is to describe a rare association of two genetic diseases.

Materials and Methods: We report the case of a female with known Turner's Syndrome (45,X0/46,Xx) associated with mild cognitive decline, hypothyroidism, diabetes mellitus, hearing loss, short stature, and mild facial dysmorphism; she had been suffering for many years from progressive gait ataxia. At the age of 72 years, she was admitted in Emergency Department because of acute balance worsening. brain MRI showed diffuse vascular leukoencephalopathy, mild cortical atrophy and multiple cavernomas in cerebellar

hemispheres, brain stem, cerebral hemispheres, and thalami, with signs of several microbleeds.

Results: Extended genetic analysis with NGS panel for cerebral vascular malformations detected a novel missense heterozygous variant of unknown significance in Hht1 gene (C.1933g>A), not included in databases (Hgmd, Clinvar). This variant involves a conserved aminoacid and is predicted as pathogenetic variant according to bioinformatic analysis with predictive software (Sift, Polyphen-2). This variant was not found in the younger sister of the proband, not affected by Turner's Syndrome. Interestingly, the older sister, affected by Turner's Syndrome, died for massive cerebral left hemorrhage; however, in this subject the genetic testing for Hht1 were not performed.

Discussion And Conclusions: We described a patient with Turner's Syndrome and Hht1 mutation. In Turner's Syndrome cerebral hemorrhage can rarely occur, usually due to arterial hypertension; in our patient the genetic evaluation contributes both to precise the diagnosis of multiple cavernomas in the proband and to assess the risk of Hht1 for the relatives. this case emphasizes the importance of extending diagnostic investigations particularly when atypical features occur, even in the presence of a genetic diagnosis of a rare disease.

## A CASE OF CREUTZFELDT-JAKOB DISEASE WITH AN ACUTE ONSET AND RAPID PROGRESSION

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Aim: To describe a case of Creutzfeldt-Jakob Disease (CJD) with an acute onset and a rapid progression.

Materials and methods: A 57-year-old man was referred to the emergency room for an acute onset of confusion and aphasia, symptoms started 3 days before the first visit and were described as worsening since the onset. He recently returned from a holiday in the USA with his family. His past medical was unremarkable and there was no history of neurological diseases in his family.

Results: Neurological examination showed mild psychomotor slowing, nonfluent aphasia, with frequent hesitations and anomie, gait hesitation due to mild postural instability. Brain computerized tomography (CT) and CT angiography of the extracranial and intracranial large vessels were normal, while EEG showed a non-convulsive status epilepticus (NCSE). Levetiracetam was started with an initial mild improvement of the aphasia, at the subsequent EEG the pattern was unchanged so other antiepileptics were progressively added, without an electroclinical improvement. Magnetic resonance imaging (MRI) showed a hyperintense signal in diffusion-weighted imaging (DWI) of the left caudate, fronto-insular left cortex, temporal inferior, and superior left cortex. In cerebrospinal fluid (CSF) cell count, glucose and protein were normal, polymerase chain reaction (PCR) test for virus and culture were negative. Total body TC and scrotal ultrasonography resulted negative for occulted malignancy. The brain 18-F fluorodeoxyglucose positron emission tomography (FDG-PET) identified hypometabolism of the frontal and parietal left cortex, the posterior cingulate left cortex and the left precuneus.

Discussion: In the hypothesis of autoimmune or paraneoplastic encephalitis, 5 days of high-dose glucocorticoids and 5 days of intravenous immune globulin (IVIG) were attempted, without clinical improvement. Indeed, serum/CSF paraneoplastic and autoimmune antibodies resulted negative afterwards. Clinical condition rapidly worsened and 3 weeks after the admission patient showed severe psychomotor slowing, global aphasia, apraxia, dysmetria and ataxia. EEG displayed periodic sharp wave complexes at 1-1.5 Hz in the frontal and central left cortex. The total tau dosage on CSF was 2216 pg/ml. The suspicion of CJD was confirmed by real-time quaking-induced conversion (RT-QuIC) and a diagnosis of probable sporadic CJD was done. He died almost a month after the onset of symptoms.

Conclusions: NCSE could be an acute onset manifestation of CJD and CJD should be considered as a possible cause of NCSE. [1,2]

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## BILATERAL SUBTENTORIAL LEUKOENCEPHALOPATHY IN A PATIENT WITH CENTRAL DIABETES INSIPIDUS: A CASE REPORT

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Objectives: The objective of this case report is to highlight the manifestations of bilateral subtentorial leukoencephalopathy in a patient with central diabetes insipidus (DI) in the absence of neurological clinical manifestations.

Materials: The materials used for this case report include the patient's medical records, MRI scans of the brain, laboratory results, spectroscopy analysis, lumbar puncture, immunophenotypic analysis, computed tomography (CT) scan, ophthalmological examination, mental and intelligence tests, visual evoked potentials, cardiology evaluation, Holter ECG, follow-up MRI scans, and positron emission tomography (PET)-CT scan.

Method: A 38-year-old Caucasian male with uncontrolled central DI was admitted to the clinic for demyelinating diseases of the CNS. Various diagnostic procedures, including imaging scans, laboratory tests, and immunophenotypic analysis, were performed to investigate the patient's condition.

Results: Laboratory results upon admission showed altered erythrocyte sedimentation rate (25 mm/h, normal range: 1-15), IgG4 levels (2.73 g/L, normal range: 0.03-2.01), total cholesterol (249 mg/dL, normal range: <200), and LDL cholesterol (162 mg/dL, normal range: <160)MRI scans revealed bilateral subtentorial leukoencephalopathy with parenchymal alterations in the posterior cranial fossa and deep brain structures. The pituitary stalk was thickened, and the neurohypophysis was absent. Spectroscopy analysis showed abnormal levels of N-acetylaspartate (NAA) and choline. Further investigations, including lumbar puncture, virology tests, and antibody screening, yielded negative results. A small nodule and a lymph node were detected in the CT scan, but no other organ abnormalities were observed. The patient's visual evoked potentials indicated mild nerve conduction disturbance.

Discussion: The case report highlights the parenchymal alterations observed in a patient with uncontrolled central DI. The absence of neurological symptoms and inconclusive investigations posed challenges in determining the underlying cause. The radiological findings did not fit the typical patterns of sarcoidosis, and PET-CT scans showed no abnormal uptake of FDG. Thorough observation over time is crucial to understand the significance of these findings before the onset of neurological symptoms.

Conclusions: This case report highlights the importance of recognizing cerebral parenchymal alterations in patients with central DI, even in the absence of neurological symptoms. Further studies are needed to better understand the underlying pathophysiological

mechanisms of these manifestations and their implications for patient management.

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## ALZHEIMER'S DISEASE AS A MOTOR DISORDER

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In Alzheimer disease (AD) motor disturbances become evident when the disease is manifest and later in the course of the disease. Motor movements that have a strong cognitive component however can be compromised since the initial phase of the disease [1]. Recently, quantitative personalized functional outcome measures are applied in clinical assessments areas but specific or highly sensitive tests that can be easily performed in clinical settings are yet to be determined [2]. The present study evaluated the finger movement in patients with AD spectrum to determine the sensitive digital biomarkers that can identify cognitive-function. Forty-five patients (age 77.7±8.03 years; MMSE 21.6±5.7) were selected. The finger dexterity was assessed using a validated HTS which measures the Touch Duration (TD), Inter-Tapping Interval (ITI), movement rate or the frequency of a complete motor task and number of Correct Sequences (CS) by specific sequences performed at maximum-velocity (MV) and metronome (M) compared with the data of healthy older adults. Mini- Mental State Examination (MMSE), Phonemic Verbal Fluency (PVF), CEP Constructive Apraxia Test (CEP-CAT), Clock Drawing Test (CDT), Digit Span (DS) and Verbal Fluency (VF) were carried out to assess cognitive function, and the association between finger function and the results of cognitive scale was evaluated. The HTS parameters was shown significantly strong correlation between CS and MMSE (Right Hand [RH]: r= 0.37, p= 0.012; Left Hand [LH]: r= 0.31, p= 0.038), including age, gender and education as covariate the correlation was highly significant (RH: rho=0.46, p=0.0021 and LH: rho=0.39, p=0.011). Negative correlation was observed between PVF and TD (RH: r=-0.38, p=0.033 and LH: r=-0.40, p=0.03). CEP-CAT shows a statistically significant correlation with CS (RH: r=0.47, p=0.009 and LH: r=0.41, p=0.02), and negative correlation with TD maximum-velocity (r=-0.41, p=0.04) and TD metronome (r=-0.49, p=0.01) in the RH. No HTS parameters correlated with CDT, DS, VF. Comparing the data of healthy older adults, 36.1% patients had a Rate MV value (RH or LH) that was out of the normal range established for Age and Sex [3]. Regarding TD and ITI with Metronome, 56.4% and 41.0% of patients respectively had the values out of the normal range. The HTS was easy and quick to apply. Patients with the finger dexterity deficits showed impaired cognitive performance, supporting the association between motor performance and cognition.

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## CASE REPORT: A FULMINATING CASE OF SPORADIC CREUTZFELDT-JAKOB DISEASE. CAN VIRAL ILLNESSES ACCELERATE THE COURSE OF PRION DISEASES?

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Goals: Sporadic Creutzfeldt-Jakob Disease (sCJD) is a prion encephalopathy for which no cure is available yet. Its course is extremely variable and different influencing factors capable of shortening the natural history of the disease have already been identified [1]. It has been shown that viral infections and the inflammatory environment they create might be responsible for the onset of status epilepticus [2], but we now suggest they may also contribute to hastening disease progression.

Materials: We present a case of a 50 years-old man who referred to our Emergency Department complaining about a three-weeks history of gradually worsening speech, walking and coordination functions. A throughout anamnesis revealed that patient had had a upper airways viral illness a few weeks before symptoms onset. Neurological examination led to a diagnosis of cerebellar syndrome and patient was hospitalized.

Methods: An extensive diagnostic work-up including head CT scan, blood tests, serology, lumbar puncture with CSF analysis, brain MRI, EEG, polygraphy and genetic testing allowed to exclude cerebrovascular events, oedema, traumas, tumours, paraneoplastic syndromes, cerebellar degeneration, autoimmune diseases, malformations, toxic, metabolic or infective causes and eventually led to a diagnosis of sCJD with cerebellar-predominant presentation. We investigated the levels of inflammatory cytokines at different stages of the disease course and of antibodies against common viruses.

Results: The disease had a fulminant course and patient died 1 month after symptoms onset. Inflammatory cytokines were not relevantly increased at the time of patient's admission, but their levels steeply raised in the more advanced stages of the disease. IgMs against Cytomegalovirus and VZV were positive, and so were also IgGs against SARS-Cov-2, HSV1 and EBV.

Discussion: Our patient had many of the already identified risk factors for an accelerated course - male sex, age >40 years old, typical EEG pattern, cerebellar presentation - and it is likely that these have concurred to determine the extremely short course of 5-6 weeks. While it is unusual for sCJD to cause an increase of inflammatory markers, it has been observed that an inflammatory environment is able to start and propagate prion formations [3].

Conclusions: The rise of inflammatory cytokines we observed is likely correlated with patient's recent exposure to a virus. As already hypothesized [2], systemic inflammation might shorten the time spanning between first occurrence of symptoms and death in patients with sCJD. It would be interesting to see if avoidance of systemic infections

in patients already diagnosed with sCJD could prevent a faster than usual demise.

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## ANTI-DPPX ENCEPHALITIS PRESENTING WITH NEURODEGENERATIVE BIOMARKERS: RARE PRESENTATION OR FULL PICTURE?

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Objectives: Anti-DPPX encephalitis is an antibody-mediated disease with a mostly indolent presentation and subacute course, sometimes hindering clinical diagnosis. Moreover, definite diagnosis relies on anti-DPPX antibody testing which is not widely available and is lengthy, complicating diagnosis and hampering therapy initiation. Hence, reported cases in the literature range in the several dozens, making it still relatively under characterized. Through the thorough clinical and test characterization of one single case of anti-DPPX encephalitis which came to our attention, our aim is to shed further light on this disease. Moreover, by presenting unreported instrumental findings we wish to give further impulse in the research of this yet mysterious encephalitis.

Materials: A 56-year-old man was admitted to the ICU at our hospital for acute respiratory distress needing invasive respiratory support. Alongside his respiratory issue, he presented a constellation of neurological signs and symptoms which brought him to our attention. He underwent extensive and repeated neurological examinations and clinical monitoring.

Methods: He also went through a series of tests comprising but not limited to: 3T MRI, serial EMGs including skin reflex, EEGs, general autoimmunity, autoimmune encephalitis antibody testing, CSF tap including neurodegeneration biomarkers, cerebral and total body PET as well as contrast enhanced total-body CT-Scan. The patient was discharged to rehabilitation, however was readmitted to our unit in order to complete diagnostics and evaluate immunotherapy response.

Results: The patient's symptoms included nystagmus, hyperekplexia, pyramidal, and extrapyramidal symptoms as well as very pronounced bulbar muscle weakness. History revealed mood disturbances and weight loss prior to symptom onset. Diagnostic testing was flawless with exception to non-evolutive fasciculations at EMG and a pathological skin reflex, pathological CSF amyloid-beta, pathological DaTScan and serum and CSF positivity to anti DPPX antibodies. Eventually a steroid trial was attempted with partial and gradual symptom amelioration.

Discussion: To our knowledge we are the first to describe a case of anti-DPPX encephalitis with biomarkers also suggesting neurodegeneration. Upon reexamination, although the disease's symptomatic presentation was quite typical, its course was remarkably chronic. Improvement after immunomodulatory therapy however suggested an autoimmune origin. Links between autoimmunity and (neuro)degeneration are beginning to be commonly accepted with examples such as MS, anti-IgLON-5 disease and inclusion-body myositis.

Conclusion: We postulate that neurodegeneration could be implied in anti-DPPX encephalitis, although further studies are warranted for confirmation, since our evidence does not exclude a superimposed neurodegenerative pathology on DPPX encephalitis.

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## COMPARING CEREBELLAR TDCS AND CEREBELLAR TACS IN NEURODEGENERATIVE ATAXIAS USING WEARABLE SENSORS: A RANDOMIZED, DOUBLE-BLIND, SHAM-CONTROLLED, TRIPLE-CROSSOVER TRIAL

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Background: Cerebellar transcranial direct current stimulation (tDCS) represents a promising therapeutic approach for both motor and cognitive symptoms in neurodegenerative ataxias. Recently, transcranial alternating current stimulation (tACS) was also demonstrated to modulate cerebellar excitability by neuronal entrainment. In this randomized, double-blind, sham-controlled, triple cross-over study we compared the effectiveness of cerebellar tDCS vs. cerebellar tACS in patients with neurodegenerative ataxia.

Methods: Twenty-six participants with neurodegenerative ataxia were enrolled. Participants were randomized into three groups in a 1:1:1 ratio. Group 1 received a single session of anodal cerebellar tDCS (real tDCS), group 2 a single session of gamma-tACS over cerebellum (real tACS), and group 3 placebo (sham) stimulation (T0). After one (T1) and two-weeks (T2), stimulation was rotated, so that each patient underwent all of the three stimulations in a randomized order. Before entering the study, each participant underwent motor assessment with wearable sensors considering gait cadence (steps/minute), turn velocity (degrees/second) and turn duration (seconds), and a clinical evaluation with the scale for the assessment and rating of ataxia (SARA) and the international cooperative ataxia rating scale (ICARS). After each intervention, participants underwent the same clinical assessment along with cerebellar inhibition (CBI) measurement, a marker of cerebellar activity.

Results: The gait cadence, turn velocity as well as SARA and ICARS significantly improved after both tDCS and tACS, compared to sham stimulation (all $p<0.010$). Comparable effects were observed for CBI ($p<0.001$). Overall, tDCS significantly outperformed tACS on clinical scales and CBI ($p<0.01$). A significant

correlation between changes of wearable sensors parameters from baseline and changes of clinical scales and CBI scores was detected.

Conclusions: Cerebellar tDCS and cerebellar tACS are effective in ameliorating symptoms of neurodegenerative ataxias, with the former being more beneficial than the latter. Wearable sensors may serve as rater-unbiased outcome measures in future clinical trials.

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## SUBCORTICAL MYOCLONUS IN PLA2G6-ASSOCIATED NEURODEGENERATION (PLAN), INAD SUBTYPE

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Background: Phospholipase A2 group VI (PLA2G6)-associated neurodegeneration (PLAN) is a heterogeneous group of diseases caused by mutations located in PLA2G6 gene, with four clinical phenotypes: infantile neuroaxonal dystrophy (INAD), atypical neuroaxonal dystrophy (ANAD), dystonia-parkinsonism (DP) and autosomal recessive early-onset parkinsonism (AREP). We present the case of a patient with INAD with a homozygous mutation in c.1786C>T (p.L596F) PLA2G6 gene presenting subcortical myoclonus.

Case Presentation: We describe the case of a 24-year-old caucasian woman affected by INAD. She had normal birth and development milestones until the age of 3, when she began to complain progressive gait disorders. At the age of 8, she manifested short episodes of reduction of awareness, treated with lamotrigine with a good response. At the age of 23, for a generalized tonic-clonic seizure, levetiracetam was added. From the same age she started to manifest jerky movements of the upper limbs, mainly during wakefulness triggered by voluntary movements, with a progressive worsening and an increase in frequency over the last month. For this reason, clonazepam and phenobarbital were started; after 3 days she presented a progressive alteration of consciousness with development of dysphagia and aspiration pneumonia. Neurological examination showed spastic hypertonia on four limbs, muscle hypotrophy in the lower limbs, subcontinuous jerky movements characterized by flexion and pronation of the upper limbs, accentuated by active and passive mobilization, bending movements of the head. EEG recordings showed widespread low-amplitude fast activity, widespread slow abnormalities and fronto-central sharp-waves bilaterally. Poligraphic recordings showed pseudo-rhythmic synchronous muscle potentials at 3 Hz frequency with an average duration of 300 msec on the flexor-extensor muscles of the upper limbs bilaterally without an EEG correlation. Brain MRI in T2 and FLAIR sequences showed hypo-intensity of the substantia nigra and globus pallidus consistent with iron accumulation, cerebral and cerebellar atrophy. During hospitalization pneumonia was treated with antimicrobial therapy. We withdrew treatment with clonazepam and phenobarbital and added clobazam 10 mg twice daily with a complete disappearance of movements.

Conclusion: The main clinical symptoms of INAD are tetraparesis, truncal hypotonia, dystonia disorders, mental deterioration, cerebellar ataxia, bilateral limb spasticity, early visual failure, epilepsy. We described the clinical, genetic, neurophysiology and neuro-imaging features of a patient with childhood-onset PLAN, with homozygous c.1786C>T (p.L596F) mutation in PLA2G6. In literature only one case with the same mutation has been described with similar clinical features. However, the presence of subcortical myoclonus seems to be peculiar of our patient.

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## HEIDENHAIN VARIANT OF CREUTZFELDT–JAKOB DISEASE: UNCOMMON PRESENATION SIMULATING A STROKE

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Objectives: The Heidenhain variant of sporadic Creutzfeldt-Jakob disease is a distinct clinical manifestation characterized by isolated visual symptoms in the early stages. We report the case of a 58-year-old man presenting with hyperacute onset of visual disturbances mimicking a stroke.

Materials and Methods: The patient, without a relevant past medical history, presented to emergency department after sudden onset of blurred vision lasting from the previous day. A left homonymous hemianopsia was detected at neurological evaluation, while CT and CT angiography were normal. An acute occipital right ischemic stroke was suspected and thus he was admitted to our stroke unit.

Results: During the first days of hospitalization the visual disturbance remained stable. Brain MRI DWI-sequences showed a small subcortical hyperintensity nearby the right occipital horn of the lateral ventricle and mild hyperintensity in right medial occipital cortex that appeared hypointense in ADC and without correlates in FLAIR sequences. For a better definition of these finds of non-univocal interpretation and to analyze their evolution a second MRI performed six days later, which showed ribbon-like hyperintensity on DWI-sequences in right occipito-parietal, bilateral mesial frontal, cingulate cortex and right caudate. Three EEGs performed at 8, 14 and 28 days from the onset showed a generalized slowdown, with subsequent appearance of periodic and triphasic peaks in the right temporo-occipital lobes with ipsi and contralateral diffusion. Total body contrast-enhanced CT and CSF examination were performed to rule out paraneoplastic and infective encephalitis. Elevated levels of proteins 14-3-3 and total tau were found. Neuropsychological assessment showed impairment in visuo-spatial abilities with left neglect and simultanagnosia. In the next few days, a rapid worsening occurred with the appearance of nausea,

ataxia, and an episode of acute psychosis with significant psychomotor agitation. Sedation with benzodiazepines (2 mg delorazepam IM) was performed which caused hypotensive shock and respiratory depression requiring oro-tracheal intubation as a likely expression of autonomic dysfunction. The diagnosis of probable CJD was further supported by positive RT-QuiC assay in CSF. The patient was transferred to intensive care, where exitus occurred one month after the onset.

Discussion: Although Heidenhain variant typically occurs with a subacute onset, our patient showed a hyperacute visual worsening which initially suggested a stroke. Clinical evolution, neuroimaging, EEG abnormalities, and CSF biomarkers led to the correct diagnosis.
Conclusion: It is important considering this rare condition of prion disease in patients with acute onset visuospatial disturbances after ruling out other more common and reversible causes.
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## A NOVEL MUTATION IN THE PRESENILIN-1 (PSEN1) GENE IN EARLY-ONSET ALZHEIMER'S DISEASE: ATTEMPTING TO DISENTANGLE THE HETEROGENEITY OF THE MUTATIONS AT CODON 226


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Objectives: Variants in the presenilin-1 (PSEN1) gene play a prominent role as genetic triggers of Early-onset Alzheimer's disease (EOAD), contributing to phenotypic variability. In this study, we report a novel 'missense' heterozygous mutation p.Leu226Val at codon 226, aiming to elucidate the clinical heterogeneity associated with mutations in this codon.

Materials and methods: We conducted clinical-neuropsychological assessment, neuroradiological examination which included analysis of volumetric hippocampal subfields using ASHS software and SPECT DAT-SCAN, NGS panel and lumbar puncture with biomarkers analysis.

Results: The index case was a 50-year-old right-handed man with episodic memory deficits, depression, and a familial history of dementia. The clinical examination revealed a left-hand tremor and ipsilateral bradykinesia. The neuropsychological assessment highlighted impairments in memory and visuo-spatial abilities, with a MOCA score of 17/30. Brain MRI showed a posterior gradient of atrophy, parieto-occipital white-matter FLAIR alterations, absence of the "Swallow Tail" sign in the SWAN sequence, and reduced perfusion in the right temporal-parietal-occipital lobe as assessed by ASL. DAT-SCAN (123I-Ioflupane) SPECT revealed decreased uptake in the right basal ganglia. CSF biomarkers indicated an A+T-N- profile and NGS analysis identified a 'missense' heterozygous mutation (c.676 C>G) p.Leu226Val in the PSEN1 gene. According to the American College of Medical Genetics and Genomics guidelines, this mutation is considered likely pathogenic, leading to the diagnosis of monogenic EOAD.

Discussion: Since the discovery of the first pathogenetic variants in the PSEN1 gene, the phenotypic variability of EOAD has been clear, including motor signs like parkinsonism. The Leu226Val mutation had not been previously reported in literature, prompting our investigation into a potential association with other mutations at codon 226. We discovered a high occurrence of parkinsonism features, early behavioral disturbances and psychiatric symptoms. Our report emphasizes the presence of extrapyramidal involvement based on the alterations observed in clinical and neuroradiological assessments. Our index case also showed the onset at the same age of his relatives, in line with the previous literature. The analysis of hippocampal subfields revealed reduced volumetric values in the CA3 and Brodmann area 36, indicating a selective vulnerability of the CA3 and perirhinal cortex to Alzheimer's pathology in the early stages of the disease.

Conclusion: In young adults and middle-aged patients presenting with extrapyramidal symptoms along with behavioral and memory deficits, and a positive family history, we suggest performing an NGS panel to investigate the potential role of PSEN1.
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## ACUTE AUTOTOPAGNOSIA: AN UNUSUAL PRESENTATION FOR THE RARE MARCHIAFAVA-BIGNAMI DISEASE


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Objectives: Herein we discuss a peculiar case of Marchiafava-Bignami disease (MBD) that manifested with acute onset autotopagnosia, mimicking stroke.

Materials: A 52-year-old man, heavy smoker and affected by alcohol use disorder presented to our emergency department complaining of a 12-hour history of acute onset autotopagnosia, described as not being able to localize his head and confusion. The neurological examination revealed disorientation, dysarthria, dysphonia, and a positive Romberg test. Head computed tomography (CT) was inconclusive. Only later, during the hospitalization, the patient reported a four months history of progressively worsening dysarthria, hypophonia, dysphagia, weight loss and bilateral hand weakness. According to his wife, in the same period, he had been experiencing short-term memory impairment and frequent but short-lasting episodes of confusion. Furthermore, the patient denied any recent changes in drinking habits.

Method: Blood tests showed macrocytic anaemia and elevated serum gamma-glutamyl transferase and IgA. Among the possible differential diagnoses, we included motor neuron disease or a paraneoplastic syndrome, therefore we completed our diagnostic work-up with electromyography, which was inconclusive, and a full-body CT scan, which excluded malignancies. Encephalitis was also ruled out through cerebrospinal fluid analysis and electroencephalography, which did not show abnormal findings. The hypothesis of posterior circulation stroke was conclusively disproved by brain magnetic resonance imaging, which revealed T2-FLAIR hyperintense lesions in the periventricular white matter bilaterally and in the corpus

callosum, particularly in the splenium, consistent with chronic toxic-metabolic demyelination.

Results: Based on the clinical history and the suggestive radiological findings, MBD was diagnosed. The patient received high-dose thiamine for one week, followed by one-month oral thiamine supplementation after discharge. After a follow-up of two months and a significant reduction in alcohol intake, the patient reported a considerable improvement in symptoms, which further corroborated the diagnosis.

Discussion: MBD is a rare neurological disorder characterized by demyelination and necrosis of the corpus callosum and the adjacent subcortical white matter and is mainly associated with chronic alcohol abuse and malnutrition. The presentation can be acute, subacute or chronic. To our knowledge, this is the first report to describe autotopagnosia as an acute manifestation of MBD.

Conclusions: The singularity of this case is represented by the acute on chronic presentation of MBD in our patient. To avoid a delayed diagnosis in rare neurological disorders that require urgent treatment, such as MBD, attention should be paid to anamnestic information like alcohol consumption even in the acute setting.

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## TOWARDS A CLINICAL APPLICATION OF A-SYNUCLEIN SEED AMPLIFICATION ASSAYS IN PARKINSON'S DISEASE


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Introduction: Cerebrospinal fluid (CSF) α-synuclein seed amplification assay (αS-SAA) represents the most promising diagnostic tool for Parkinson's disease (PD), demonstrating excellent performance in discriminating PD from healthy controls and other α-synuclein-unrelated disorders [1]. It showed the capability to detect prone-to-aggregate α-synuclein in the prodromal stage of disease, i.e. isolated REM sleep behavior disorders. However, the diagnostic role of αS-SAA in the pre-motor stage of PD is still matter of debate. CSF αS-SAA may be valuable to monitor disease progression and treatment efficacy in clinical trials with disease-modifying therapies targeting α-synuclein misfolding and aggregation. Before this biomarker can be implemented in clinical setting, pre-analytical and analytical variability factors need to be addressed [1]. Preliminary data showed that CSF proteins have an inhibitory effect on α-synuclein aggregation in SAAs. Donor-specific inhibition of CSF on α-synuclein aggregation may explain the lack of correlation between kinetic parameters measured in SAAs and clinical features [2].

Objective: We sought to investigate whether, in a cohort of well-characterized PD patients, CSF protein concentration influences kinetic parameters of aggregation in CSF αS-SAA and their correlation with clinical measures.

Materials and methods: Among patients referring to our Centre, we retrospectively selected a consecutive series of PD patients (n. 94) for whom CSF samples and a thorough clinical characterization were available. Patients with other minor neurological diseases undergoing lumbar puncture within the diagnostic work-up were included as control group (OND, n.112). CSF αS-SAA was performed according to a previously described protocol [3]. In PD patients, motor impairment and disease severity were assessed using MDS-UPDRS III and H&Y, respectively. Cognitive assessment included MMSE and MoCA.

Results: The assay showed 88% specificity and sensitivity in detecting PD vs. OND. Time-to-threshold (TTT), maximum fluorescence (F-max), fluorescence at 24 h (F-24), maximum slope of the sigmoid (S-max) and time to maximum slope (TMS) were significantly correlated with CSF protein concentration ($p<0.05$). After adjusting for CSF protein concentration, MDS-UPDRS III resulted to be negatively associated to TTT ($r=-0.27$, $p = 0.018$) and TMS ($r=-0.27$, $p = 0.02$).

Discussion and conclusion: In our series, CSF αS-SAA confirmed satisfactory accuracy for PD diagnosis. Kinetics of α-synuclein aggregation and its association with some clinical features were significantly influenced by CSF protein concentration. In view of potential clinical applications of αS-SAA, CSF protein content should be taken into account to eliminate possible confounding effects.

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## STRUCTURAL VARIATION DETECTION BY GENOME MAPPING: C9ORF72 EXPANSION


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Background: Specific variant types, which are not commonly detectable by currently used analysis methods, such as repeat expansions, variants in non-coding regions and structural variants, are frequent in neurological disorders. Among these, repeat expansions are an important cause of several neurodegenerative diseases [1]. The size of repeat expansions has been proven to quantitively affect disease severity, with larger expansions often associated with earlier onset of disease and more severe symptoms. Hexanucleotide (G4C2)n repeat in C9orf72 is the most common cause of amyotrophic lateral sclerosis (ALS) and familial frontotemporal dementia (FTD) [2]. Genetic counselling for C9orf72 is very complex due to the highly variable

clinical presentation and technical difficulties in determining the size of the large G4C2 expansions. The detection in clinical routine is still based on repeat-primed (RP) - PCR and Southern blot (SB). The disadvantages of these tests are the detection of small expansions (<80 bp) on the one hand and the labor intensive use, background noise and high signal strength required on the other. Furthermore, somatic mosaicism as well as the unclear cut-off between normal alleles and expanded pathogenic alleles can make the diagnosis difficult. Here, we investigated the ability of optical genome mapping (OGM), a novel imaging and mapping tool for high-throughput detection of structural genetic variants and sizing of tandem repeats [3], to detect G4C2 hexanucleotide repeat in C9orf72.

Methods and Materials: Ultra-high molecular DNA from 15 historical C9orf72 ALS patients were selected. Optical genome mapping (OGM) was performed on the Saphyr Genome Imaging Instrument recently established in the Neurogenetics lab at UCL Queen Square Institute of Neurology.

Results: We confirmed C9orf72 - hexanucleotide repeat expansion in 14 of 15 ALS patients. Repeat sizes ranged from 6 to 25 Kbp. The negative case was repeated with RP-PCR and confirmed to be a C9orf72 negative case. In addition, we assessed somatic instability in the tissue examining the size distribution of the molecules in our patients.

Discussion and Conclusion: In this study, a non-sequencing-based technique was used for the first time in C9orf72-ALS patients carrying more than (G4C2)1000 repeats. Our preliminary data showed the potential of OGM to provide a convenient and easy-to-use alternative that would enable comprehensive detection of structural variants and repeat size variability for most patients by better defining cases of somatic mosaicism.

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## NEUROGRANIN AND SYNAPTIC DYSFUNCTION MARKERS INTERACTION WITH NEURONAL AND INFLAMMATORY CEREBROSPINAL FLUID MARKERS IN EARLY ALZHEIMER'S DISEASE

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Objective: Synaptic dysfunction is an important early mechanism involved in Alzheimer's disease (AD) but its correlation with neuronal, glial and inflammatory markers is still debated [1]. Objective of this study was to evaluate the levels of synaptic markers Neurogranin, SNAP25 and CAP2 in cerebrospinal fluid of AD and their correlation with neuronal, glial and inflammatory markers in vivo.

Material: Sixty AD patients and 20 age-matched controls underwent CSF analyses for tau, p-tau and amyloid to define A+T+N+ Alzheimer's disease patients

Methods: Each subject underwent an extensive cognitive, behavioral and motor assessment. CSF analyses for neurogranin, SNAP-25, CAP2, NfL, and inflammatory markers were performed using SIMOA and Luminex platforms. Correlations between CSF biomarkers were evaluated using partial correlation adjusted for the effect of age, sex and disease duration.

Results: AD patients exhibited higher synaptic markers namely neurogranin, SNAP-25 and CAP2 levels compared to controls. SNAP-25 showed a stronger correlation with the Neuronal marker NfL compared to neurogranin and CAP2. Neurogranin correlated with tau pathology and inflammatory markers in partial correlation analyses.

Discussion: The synaptic markers neurogranin, SNAP-25 and CAP2 are leveted in AD already in prodromal stages together with mild inflammatory cytokines and neuronal markers.

Conclusion: The preliminary findings indicate a possible correlation between synaptic markers and inflammation in AD, whereas neuronal loss might be related to mild inflammatory alterations in CSF.

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## A BAYESIAN RE-ANALYSIS OF LECANEMAB (CLARITY AD) PHASE 3 TRIAL USING INFORMED T-TEST

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Objective: Clinical trials for Alzheimer's disease (AD) strive to enhance clinical symptomatology and modify the course of this intricate neurodegenerative disorder. Nonetheless, the conventional approach of null hypothesis significance testing (NHST) generally employed in these trials possesses limitations in evaluating the clinical significance and capturing detailed evidence for effectiveness on a gradual scale. In this study, we re-analyzed the phase 3 (Clarity-AD) trial of Lecanemab, a recently proposed humanized IgG1 monoclonal antibody that binds with high affinity to Aβ soluble protofibrils, using a Bayesian approach with informed t-test priors.

Materials and Methods: We selected data from the trial and obtained effect size estimates for the primary endpoint, the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB). Then, a set of Bayes Factor analyses was performed to compare the evidence for the null hypothesis (no effect of treatment) and the alternative hypothesis (effect present). Based on previous literature data and Lecanemab phase 3 trial, we used different minimal clinically important difference (MCID) values for the primary endpoint CDR-SB as priors.

Results: Our results indicated anecdotal evidence in favor of the null hypothesis when using a standard prior. Robustness checks showed consistent results. Using informed priors, we found varying evidence for different MCID values, but overall, there was no evidence supporting the effectiveness of Lecanemab compared to the placebo.

Discussion and Conclusion: Our study shows the value of Bayesian analysis in clinical trials while emphasizing the criticality of incorporating minimum clinically important difference (MCID) and effect size granularity when assessing treatment efficacy.

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## FRONTOTEMPORAL DEMENTIA IN VALOSIN CONTAINING PROTEIN MUTATIONS: A CASE FAMILY REPORT AND SYSTEMATIC LITERATURE REVIEW

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Aim: Mutations in the Valosin-Containing Protein (VCP) gene cause autosomal dominant multisystem proteinopathy 1 (MSP1), characterized by a variable combination of inclusion body myopathy (IBM), Paget's disease of bone (PDB), and frontotemporal dementia (FTD). Here we report a novel VCP missense mutations in an Italian family, with FTD as the prevalent manifestation, and compared our results with those described in literature.

Materials and Methods: We described clinical, molecular and imaging data from the studied family. We also conducted a literature systematic review (PubMed, Scopus and Web of Science databases using "VCP" as keyword) with the aim to compare our findings with previously reported VCP-related phenotypes.

Results: A novel heterozygous VCP missense mutation (c.473T>C/p.Met158Thr) was found in all the affected family members. The proband is a 69-year-old man affected by progressive muscle weakness since the age of 49. At age 65, he presented a cognitive disorder suggestive of behavioral variant FTD. A bone scintigraphy also revealed PDB. The patient's mother, his maternal aunt and her daughter had died following a history of cognitive deterioration consistent with FTD; the mother also had PDB. No relatives had any muscular impairments. Reviewing the literature, we observed a different sex distribution of VCP-related phenotypes, being FTD prevalence higher among women as compared to men (51.2% vs 31.2%) and IBM prevalence higher among men as compared to women (92.1% vs 72.8%).

Discussion: We described a novel mutation in VCP in an Italian Family, asserting its pathogenicity by analyzing the site of mutation and protein structure, and the correlation between mutation positivity and the clinical manifestation of the affected members. The clinical findings of our proband were suggestive for the complete triad of MSP1 (present in 12% of cases), though the biopsy did not show the pathognomonic inclusion bodies. We showed that FTD affects a higher percentage of VCP mutated patients as compared to what previously reported. We also documented that FTD mainly affects women and a higher incidence of IBM among men.

Conclusion: Sex has been shown to be a potential factor determining FTD and MSP-1 phenotype, although VCP is not biologically related to sex differentiation, suggesting different mechanisms either protective or worsening the neuromuscular system in the two genres. We also emphasized the importance of VCP genetic testing, even in the absence of the full syndromic complex, in atypical neuro-muscular or neurodegenerative pathologies which result negative for the most common genetic alterations.

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## RIGHT TEMPORAL VARIANT FRONTOTEMPORAL DEMENTIA AND CEREBROSPINAL FLUID BIOMARKERS FOR ALZHEIMER'S DISEASE: A CASE REPORT WITH A MULTIMODAL MRI ANALYSIS

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Introduction: Right temporal variant frontotemporal dementia (rtvFTD) is currently defined by a predominant neurodegeneration of the right anterior temporal lobe (ATL) and a peculiar clinical presentation, involving face and emotions recognition deficits, profound behavioral features, memory-loss, and naming difficulties. Having been for long considered a right-sided variant of the semantic variant of primary progressive aphasia (svPPA), it has been linked almost exclusively to TDP-43 type C frontotemporal lobar degeneration (FTLD). However, recent studies have highlighted the pathological variability underlying this syndrome. In particular, little is known about the association between rtvFTD and Alzheimer's disease (AD) pathology. Here we present the case of a rtvFTD patient with cerebrospinal fluid (CSF) biomarkers suggesting AD and FTLD co-pathology.

Case presentation: A 74-year right-handed man with memory-loss, naming difficulties and behavioral disturbances, including apathy, obsessive behaviors, and dietary changes presented to our clinic. An extended neuropsychological evaluation showed semantic deficits for both verbal and non-verbal modalities, and anterograde memory dysfunction, with encoding rather than retrieval difficulties. The magnetic resonance imaging (MRI) documented marked focal atrophy in the right temporal lobe, leading to the diagnosis of rtvFTD, accordingly to the most recent proposed criteria. Surprisingly, CSF analysis showed an elevation in total and phosphorylated tau and a reduction in beta-amyloid 1-42 and 1-42/1-40 beta-amyloid ratio, consistently with AD neuropathology. However, CSF neurofilament light chain (NfL) was 2541 pg/ml, suggesting a co-existing FTLD-TDP pathology. We compared our proband to 3 rtvFTD patients with negative AD biomarkers and to 27 healthy controls, using multimodal MRI analysis, including voxel-based morphometry (VBM) to assess

grey matter (GM) volume and tract-based spatial statistics (TBSS) to assess white matter (WM) microstructural integrity. Compared to controls, rtvFTD patients showed diffuse GM atrophy in the frontal and temporal lobes of both hemispheres, while our patient presented a more lateralized GM loss, involving right fronto-temporal regions. On the contrary, rtvFTD patients had decreased WM integrity affecting predominantly the right hemisphere, in the inferior fronto-occipital, inferior longitudinal, and uncinate fasciculi, while our patient showed reduced WM integrity in the inferior longitudinal and inferior fronto-occipital bundles bilaterally, in the right uncinate and in the left superior longitudinal fasciculi.

Conclusion: We presented the case of a rtvFTD patient with underlying both AD and FTLD-pathology, who shows a pattern of brain atrophy and WM involvement different from rtvFTD AD-negative patients. We speculate that the co-pathology may determine a peculiar phenotype due to greater disruption of WM integrity than GM volume loss.

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## FATIGUE IN PARKINSON'S DISEASE: DIFFERENCES BETWEEN CAREGIVER'S REPORT AND SELF-EVALUATION


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Objectives: 1) To investigate the differences in fatigue prevalence in Parkinson's disease (PD) according to the point of view from which fatigue is reported self-evaluation (SE) and caregiver reporting (CR); 2) to identify the possible correlates between each of the two evaluations the main motor and non-motor symptoms.

Materials: Eighty-five patients with early PD (45.05% male; age 63.61±9.37 years; disease duration 3.43±2.28 years) were assessed using the Fatigue Severity Scale (FSS) in its SE version (FSS-SE). The FSS-CR was made ad hoc to collect the point of view of the caregiver about the patients' fatigue experience Moreover, all patients underwent a comprehensive examination, including Epworth Sleepiness Scale (ESS), Parkinson's Disease Sleep Scale (PDSS), Beck Depression Inventory (BDI), Parkinson's Anxiety Scale (PAS), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease and Rating Scale, and self-rated/caregiver reporting Apathy Evaluation Scale (AES), and a cognitive evaluation exploring attention and working memory, executive functions, memory, visuospatial abilities, and language domains.

Methods: We used Pearson's chi-square test to investigate the differences in fatigue prevalence estimated by FSS-SE and FSS-CR. We employed the linear regression analyses to identify the possible correlates of FSS-SE and FSS-CR with the main motor and non-motor symptoms. In detail, firstly, we used bivariate regression analyses to identify demographic, clinical, cognitive, and behavioural correlates of FSS-SE and FSS-CR. Secondly, we explored the unique associations of FSS-SE and FSS-CR with the variables that resulted in the first step being statistically significant.

Results: No difference in fatigue prevalence was found between FSS-SE and FSS-CR. The multivariate linear regression analyses showed that FSS-SE was associated with PDSS (B=-0.21, p=0.039), while FSS-CR was related to AES-CR (B= 0.26, p= 0.035).

Discussion: The prevalence of fatigue was between 30-40% for patients and caregivers, with a tentative tendency for overestimation by caregivers. In addition, when the correlates of fatigue were analyzed through multiple regression models and separately for the patient and caregiver, it emerged that the presence of fatigue was associated with sleep disturbance for the patient and associated with indolence toward external reality for the caregiver.

Conclusion: Although no difference was found between SE and CR of fatigue prevalence, the caregivers understood the patients' fatigue experience in terms of anxious or apathetic symptoms. This evidence should encourage involving the caregivers in the assessment and treatment of fatigue to reduce the patients' frustration induced by the lack of understanding of their own experience of fatigue.

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## CORTICAL AND EXTRACORTICAL INVOLVEMENT IN POSTERIOR CORTICAL ATROPHY IS SUGGESTED BY ELECTROPHYSIOLOGICAL FINDINGS: LITERATURE REVIEW AND A CASE SERIES


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Objective: To investigate and describe the neurophysiological alterations of the visual pathways in patients with Posterior cortical atrophy (PCA), reported in literature and from a case series.

Materials: Literature data including findings from Visual evoked Potentials (VEP), Electroretinogram (ERG) and/or Visual field test (VF) in subjects affected from PCA, and data of a cohort enrolled at the IRCCS Mondino Foundation.

Methods: Three-hundred-two articles emerged from the Pubmed search and only one article from the reference re-assessment. Of these articles, we evaluated title and abstract, and 25 were judged to be suitable and were submitted to full-text assessment. (Figure 1). Patients enrolled at our clinic underwent to VF, VEP with 15' and 30' checks and ERG.

Results: Seventeen studies included outcomes of interest. Literature cohort consisted of 140 patients. VF is described in 115 patients (16/17 studies, 94%), the most frequent finding was homonymous hemianopsias or quadrantopsias (12/17 studies, 71%). VEP were performed in 4 patients (4/17 studies, 24%), two were normal, one showed a reduction in amplitude and the last one showed a delayed latency. ERG was performed in 3 cases (3/17 studies 18%), just one showed a delayed latency and low amplitude of both P50 and N95 (Table 1). The study cohort comprised six patients. VF was performed in all patients, three patients showed homonymous lateral hemianopia (50%), the others showed altered values but of low reliability. VEP were performed in

all patients and just one showed normal results (17%). Three patients showed low or borderline amplitude (50%). Five patients had delayed or borderline latency (83%) with involvement of both eyes in 50% of cases. Latency was delayed in 50% of cases with stimulation at 30' check, compared to 33% with stimulation at 15' check. ERG was performed in all cases except one, with normal findings (Table 2).

Discussion: Data related to VEP and ERG are largely absent in literature and when available (2/17 papers, 12%) were normal. VEP from our case series demonstrate an impairment of the central visual pathways (normal ERG). This involvement is mixed, both in amplitude and latency. The latter is partly unexpected and not related to subcortical vascular damage, suggesting a potential involvement of the pre-cortical and post-geniculate axonal component of the visual pathway, not due to cortical neuronal damage.

Conclusions: Our data on a small sample represent a starting point to sensitize the scientific community to pay attention to a possible functional involvement of subcortical structures in patients with PCA for a long time considered spared.

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## CHARACTERIZATION OF GAIT COMPARISON WITH WEAREABLE SENSORS IN DIFFERENT TYPES OF DEMENTIAS


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Objective: The aim of this study was to characterize gait in three groups of patients with different types of dementia using wearable sensors (OPAL). These sensors have already been applied to have an objective estimate of gait in other neurodegenerative pathologies [1].

Materials: We recruited 13 patients within the Fronto-Temporal Dementia (FTD) spectrum (8 with behavioural variant, 5 with Primary Progressive Aphasia which included 2 with non fluent-agrammatic variant and 3 with semantic variant), 8 patients with Lewy-Body Dementia (DLB) and 9 patients with Alzheimer Disease (AD).

Methods: All patients underwent to an extensive motor evaluation which included MDS-Unified Parkinson Disease Rating Scale part III (MDS-UPDRS III), a video protocol assessment including evaluation of eye movements, myoclonus and dystonia. All patients performed a gait protocol with OPAL applied on both wrists, sternum, lumbar and both feet which consisted in 2 minute walking test, sway and 360 degree turn. Due to the small sample size for each group, Kruskal–Wallis test (Non-parametric testing) was applied to do a comparison of variance between the groups, subsequently an ANCOVA analysis was performed using the statistically significant variables.

Results: The three gruops did not show differences in terms of demographic features and disease duration. As expected, the MDS-UPDRS part III was higher in DLB compared to FTD and AD ($p<0.05$). Then DLB performed worst than FTD and AD on several gait parameters (i.e. gait speed, gait stride length, gait turns duration, gait turns velocity, gait turns steps in turn, 360° angle and 360° turn velocity) ($p<0.05$). Complementary FTD group performed worse than AD group on the same gait parameters ($p<0.05$). Adding the MDS-UPDRS part III as covariate, ANCOVA model still showed gait speed was worse in FTD spectrum compared to AD (0.75 m/s vs 0.97 m/s, $p<0.05$)

Discussion: Our results suggest that most of the gait impairment detected with OPAL in different groups of dementia is related to parkinsonian syndrome. Still, gait speed seemes to be worse in FTD spectrum irrespective to parkinsonism assessed with MDS-UPDRS part III.

Conclusions: Our preliminary data suggest gait speed may differentiate different types of dementia irrespective of the presence of parkinsonism.

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## THE CONTRIBUTION OF SMALL VESSEL DISEASE TO CLINICAL PHENOTYPE IN PROGRESSIVE SUPRANUCLEAR PALSY


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Introduction: Emerging evidence has suggested that cerebral small vessel disease (CSVD) may have an impact on motor, cognitive and behavioral symptoms in many neurodegenerative diseases. White matter hyperintensities (WMHs) are considered imaging biomarkers of CSVD but it's still debated whether they reflect atherosclerotic cerebrovascular changes or neurodegenerative-related pathology. A recent anatomopathological study reports CSVD was the most frequent co-pathology found in a cohort of 101 PSP (65%) [1]. However, the contribution of CSVD on clinical features of Progressive Supranuclear Palsy (PSP) remains unknow.

Objectives: This study explores the possible influence of CSVD on presentation of the disease and describes the burden and distribution of WMHs on brain magnetic resonance imaging (MRI) in PSP patients.

Materials and Methods: This study included 60 subjects with PSP diagnosed according to the MDS-PSP criteria and referred to the Center of Neurodegenerative Disease (CEMAND) of the University of Salerno, Italy, from May 2016 to July 2022. Motor (PSP-rating scale, MDS-UPDRS-III, S&E), cognitive (MOCA) and behavioral (NPI) symptoms, Milestones (falls, ocular motor dysfunction, impossible to gait, dysarthria, dysphagia and dementia) and cardiovascular risk factors were assessed in these patients. CVSD imaging markers were captured with MRI and age-related white matter changes scale (ARWMC) score (range 0-30) was calculated. The associations of CSVD with these outcomes were analyzed using Pearson's correlation and linear or logistic regression models.

Results: CVSD was present in 41 (68%) of PSP patients (ARWMC+). Compared to ARWMC-, ARWMC+ did not have major disease severity or more cardiovascular risk factors, except for a trend towards significance for hyperlipidemia ($p=0.008$). Median ARWMC total score was 2 (IQR=4). WMHs were localized in fronto-temporal lobes and were mild in severity (Fazekas I). There were a relationship

between ARWMC total score and PSP-rating scale (β=0.312, p=0.029), MDS-UPDRS-III (β=0.302, p=0.05) and some Milestones (dysarthria OR=1.1, p=0.55 and impossible to gait OR=1.3, p=0.26) but not with S&E (r=-0.191, p=0.23), MOCA (r=-0.145, p=0.407) and NPI (r=-0.068, p=0.789). No differences were found between clinical phenotypes.

Conclusions: Our results may indicate that WHMs in PSP is more related to the physiopathology mechanism of the disease rather than atherosclerotic cerebrovascular risk factors.

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## INVESTIGATING α-SYNUCLEIN COPATHOLOGY IN ALZHEIMER'S DISEASE WITH CSF α-SYNUCLEIN SEED AMPLIFICATION ASSAYS

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Introduction: Alpha-synuclein seed amplification assays (αS-SAAs) are the most promising techniques for the in vivo detection of synucleinopathy. Several studies reported high accuracy of cerebrospinal fluid (CSF) αS-SAAs in discriminating α-synuclein-related disorders, i.e. Parkinson's disease (PD) and dementia with Lewy bodies (DLB), vs. healthy controls. Notably, neuropathological studies revealed the presence of α-synuclein copathology in Alzheimer's disease (AD).

Objectives: We aimed to investigate the prevalence of CSF αS-SAA positivity in AD patients, also exploring its potential association with clinical features.

Materials: We retrospectively selected, from our cohort, a total number of 456 individuals, including subjects in the AD continuum (n=240), patients with Lewy body disorders (LBD), (n=104), and subjects with other minor neurological disorders (OND, n=112) as control group. All the individuals included underwent clinical and neuropsychological evaluation, CSF AD core biomarkers assessment, and a highly reliable CSF αS-SAA.

Methods: Associations between αS-SAA positivity and AD clinical variants, neuropsychological tests and AD core biomarkers were assessed by means of Fisher's exact test and logistic regression.

Results: In our series, αS-SAA demonstrated high sensitivity (86.5%) and specificity (87%) for differentiating PD and DLB from controls. We observed significantly higher αS-SAA positivity in AD patients (30%) vs. controls (13%) (p=0.0017, adjusted for age and sex). Among the AD clinical variants, patients with posterior cortical atrophy (PCA)-AD exhibited significantly higher αS-SAA positivity with respect to those with amnestic/typical presentation (75% vs. 29.2%, respectively, p=0.0061, adjusted for age and sex). αS-SAA positivity increased across the stages of AD continuum (25% in preclinical AD vs. 36% in dementia due to AD). We found a significant association between the copy of drawing test from the Mental Deterioration Battery and positivity of αS-SAA in AD patients (p=0.00579, adjusted for age). αS-SAA positivity was significantly associated with reduced CSF levels of Aβ40 (p=0.0278, adjusted for age) and Aβ42 (p= 0.023, adjusted for age).

Discussion: Our data revealed that a substantial proportion of AD cases (30%) shows positivity for CSF αS-SAA, which is also linked to clinical presentation and disease stage. Our results suggest the expansion of the A/T/N system to include an A/T/N/S classification, where "S" stands for "synucleinopathy." Detection of α-synuclein copathology in AD holds great relevance for designing personalized disease-modifying therapies. Further longitudinal investigations are warranted to elucidate the potential prognostic value of αS-SAA for AD clinical course.

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## BEHAVIORAL AND COGNITIVE ABNORMALITIES IN SECONDARY FRONTOTEMPORAL DEMENTIA ASSOCIATED WITH SPONTANEOUS INTRACRANIAL HYPOTENSION: A CASE REPORT

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Objective: To describe the case of a 59-year-old male patient who experienced spontaneous intracranial hypotension (SIH) and subsequently developed sudden cognitive and behavioral changes.

Materials and Methods: The patient initially complained of orthostatic headache, fatigue, and cognitive difficulties. A brain MRI scan revealed characteristic findings, including "sagging brain," diffuse pachimeningeal enhancement, and tonsillar displacement. A possible cervical leak was identified on the spinal cord MRI. The patient received a diagnosis of SIH and underwent blood patching, which successfully alleviated the headache symptoms. However, cognitive impairments persisted, accompanied by behavioral changes such as apathy and disinhibition. The patient scored 24 out of 30 on the baseline Montreal Cognitive Assessment (MoCA) test. Extensive cognitive assessments indicated deficits in attention, executive functions, and episodic memory. FDG-PET brain scan showed reduced metabolism in the prefrontal cortex, caudates, and thalamus bilaterally. SPECT DATscan revealed no abnormal findings. A follow-up brain MRI after one year showed no changes, and the patient's cognitive impairments remained stable.

Results: Both the radiological and clinical data support a diagnosis of frontotemporal syndrome, likely attributed to SIH. The acute onset of symptoms suggests that an underlying neurodegenerative disorder is less probable.

Discussion and conclusions: While cognitive disturbances and alertness alterations are common in SIH1, fully developed frontotemporal syndrome cases are rare in the existing literature2,3. The stretching of the frontotemporal cortex and/or venous stagnation at the confluence of the straight sinus and vein of Galen may contribute to this condition. Although SIH is an uncommon cause and red-flag symptoms like headache may be absent, it should be considered during the diagnostic evaluation of frontotemporal dysfunction, especially in cases with acute

or sub-acute onset. Identifying SIH is crucial as it is one of the few potentially treatable causes of cognitive decline.

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## DEMENTIA

### COULD PSYCHIATRIC DISORDERS PREDICT THE EVOLUTION OF SUSPECTED NON-ALZHEIMER'S DISEASE PATHOPHYSIOLOGY (SNAP) PATIENTS INTO ESTABLISHED DEMENTIA?

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Objectives: Suspected non-Alzheimer's disease pathophysiology (SNAP) is a condition characterised by an often subtle cognitive decline and, although it resembles Alzheimer's disease (AD) in some respects, it differs from AD in terms of less impairment of verbal episodic memory and the absence of amyloid pathology in CSF and PET. Even if it often has a benign course, numerous cases have been described with an evolution towards established forms of dementia, such as Fronto-Temporal Dementia (FTD) and Lewy Body Disease (LBD). Therefore, it is still complex to predict the evolution of SNAP patients and, consequently, to tailor their multidisciplinary management. Here, we assess whether the presence of neuropsychiatric disorders at the time of SNAP diagnosis can help predict the patient's subsequent evolution.

Materials: 21 SNAP patients underwent a 3-years follow-up.

Method: All patients underwent an extensive neuropsychological evaluation, diagnostic lumbar puncture, brain MRI and FDG-PET at baseline and annually (with the exception of lumbar puncture). Moreover, clinical, demographic, and pharmacological data were collected.

Results: All patients at recruitment presented a clinical condition compatible with mild cognitive decline (MCI). Furthermore, both FDG-PET data (i.e. significant parietal and limbic hypometabolism) and CSF data (i.e. abnormal values for Tau protein and normal for Beta amyloid protein) were consistent with the clinical suspicion of SNAP. Interestingly, 16 patients had a positive history of psychiatric disease: specifically, 8 were depressed, 5 had a generalised anxiety disorder, 2 had a bipolar disorder and 1 had a schizoaffective personality disorder. Of note, after 3 years, among the 5 patients without psychiatric comorbidity, 3 remained stable as MCI and 2 returned to a normal cognitive profile. In contrast, only 4 of the psychiatric patients remained stable, while the other 12 evolved to dementia, namely 8 FTD, 3 LBD and 1 a cortico-basal syndrome, as demonstrated by clinical, neuropsychological and PET data.

Discussion: Although the sample is limited, our data show that the presence of a psychiatric comorbidity at the time of SNAP diagnosis can predict with a good probability an evolution into an established dementia within a relatively small time span. In particular, the risk of evolution towards a form of FTD is very significant, which is consistent with the link between psychiatric disorders and this form of neurodegeneration.

Conclusions: We suggest that psychiatric comorbidity is an unfavourable prognostic factor in patients diagnosed with SNAP, specifically increasing the likelihood of the SNAP patient evolving into an FTD.

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### MONOAMINERGIC SYSTEM DEFICIT AS A CONSEQUENCE OF PATHOLOGICAL PROTEIN ACCUMULATION IN THE ALZHEIMER'S DISEASE CONTINUUM

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Aim: The alteration of monoaminergic systems in Alzheimer's disease (AD) might be a potential target for pharmacological intervention. However, to date which system is the most clinically relevant and how it progresses from the early to the most severe stage of AD is still unclear. Hence, the interaction between the pathological accumulation of misfolded proteins and these diffuse projection systems in the AD continuum is of clinical relevance.

Materials: We included 50 patients with AD (mean age: 72.66 ± 8.03; 68% males) and 42 Healthy Controls (mean age: 70 ± 8.53; 35% males). We acquired brain [18F]FDG-PET images as a marker of neurodegeneration, CSF for β-amyloid42, β-amyloid40 and tau protein quantification, and MMSE as a measure of global cognitive functioning. We divided the AD patients in two groups based on MMSE score (AD Dementia -ADD- <24; MCI-AD ≥24) to study different stages of the disease.

Method: We performed voxel-based analysis between AD vs HC, both in the whole group, then in ADD and MCI-AD groups, separately. Using JuSpace toolbox we explored the correlation between [18F]FDG-PET images and PET maps of dopamine (DAT), serotonin (SERT), noradrenaline (NAT) and choline vesicular (VAChT) transporters cortical distribution. Moreover, we evaluated relative hypometabolism in the main cholinergic nucleus (Meynert nucleus).

Results: In the whole AD group, the distribution of relative cortical hypometabolism was associated with a significant reduction of VAChT availability ($p = 0.018$) only. This association remained significant when exploring the ADD group ($p = 0.006$), but not the MCI-AD one. β-amyloid42 levels and β-amyloid42/40 ratio was

inversely correlated with VAChT in the ADD group (p= 0.003; p = 0.038, respectively), independently from the damage of the Meynert nucleus. No correlation was found in the MCI-AD group.

Discussion: In the ADD phase we showed a significant damage in the cortical regions targeted by the cholinergic system. This provides an explanation of the reduction of the cholinesterase inhibitors efficiency in the dementia phase.

Conclusions: The damage of monoaminergic diffuse projection systems in the AD continuum primarily impacts the cholinergic system, which, at a more advanced stage of the disease, is too impaired to respond to specific neurotransmitter stimulation.

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## FRONTOTEMPORAL INVOLVEMENT IN RAPIDLY PROGRESSIVE DEMENTIA DUE TO INTRAVASCULAR LYMPHOMA: A CLINICAL AND NEUROPATHOLOGICAL DESCRIPTION OF FOUR CASES

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Objectives, materials, and methods: Intravascular large B-cell lymphoma (IVLBCL) is an extranodal lymphoma characterized by the selective growth of neoplastic cells within the lumen of blood vessels, representing a rare but potentially treatable cause of rapidly progressive dementia (RPD). Nevertheless, due to its heterogeneous clinical and instrumental presentation, it is often misdiagnosed with more common causes of RPD, e.g., sporadic Creutzfeldt-Jakob disease (sCJD) or vascular dementia. In this study, we retrospectively analyzed the clinical and histopathological data of the only four IVLBCL cases we diagnosed posthumously over 20 years at our prion disease reference center, among over 600 brain samples received as CJD suspects.

Results: Three patients showed a subacute onset, two with neuropsychiatric symptoms (apathy, depression, emotional lability, and behavioral disturbances), and the third with disorientation and alertness fluctuations. The fourth had an acute onset with transient loss of consciousness followed by a delirium-like state. All patients underwent a rapidly progressive decline, sometimes characterized by ictal episodes with altered alertness and/or focal neurological signs, variably diagnosed as newly-onset seizures, TIA, or stroke. The diagnostic blood work, cerebrospinal fluid (CSF) analyses, electroencephalography (EEG), and neuroimaging, yielded non-specific results. In three patients, the presence of generalized periodic sharp/wave complexes at EEG and positive CSF protein 14-3-3 western-blot assay mistakenly supported a CJD diagnosis. Other common misdiagnoses included epilepsy, vascular dementia, and encephalitis. The stored CSF samples of two patients tested negative at prion RT-QuIC, which we performed retrospectively for research purposes. Neuropathological analysis revealed that frontotemporal neocortices were the most affected brain areas in terms of vascular infiltration, neuronal loss and gliosis, and petechial lesions.

Discussion and conclusions Our results confirm the diverse clinical and instrumental presentation of IVLBCL. The findings underscore the need to consider IVLBCL and other potentially treatable conditions in the diagnostic workup of patients with RPD. Specifically, given the therapeutic implications of its misdiagnosis with CJD, we emphasize the utility of prion RT-QuIC as a confirmatory test for accurate antemortem detection of prion diseases. Neuropathological evidence of preferential involvement of frontotemporal neocortices may explain the neuropsychiatric symptoms and cognitive deficits commonly observed and could be thus relevant to reach an early diagnosis. Further research is needed to validate these findings, improve antemortem recognition, and explore therapeutic approaches for IVLBCL.

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## CSF LEVELS OF ENDOTHELIN-1, VEGF AND MMP2 WITHIN THE ALZHEIMER'S DISEASE CONTINUUM

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Objective: Recent evidences highlighted the involvement of vascular dysfunction and neuroinflammation in the pathogenesis of Alzheimer's Disease (AD). A key role is played by the dysfunction of the Neurovascular Unit (NVU), a functional structure composed by vascular/glial cells and neurons, and by the alteration of several vascular factors, such as Vascular Endothelial Growth factor (VEGF) and Endotheiln1 (ET1), both modulated by amyloid (Aβ) oligomers. Other important factors are matrix metalloproteinases (MMPs), among which MMP2 and MMP9, which are involved in the maintenance of the integrity of the blood brain barrier (BBB) and in the clearance of toxic Aβ aggregates. To better understand the role of the NVU and cerebral blood flow (CBF) regulation in the pathogenesis of AD, the aim of this study was to evaluate levels of Endothelin-1, MMP2, MMP9 and VEFG, which are released by astrocytes, in cerebrospinal fluid (CSF) samples of patients classified by the AT(N) system and by ApolipoproteinE genotype (ApoE3 and ApoE4), compared to age-matched control patients (HC).

Methods: We recruited 159 consecutive patients admitted to our memory clinic for cognitive impairment and that underwent lumbar puncture for diagnostic purposes. They all fulfilled NIA-AA diagnostic criteria for AD continuum (ADc). We measured CSF levels of VEGF, ET1, MMP9 and MMP2. Data were compared to those from 24 aged-matched controls.

Results: Our data showed a significative reduction of VEGF (p<003), MMP2 (p=0.005) and MMP9 (p=0.002) in ADc CSF, compared to HC, whereas we didn't find a significative difference of ET1 CSF compared to HC. Patients stratified both by ATN (A+T+ vs A+T-) and by APOE genotype (E3 vs E4) didn't show any significative difference for all the vascular markers. Interestingly, we found a positive correlation between MMP2 and AD related brain burden ($\tau$ = 0.115, p=0.032), measured as p-tau/Aβ42 ratio. The multivariate analysis highlighted a contribution of diabetes mellitus on CSF levels of VEGF, MMP2 and MMP9 (p<0.05).

Discussion: We suggest that the reduction of MMP2, MMP9 and VEGF in CSF in ADc determines the failure of important protective pathways leading to the progression of the disease, probably due to a dysfunction of astrocytes and is a mechanism amyloid-related and the presence of diabetes may worsen the progression of the disease.
Conclusions: Early vascular dysfunction plays an important role in AD pathogenesis and could be the result of a failure of compensatory mechanisms, thus suggesting a possible contribution to AD neurodegeneration.
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## THE SUBJECTIVE COGNITIVE DECLINE MISCLASSIFICATION USING COMMONEST SCREENING TESTS


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Objectives: Subjective Cognitive Decline (SCD) refers to self-perceived cognitive decline experienced by individuals without any objective evidence of impairment on standardized neuropsychological tests [1]. Its potential of reflecting a prodromal stage of neurodegenerative disease and a risk factor for future cognitive decline highlights the importance of distinguishing SCD from normal age-related cognitive changes. Aim of the study was to examine the sensitivity, specificity and accuracy of two widely used cognitive screening tests for dementia, the Addenbrooke's Cognitive Examination Revised (ACE-R) [2] and the Mini Mental State Examination (MMSE) [3], in detecting individuals with SCD and differentiating them from those with objective cognitive impairment.

Materials and Methods: 22 healthy subjects (HS), 25 individuals with SCD, 31 Mild Cognitive impairment (MCI), 32 Alzheimer's Disease (AD) patients were recruited. All participants underwent a neuropsychological battery and the Italian version of the ACE-R, which incorporates the MMSE. By subtracting the MMSE score, partial ACE-R scores were also derived and divided into sub-domain scores. One-way ANOVAs were used for between-group comparisons in total MMSE scores, total ACE-R scores, and ACE-R sub-domain scores. Discriminant analyses were performed to examine the ability of ACE-R and MMSE in discriminating SCD from the other groups by sensitivity (Se), specificity (Sp) and accuracy (A) indices.

Results: Statistically significant group differences and a progressive downward trend across groups on ACE-R and MMSE total scores were observed. SCD and HS reported comparable performances. The discriminant analyses showed that AD, MCI patients and HS are correctly classified by total ACE-R (Se=84.4% Sp=15.6% for AD, Se=51.6% Sp=48.4% for MCI; Se=68.2% Sp=31.8% for HS, general A=59.1%), partial ACE-R (Se=78.1 Sp=21.9 for AD, Se=41.9% Sp=58% for MCI; Se=59% Sp=40.9% for HS, general A=52.7%), MMSE (Se=71.9% Sp=28.1% for AD, Se=41.9% Sp=58.1% for MCI, Se=77.3% Sp=22.7% for HS, general A=53.6). SCD individuals are hardly distinguishable from other groups (Se=28% Sp=72% for total and partial ACE-R; Se=25% Sp=76% for MMSE) and showed an opposite trend, resulting misclassified either as HS or MCI by all considered screening tests.

Discussion: Screening tests that are currently used in clinical practice are unable to identify SCD, who are misclassified as HS or MCI.

Conclusion: This study highlights the need to develop new screening tools to identify those SCD individuals seeking for medical interventions. Validation and implementation of accurate screening-tests for the identification of SCD to be used in primary care settings are essential steps for a successful use of future disease modifying treatments.
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## CLINICAL FRAILTY MODULATES COGNITIVE PERFORMANCE IN MCI-AD INDEPENDENTLY FROM PTAU LEVELS


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Introduction: Frailty is a clinical syndrome in which there is increased vulnerability to endogenous and exogenous stressful events. It is associated with an increased risk of adverse health events and severe loss of autonomy. [1] The elderly show extremely heterogeneous (and often unpredictable) responses to stressors and age-related chronic conditions, such as cognitive impairment. This heterogeneity may (at least in part) be explained by differences in resilience (i.e., the body's ability to cope with stressors)[2] and cognitive reserve. [3] We employed a Comprehensive Geriatric Assessment, focusing on the degree of multimorbidity (Cumulative Illness Rating Scale, CIRS) and clinical frailty (CFS; using the Clinical Frailty Scale) to improve our understanding of the extent to which these variables may affect the development and progression of mild cognitive impairment due to Alzheimer's disease (MCI-AD).

Materials and Methods: The population, consisting of 50 subjects with MCI due to AD was evaluated by multidimensional assessment collecting the following data: educational level, functional autonomy in basal and instrumental activities of daily living, number of prescriptions and associated anticholinergic load (ACB score), degree of

multimorbidity (CIRS) and level of clinical frailty (CFS). We then explored the relationship between MMSE at the time of the first visit and the other variables, including P-tau levels in CSF sampling, using Pearson's correlation test.

Results: Univariate analysis, conducted on both the overall sample and the two populations identified by a median split on P-tau, showed a correlation between MMSE and the CFS scale values severity index ($\rho = -0.67$; $p = < 0.001$). The correlation remained significant correcting for total ptau values as evaluated in a linear regression model. Conversely, CIRS severity presented with a borderline correlation with MMSE scores in the whole MCI group and there was no correlation between MMSE and ACB scores.

Discussion: Our analysis show that in MCI due to AD clinical frailty is a predictor of cognitive performance independently from CSF p-tau levels and outperforms other measures of comorbidity assessments. This finding is in line with the notion that frailty, accompanied by cognitive reserve, is an important modulator of phenotypic expression in cognitive impairment.

Conclusion: The evaluation of clinical frailty via the clinical frailty scale can help refine the assessment of the patient with MCI-AD.

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## EXTENDED RT-QUIC ANALYSIS OF OLFACTORY SWAB DIAGNOSTIC ACCURACY IN PATIENTS WITH PRION DISORDERS

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Objectives: Prion disorders are a group of rare, rapidly progressive, and fatal neurodegenerative diseases, which occur in sporadic, genetic, or acquired forms. Recently, real-time quaking-induced conversion (RT-QuIC) assay has been set up for CJD diagnosis. In previous studies we showed that RT-QuIC assay was around 90% sensitive and 100% specific in detecting prion seeds in olfactory mucosa of patients with prion disorders. This level of diagnostic accuracy was comparable to that of CSF and RT-QuIC combination analyses of both OM and CSF samples provided a 100% diagnostic specificity and sensitivity. Still, RT-QuIC accuracy in a large number of patients with prion disorders has never been evaluated.

Materials and methods: Eighty-four patients with definite, probable CJD or with genetic prion disorders and 238 patients with non-prion neurodegenerative disorders were recruited from 2018 to 2022 in Milan, Verona and Rome neurologic clinics. All patients underwent OM swabbing (FloQBrush, Copan, Brescia) at different sites. CSF was also obtained from sixty-six patients with prion disorders. RT-QuIC analysis in OM and CSF was performed using truncated hamster PrP, but at 42°C and 55°C respectively.

Results: We found that RT-QuIC was positive in 69 out of 84 OM of patients with prion disorders and 0/238 with non-prion neurological disorders resulting in a sensitivity of 82.1% %, and a specificity of 100%. Among patients with prion disorders 18 patients underwent OM swabbing only, because lumbar puncture was impracticable and 15 were RT-QuIC positive. CSF was also obtained in 66 patients with prion disorders and 57 were RT-QuIC positive 86% sensitive. Still, when both OM and CSF samples were considered in the same patient the sensitivity of 97%. In genetic cases RT-QuIC sensitivity was 75% lesser than sCJD but depending on PRNP point mutation.

Conclusions: Here we showed that RT-QuIC diagnostic accuracy in OM sampling is 82% and that olfactory swabbing might replace CSF analysis when lumbar puncture is unpracticable. As we previously showed, the RT-QuIC diagnostic accuracy obtained from the combination of both CSF and OM is nearly to 100%. Of course, among "the other tissues" analyzed by RT-QuIC reported in the diagnostic criteria, OM is the best candidate.

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## ADAM17 AND NGFR/P75NTR POLYMORPHISMS INTERACT TO INCREASE THE RISK OF SPORADIC ALZHEIMER'S DISEASE

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Introduction: NGFR/p75NTR represents a similar-affinity receptor for all known mammalian neurotrophins - i.e., NGF, BDNF, NT-3, and NT4/5 - and a higher affinity receptor for their immature forms (i.e., proNGF, pro-BDNF) [1]. Moreover, the binding of Ab1-42 to NGFR/p75NTR increases the extracellular levels of Ab1-42, causes neurotoxicity, mediates Ab-induced tau hyperphosphorylation and neurodegeneration (i.e., synaptic disorder and neuronal loss) and increases the expression of another pro-apoptotic neurotrophin receptor, sortilin, via the RhoA pathway, that in turn could interact with NGFR/p75NTR to induce neuronal apoptosis [1]. NGFR/p75NTR could undergo a three-step proteolytic cleavage that could modify its functional properties. During the first step, the extracellular domain (ECD) of NGFR/p75NTR is cleaved by the sheddase ADAM17, generating a membrane bound C-terminal fragment (CTF). Then, CTF undergoes a second cleavage by the PSEN-dependent -secretase, releasing the intracellular domain (ICD) into the cytoplasm [1]. Beyond NGFR/p75NTR, ADAM17 also participates in the proteolysis of several substrates, such as APP, which play a key role in Alzheimer's disease (AD). Preliminary data indicated that both NGFR/p75NTR and ADAM17 could play a key role in the pathogenesis of sporadic AD (sAD) also from a genetic perspective [1, 2]. The general aim of this study was to characterize the interaction between NGFR/p75NTR and ADAM17 Single Nucleotide Polymorphisms (SNPs) and risk of sAD.

Materials and Methods: This case-control association study was conducted in a Southern Italian cohort consisting of 155 AD patients and 139 age- and sex-matched controls. Nineteen NGFR/p75NTR and seven ADAM17 tag-SNPs were selected and genotyped TaqMan SNP genotyping assays. The epistatic and dominant interactions between SNPs were analyzed by log-likelihood ratio test (LRT) using the SNPassoc package for R [3].

Results: SNP-SNP interaction analysis of NGFR/p75NTR and ADAM17 SNPs yielded statistically significant signals in predicting the onset of sAD. In particular, a total of 3 pairs of SNPs reached the significance, among which the pair composed of rs4648975 and rs7078160 within the NGFR7/p75NTR gene yielded the most significant signals ($p<0.001$) in predicting the onset of sAD. Within the NGFR/p75NTR gene, rs4648975 polymorphism also showed a significant interaction with rs4794056 ($p<0.001$). Finally, SNPs rs11466150 within the NGFR/p75NTR gene showed significant evidence of interaction with rs11690078 of ADAM17 gene ($p<0.001$).

Discussion and Conclusion: Our results reveal a new role of NGFR/p75NTR and ADAM17 genes in sAD from a genetic perspective. SNPs-SNPs of some tag-SNPs on these genes should be considered for the genetic screening of sAD.

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## BLOOD-BRAIN-BARRIER PERMEABILITY IS ASSOCIATED WITH DIFFERENT NEUROINFLAMMATORY PROFILES IN ALZHEIMER'S DISEASE


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Introduction: In the recent years, inflammation has emerged as a vital player in Alzheimer's disease (AD) pathogenesis [1]. Previous studies have evidenced how also the Blood-Brain Barrier (BBB), as a gateway for immune trafficking, may play a role in disease pathogenesis. Here, we investigated the relationship between BBB permeability, indicated by cerebrospinal fluid (CSF) plasma albumin ratio (Qalb), and CSF indexes of humoral neuroinflammation in a cohort of biologically defined AD patients.

Materials and Methods: 59 consecutive patients with MCI or early AD (MMSE>22) underwent CSF analysis for inflammatory cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, Il-10, IL-12, IL-13, IL-17, TNFα, IFN-ϒ, GM-CSF, G-CSF). We used a backward stepwise linear regression analysis to explore the potential influence of each cytokine CSF level on QAlb considering age, sex, and APOE as covariates.

Results: CSF data were expressed in terms of mean ± standard deviation. At each step of the backward regression, variables were excluded based on the highest p-value. Eventually, the candidate variables were reduced to 4: IL-4, IL-8, TNF-a, MIP-1. Among AD patients, higher values of IL-4 (β =0.356, 0.005) and IL-8 (β =0.249, 0.05) were associated with higher Qalb values, while MIP-1 (β=-0.274; p=0.032) and TNF-a (β=-0.248; p=0.031) showed a significant negative association. Age was also positively associated with Qalb (β=0.283; p=0.016).

Discussion: Despite the overall integrity of the BBB, its permeability could either influence or be influenced by central neuroinflammation, reflected by CSF cytokine levels. In particular, CSF levels of IL-4 and IL-8, neuroprotective cytokines, were positively associated with BBB permeability, while levels of TNF-a and MIP-1, proinflammatory and chemotactic, were negatively associated with BBB permeability. This is in line with previous studies that showed that patients with a more intact barrier are those with a more prominent neurodegeneration (e.g. higher CSF tau-pathology), that could in turn support a pro-inflammatory pattern. [2]

Conclusions: Higher levels of intrathecal neuroprotective cytokines are correlated with higher BBB permeability, while a tighter BBB is associated with increased proinflammatory activity in the CSF. These results suggest that BBB integrity and neuroinflammation can influence each other in AD, in a likely non-univocal way. More studies are needed to verify the mechanisms behind this interplay.

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## THE RELATIONSHIP BETWEEN VISUAL HALLUCINATIONS AND RESTING-STATE EEG SPECTRAL AND FRACTAL FEATURES IN DEMENTIA WITH LEWY BODIES


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Introduction: Recurrent complex visual hallucinations (VH) are one of the core features of Dementia with Lewy Bodies (DLB) [1]. VH have been shown to have high specificity for DLB especially in differential diagnosis with Alzheimer's disease (AD). Previous work has shown that power spectral density (PSD) analysis of resting-state EEG (rs-EEG) shows correlations between some frequency bands (e.g., θ), individual alpha frequency (IAF) and VH. However, new tools that improve early diagnosis and fine-grained symptom-based stratification also within the DLB population with higher sensitivity and specificity are desirable.

Aim: To assess differences of rs-EEG data between hallucinated and non-hallucinated DLB patients using innovative non-linear approaches and compare findings with AD and healthy controls

Methods: We retrospectively analyzed rs-EEG recording (eyes-closed, 19 channels with 10/20 system) of 49 hallucinated DLB patients (DLB-VH+), 39 non-hallucinated DLB (DLB-VH-), 34 AD patients and 20 healthy controls (HC). Groups did not differ for age, sex, gender and education. EEG data were analyzed using a nonlinear method called Higuchi's Fractal Dimension (HFD) [2,3] and the results were compared with a standard linear method based on PSD and IAF. A repeated-measures ANOVA was performed on band values to investigate the GROUP×BAND interaction effect.

Results: Alpha band power was significantly higher for HC than for the other groups (ps < 0.001). One-way ANOVA showed statistical

differences between groups for IAF [F(3,126)=6.026; p<0.001] and HFD [F(3,131)=8.021; p<0.001]. IAF values were significantly lower for the DLB-VH+ (mean: 7.51 Hz±SE: 0.25 Hz) compared to the other groups (AD: 9.04 ± 0.19; HC: 8.71 ± 0.21; DLB-VH-: 8.58 ± 0.26). No differences were observed among other groups. Fractal dimension values were significantly lower for the DLB-VH+ (mean: 1.71±se: 0.02) compared to the other groups (AD: 1.83 ± 0.01; HC: 1.86 ± 0.01; DLB-VH-: 1.80 ± 0.01). No differences were observed among other groups. A comparison of Bayes factors found that differences between DLB-VH- and VH+ were three times more likely to be detected using HFD than the best-performing linear method (i.e., the IAF) and six times more likely than the theta band.

Discussion: rs-EEG differences between DLB with and without VH might be better characterized by fractal dimension analysis than to a more traditional power spectrum approach. HFD is at least 3 times more sensitive than linear analysis. This suggests that less complex brain dynamics at rest, as expressed by the HFD metric, might be associated with the presence of VH.

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## RAPIDLY PROGRESSIVE DEMENTIA ASSOCIATED WITH SIAD AND MYOCLONUS

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Introduction: We describe a man who developed, after a minor head trauma, SIAD, cognitive disturbances and mild myoclonus. Head trauma is a common cause of SIAD with consequent hyponatremia that causes mental confusion, cognitive impairment and myoclonus. However, the temporal profile should prompt the clinician to investigate further explanations. The man we described did not improve after correction of hyponatremia and allowed our team to explore a broader differential diagnosis.

Case report: A 59-year-old man, with no past medical history, came to our attention complaining about a one-month history of progressive cognitive problems. Neurologic examination revealed mild temporo-spatial disorientation, severe psychomotor slowing, working-memory and attentional deficits with fluctuations and tangential speech. Myoclonic movements were present (limbs and perioral region). Blood examinations showed severe hyponatremia, with reduction of blood osmolarity. About one month before he had an episode of loss of consciousness, with consequent head trauma. The clinical history suggested a post-traumatic Syndrome of Inappropriate Antidiuresis (SIAD) and intravenous sodium infusion and tolvaptan were administered. Brain MRI with gadolinium showed normal findings. The patient developed a gradual improvement; sodium level gradually increased and, when stable, he was discharged. One month later, he was admitted to our hospital because he developed the same symptomatology previously described. At the admission, sodium and blood osmolarity levels were normal. 3-T brain MRI with gadolinium, associated with brain FDG-PET, showed findings compatible with encephalitis. Then we found positive CSF antibodies anti-leucine-rich glioma-inactivated 1 (LGI1). The patient was treated with high dose steroid (methylprednisolone 1 g intravenously for 5 days), associated with a cycle of intravenous immunoglobulins (2 g/kg over 5 days). Symptoms remitted completely and the patient was discharged with a steroid taper. The last neurologic follow-up at 6 months showed complete clinical remission.

Discussion: According to clinical symptoms, radiological signs and laboratory results, we made diagnosis of anti-LGI1 encephalitis. Our first diagnosis of post-traumatic SIAD was the most probable in light of the clinical improvement with the correction of hyponatremia and the normal findings of all the other exams performed, but the clinical evolution took us towards a different direction.

Conclusion: This case-report emphasizes that clinical observation of the patient and the temporal profile of clinical signs are a central key of the diagnostic process.

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## AN ATYPICAL PHENOTYPE OF VCP MUTATION WITH EPILEPTIC SEIZURES AND BEHAVIOURAL FRONTOTEMPORAL DEMENTIA

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Introduction: Valosin-Containing Protein (VCP) mutations are rare causes of behavioural frontotemporal dementias (bvFTD) with TDP43-immunoreactive inclusions. This gene encodes for an AAA-ATPase involved in protein quality control and clearance. Studies of phenotype-genotype correlations reported a few cases of isolated bvFTD but never with epilepsy among clinical findings.

Aim: To describe clinical and neuroimaging findings of a patients with VCP mutation presenting with epilepsy and isolated bvFTD.

Case summary: A 58 years-old woman came to our attention for a subacute deterioration of general conditions with psychomotor slowness, marked abulia, perseveration and repeated falls with a progressive loss of autonomy occurring in the last few weeks. In the ten months before she presented important behavioural changes (disinhibition, socially inappropriate behaviour, hyperorality), attentive problem, delusions, sleep disturbances, incontinence and the recrudescence of epileptic seizures appeared for the first time 6 years before. Medical history was positive for psychiatric disturbances (eating disorder and recurrent depression). Her mother and aunt had dementia with behavioural changes and epileptic seizures by the age of 70s (mother and aunt). At the admission her neurologic examination showed prominent negative frontal signs (apathy and reduction of global initiative), perseveration and emotional lability with decontextualized crying fits. Neurological examination showed reduced fluency, rare phonemic paraphasias. Neuropsychological assessment showed executive deficits, constructive apraxia and a dysregulation of emotions (FAB 5/18, MoCA p.c. 7,52). The patient underwent brain FDG-PET/MRI that showed a marked hypometabolism of the frontal lobes, and mild hypometabolism of parietal, lateral temporal lobes and anterior caudates, and only a slight frontal lobe atrophy. CSF analysis showed only a slight hyperproteinorrachia (0.50 g/L) and brain barrier damage, with the absence of auto-antibodies. Finally, the genetic test showed a mutation on the N-terminal domain of the VCP gene (R93C), and it was possible to formulate the diagnosis of definite bvFTD. There were not signs of muscles or bone involvement.

Conclusion: VCP gene mutations have been associated with a plethora of diseases including inclusion body myopathy with Paget's disease and frontotemporal dementia. The VCP R93C mutation is the one of the first 4 more frequent VCP mutations, and it has never been associated with epilepsy. Our report confirms the high degree of heterogeneity of VCP disease and the importance of VCP genetic assay even in cases with seizures and frontal lobe syndrome.

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## INTRANASAL ESKETAMINE IMPROVES DEPRESSION AND COGNITIVE DEFICITS IN ELDERLY PATIENTS WITH LATE-ONSET RESISTANT DEPRESSION: A CASE SERIES WITH COGNITIVE AND EYE-TRACKING STUDY

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Introduction: Depression is often accompanied by cognitive dysfunctions, representing a clinical challenge for the differential diagnosis and for the selection of patients that could benefit from new generation antidepressant therapy. [1,2] Eye movement analysis may offer a physiological surrogate marker of brain efficiency. [3]

Aim: To analyse long-term changes of psychiatric and cognitive performances and eye movements patterns in a series of 3 patients with late-onset resistant depression undergoing treatment with intranasal Esketamine.

Materials and methods: Patients were studied at baseline and 3- and 6-months interval after Esketamine treatment with neuropsychological tests, psychiatric scales (Hamilton scale and Montgomery-Asberg Depression Rating Scale) and eye tracker (Eyelink 1000 Plus, SR Research) recordings. The session consisted of a free-viewing task with observation of 20 images with emotional and/or neutral content presented on a PC screen for 10 seconds. The following descriptive parameters were extracted: saccades amplitude and velocity, blink rate, duration of fixations and pupillary dilation.

Results: One woman aged 79 years and two men both aged 71 suffering of resistant major depressive disorder were recruited. At baseline depression was moderate-severe with coexisting impairment of cognitive functions (MoCA: score range 18 - 27), with deficits of executive functions, verbal and visual memory, visuoconstructive functions. All three patients underwent intranasal Esketamine treatment up to maximal doses within 4 weeks, in add-on to standard and stable antidepressant therapy. In all patients a significant psychiatric response was documented already after one month, with marked improvement of depression achieved after 6 months, with regression in one patient. Global cognitive improvement was observed at 3 and 6 months in 2 patients (MOCA values changed from 18 to 24 in the 1st and from 21 to 24 in the 2nd) while the third patient with minimal cognitive deficits remained stable (MOCA: 27). The recording of eye movements suggests improvements towards the values of age-matched healthy controls for blink-rate, speed of saccadic movements and pupillary dilation, despite these results were affected by interindividual variability.

Conclusions: Cognitive dysfunction associated with depression represents a clinical challenge for the differential diagnosis with neurodegenerative disease. The stable improvement of depressive symptoms and cognitive deficits, along with neurophysiological markers of whole brain efficiency such as eye movements, makes esketamine effective as add-on therapy even in late-onset older depressed patients.

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## RIGHT TEMPORAL VARIANT OF FRONTOTEMPORAL DEMENTIA AND PAGET'S DISEASE OF BONE IN A PATIENT WITH BIOMARKER FEATURES OF ALZHEIMER'S DISEASE

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Aims: To describe the clinical, neuropsychological, neuroradiological and neurophysiological characteristics of a patient with right temporal variant of frontotemporal dementia (rtvFTD) and Paget disease of bone (PDB) with biomarkers features of Alzheimer's disease (AD).

Materials and methods: The patient underwent complete clinical, neuropsychological assessment, brain MRI and FDG-PET, paired-pulse TMS (pp-TMS) examination, CSF and genetic NGS analysis.

Results: The patient presented at the age of 64 behavioural abnormalities with mild disinhibition and impulsivity associated with episodic memory and attention deficits. He had previously been diagnosed with Paget's disease of bone (PDB). Neuropsychological evaluation 2 years after onset showed deficits in verbal memory, attention and executive skills, and impaired social cognition. Also present were naming and verbal fluency deficits, and prosopagnosia. Visuo-spatial, constructional and perceptive abilities were spared. Brain MRI showed asymmetric right temporal atrophy particularly involving the anterior temporal lobe. The neuropsychological battery specific for the right hemisphere, Batteria sul Linguaggio dell'Emisfero Destro - BLED [1], showed a score below the cut-off (28/60). In pp-TMS, Short-interval IntraCortical Inhibition was reduced, and IntraCortical Facilitation increased only for right cortical stimulation, indicating hyperexcitability, according with atrophy. FDG-PET showed severe cortical hypometabolism in lateral temporal cortex predominant at right, associated with moderate hypometabolism in mesial, lateral frontal and inferior parietal regions. Temporo-mesial regions were spared. CSF markers were consistent with AD pathology, showing increased levels of tau and p-tau and decreased Abeta42. Family history was positive for dementia. However, preliminary NGS analysis of AD/FTD genes did not find any clear pathogenic mutations.

Discussion: rtvFTD is a rare clinical phenotype, characterized by early behavioural disorders, prosopagnosia and episodic memory impairment [2]. FTLD-TDP type C pathology, pure or associated with tauopathy has been demonstrated in almost all rtvFTD patients while Alzheimer's disease is very rare [2]. The association

of rtvFTD, PDB and AD biomarkers, as in our patient, is even more unusual as PDB has been associated with FTD in the so-called multisystem proteinopathies, most of them linked to VCP mutations [3]. The co-occurrence of different neurodegenerative pathologies could explain this complex clinical presentation.

Conclusions: We emphasize the importance of deep clinical characterisation and assessment of amyloid status also in patients with relatively clear rtvFTD.

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## CLINICAL EEG DISTINGUISHES AMYLOID-POSITIVE AND FDG-PET-POSITIVE PATIENTS: A COMPREHENSIVE STUDY OF A HOSPITAL-BASED POPULATION

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Background and aims: Alzheimer's disease (AD) is a significant global health concern. Currently, three anti-beta amyloid monoclonal antibodies are approved or under examination in U.S. and in Europe for the treatment of patients with early AD. The increasing need for a reliable aetiological diagnosis of AD has led to the grouping of already available and possible future biomarkers into the AT(N) framework. Considering the high cost-effectiveness, availability and low invasiveness of the technique, we aimed at exploring the usefulness of EEG for stratifying cognitively impaired patients within and outside the AD continuum from a hospital-based cohort.

Materials and methods: We conducted a retrospective evaluation of 212 patients referred to the Memory Center of IRCCS San Raffaele Hospital, Milan, Italy. All patients underwent clinical and neuropsychological assessments, along with lumbar puncture and 19-channel EEG. Structural neuroimaging with MRI or CT scans and brain FDG-PET were also performed. Individual alpha frequency (IAF), i.e., the frequency within the extended alpha range (5–13 Hz) showing a power peak in the parieto-occipital power spectrum, was extracted from the EEG of each patient. The cohort was stratified according to the AT(N) classification, and IAF was compared among patient groups. Correlations between IAF, clinical data and CSF biomarkers were also explored.

Results: Sociodemographic and clinical features were similar across groups. IAF was significantly lower in A+ than in A- patients ($p=0.03$) and in FDG-PET-positive (FDG-PET+) than in FDG-PET-negative (FDG-PET–) patients ($p<0.01$). After stratifying patients according to amyloid and FDG-PET status, IAF could distinguish A+/FDG-PET+ patients from A–/FDG-PET+ ($p=0.02$) and A–/FDG-PET– ($p<0.01$) subjects. The comparison between T+ and T– patients and between subjects showing or not brain atrophic changes at structural neuroimaging did not offer significant differences. IAF correlated neither with MMSE, nor with disease duration, nor with CSF biomarkers levels.

Discussion and conclusions: Findings are in line with previous evidence, showing a global slowing of the cortical electrical activity as a consequence of AD. Furthermore, our results suggest that EEG alteration may be directly linked to amyloid rather than tau accumulation, emerging thus as a possible early biomarker of AD. EEG also showed a close relationship with cerebral metabolic status, further supporting its use for the identification of patients in greater need for further diagnostic and therapeutic interventions. In the upcoming era of disease-modifying therapies for AD, EEG is a valid and cost-effective tool for the stratification of cognitively impaired patients.

## LITHIUM INTOXICATION MIMICKING A RAPIDLY PROGRESSIVE DEMENTIA: CLUES INTO AN IMMUNOMEDIATED ETIOLOGY

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Objectives: To present a case of lithium intoxication mimicking a rapidly progressive dementia.

Material: A 68-year-old man with a past medical history of bipolar disorder on chronic lithium therapy and moderate chronic renal failure was admitted due to alterations of his level of consciousness and visual hallucinations started 20 days before. Glasgow Coma Scale upon admission was 10.

Methods: Case report.

Results: Baseline routine blood tests excluded underlying systemic infections, toxic and metabolic causes. Lithium serum concentration was mildly elevated (1.56 mmol/L [range 0.50-1.50]). Electrocardiogram and brain magnetic resonance imaging showed no significant abnormalities and an electroencephalogram (EEG) performed on day 12 showed non-specific encephalopathic signs. Cerebrospinal fluid (CSF) routine analysis including DNA testing for common viral, bacterial, and fungal pathogens did not reveal abnormalities, except for a non-specific mild increase in protein levels. Most serum and CSF cytokines were elevated, except for serum interferon-gamma (IFN-gamma) and IL-17A, and for CSF IL-10, INF-gamma and IL-17A. Lithium was withdrawn and both the patient's neurological state and EEG started gradually to improve.

Discussion: This case highlights the lack of a reliable parameter to support the diagnosis of lithium neurotoxicity. The discrepancy between mildly increased lithium levels and the severe neurological presentation could be partly explained by the delayed lithium elimination from brain parenchyma when compared to plasma, which can be further increased by concomitant renal failure as in the present case. We then provide evidence for a potential role of an immune mediated response in the central nervous system driving this clinical manifestation. In fact, lithium has differential effects on immune cells lines, as it increases granulocytes number and activity, while inhibiting T-cells production. The only non-elevated cytokines in both in serum and CSF were IFN-gamma and IL-17 which are known to be associated with CD4+ helper, CD8+

cytotoxic and Th17 cells but not with granulocytes, suggesting that this immune signature could be driven by lithium itself.

Conclusion: Lithium-induced neurotoxicity can be challenging to recognize due to the lack of specific tests. Its diagnosis is currently based on the exclusion of other causes of neurological impairment and on symptoms regression after therapy discontinuation. This case supports the need for a more reliable laboratory parameter to help detect this condition which can be reversible if promptly recognised, avoiding the development of permanent neurological damages. Finally, we provide clues into the possible role of intrathecal cytokines release in its pathophysiology.

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## MERGING SERUM OREXIN-A AND NEUROFILAMENT LIGHT CHAIN IN ALZHEIMER'S DISEASE AND FRONTOTEMPORAL DEMENTIA: NEW EVIDENCE OF OREXIN SYSTEM DYSREGULATION ASSOCIATED WITH NEURODEGENERATION


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Objective: Orexin-A (OXA) determination in cerebrospinal fluid (CSF) in neurodegenerative dementias (NDs) is an invasive technique and of limited utility when not associated with other biomarkers. The main aim of this study is to evaluate OXA in different biological fluids, in particular serum, in patients affected by several NDs. The secondary aim is to evaluate OXA concentration compared to other neurodegeneration-associated peptides, in particular serum neurofilament light chain (NFL).

Materials: Patients affected by several NDs were enrolled at IRCCS Istituto Auxologico Italiano, Departments of Neurology of Milan and Piancavallo. A group of patients with no evidence of NDs served as controls.

Methods: Both patients and controls underwent OXA determination in CSF and serum (ELISA). Other neurodegeneration-associated peptides measured were: serum NFL (Simoa), CSF total-tau (t-tau, ELISA), CSF phospho-tau (p-tau, ELISA), CSF Amyloid beta 1-40 (Abeta 1-40) and Amyloid beta 1-42 (Abeta 1-42, ELISA).

Results: Sample size was the following: 10 Alzheimer's Disease patients (pts), 19 bv Fronto-Temporal dementia pts, 20 Normotensive Hydrocephalus patients and 20 controls. We found a positive correlation between OXA levels in CSF and blood in the whole group of subjects (ND plus controls; Pearson correlation coefficient CC= 0,32, p=0,026). Mean OXA concentration in CSF was significantly reduced in patients with NDs compared to controls (p=0,04). We also found an inverse correlation between OXA and NFL in ND group (CC= -0,37, p=0,04).

Discussion: Despite the small sample size, combining NFL and OXA measures in serum we found some evidence of a link between neurodegeneration progression and orexin system dysregulation in a non-invasive and cost-effective way. Furthermore, the positive correlation between OXA levels in CSF and blood both in ND and control groups could pave the way to peripheral OXA dosage in neurodegenerative dementias.

Conclusion: OXA level in different biological fluids may represent a biomarker of degeneration in ND, especially when correlated to NFL.

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## CAG REPEATS WITHIN THE NON-PATHOLOGICAL RANGE IN THE HTT GENE INFLUENCE PLASMA NEUROFILAMENT LIGHT CHAIN CONCENTRATION IN PRODROMAL ALZHEIMER'S DISEASE


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HTT is a gene involved in axon trafficking. It contains a key region of CAG repeats which is responsible, when expanded beyond 39 repeats, of Huntington's disease (HD). CAG expansions ranging from 27 to 35 repeats are termed as intermediate alleles (IAs)[1]. Several studies suggest an association between HTT and AD and we previously showed that IA increase the risk of progression from SCD to MCI [2]. In the present work we aim to explore the association between CAG repeats and the concentration of AD CSF biomarkers and plasma neurofilament light chain (NfL). Ninety-six patients (36 SCD and 60 MCI) underwent blood collection

for measurement of plasma NfL concentration and HTT genotype analysis, CSF collection for Aβ42, Aβ42/Aβ40, total-tau (t-tau) and phosphorylated-tau (p-tau) measurement. They were rated according to the A/T(N) system[3] and classified AP+ when A+ was associated with either T+ or N+, or AP- when they were rated as A- (regardless of T and N classification), or as A+/T-/N. There were no significant correlations between the number of CAG repeats and any CSF AD biomarkers. Nevertheless, in the AP+ group, NfL showed a non-linear distribution in relation to HTT CAG repeats. A quadratic model best fits the relationship between HTT length and NfL (F [2, 34]=5.45, p=0.009, adj.R2=0.243). The relationship was described by the equation: y= -17.86x^2+0.39x+222.61. As there were only four IA carriers in the ATN+ group, for the further analysis we focused on patients in the AI- group. To ascertain that CAG repeats length was independent from other confounding factors, we performed a backward linear regression analysis. We considered plasma NfL as the dependent variable. Age at baseline, age at onset, APOE ε4+, Aβ42, Aβ42/ Aβ40 ratio, t-tau, p-tau and HTT were included as covariates. The final model was significant (F [1,27]=5.18, p=0.031, adj.R2 =0.161) and included only HTT (B = -1.42 [95%C.I. = -2.71: - 0.14, p=0.031) as the significant variable. Several reports showed that increasing repeats length below the disease threshold in HTT confers advantageous changes enhancing the function of HTT, stabilizing the interaction with the brain-derived neurotrophic factor (BDFN). This positive effect seems to decrease in the IA range. In line with this evidence, our data suggest that a higher number of CAG repeats, below the IA threshold, may confer a sort of protection against neurodegeneration associated with Alzheimer's disease.

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## FREQUENCY AND ASSOCIATED FACTORS OF SCD IN ITALIAN MEMORY CLINICS: THE PRECLINICAL COGNITIVE IMPAIRMENT STUDY IN THE ELDERLY (PRECISE)


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Background and objectives: Subjective cognitive decline (SCD) is a condition characterised by the subjective reporting of a deterioration in cognitive abilities, which is not then confirmed by formal cognitive testing. The prevalence of SCD in studies is about 25%, but prevalence estimates vary widely between studies (1). To assess the frequency and clinical factors of SCD in a large hospital cohort of non-demented elderly subjects.

Methods: The Preclinical Cognitive Impairment Study in the Elderly (PreCISE), is a multicentre study on SCD involving three memory clinics located in central and southern Italy. SCD was diagnosed according to the criteria of Jessen et al. (2). Mild Cognitive Impairment (MCI) was diagnosed according to the modified criteria of Petersen et al. (3).

Results: From a total of 1,675 subjects consecutively evaluated over a 5-year period in the three memory clinics, after exclusion of subjects with dementia, low MMSE and parkinsonism/psychosis, 1,080 subjects without dementia were included. Of these, 195 (11.6%) were controls (subjects without SCD and MCI; 47.7% men; mean age 66.3 ± 9.6 years), 269 (16.1%) were subjects with SCD (69.1% men; mean age 65.9 ± 8.7 years) and 616 (36.8%) subjects with MCI (55.2% men; mean age 70.9 ± 8.5 years). Comparing controls and MCI with SCD, the latter group was statistically more frequent in women than in men (p .0001 for both comparisons). In contrast, education was statistically lower in the MCI group than in controls and the SCD group (p .0001 for both comparisons). Similar values were found between controls and SCD in the Montreal Objective Cognitive Assessment, the Geriatric Depression Scale, the number of instrumental ADL lost and the Unified Parkinson's Disease Rating Scale-part III (p 0.1 for all comparisons). In contrast, subjects with SCD and MCI had a higher total burden of neuropsychiatric symptoms (Neuropsychiatric Inventory, total score) than controls (p .0001 for both comparisons).

Conclusions: The frequency of SCD in the PreCISE study was over 15%. SCD appears to be more frequent in women than in controls and MCI. Compared to controls, SCD is associated with a higher burden of neuropsychiatric symptoms, but no differences in overall cognition.

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## LANGUAGE VARIANT OF ALZHEIMER'S DISEASE. A TWO CASE SERIES


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Objectives: Alzheimer's disease (AD) is the most common age-related dementia, and it usually presents with episodic memory impairment at onset. Presenile and atypical forms are described in about 15% of the cases and despite they are increasingly recognized, no universally accepted classification of the phenotypic variants has been established.

Differential diagnosis of atypical forms may be tricky. Here we present our case series of two AD language variants (lAD).

Materials and Methods: We used neuro-psychological profile to assess cognition, neuroimaging tools to detect neurodegeneration, amyloid tracer PET (AMY-PET) and/or tau protein, amyloid-β 40– 42 (Aβ40-42) and Aβ42/Aβ40 in cerebrospinal fluid (CSF), for identify pathology biomarkers.

Results: GM is a 74 years-old male that presented at our Clinic with a 4 years history of dysphonia and 2 years of language fluency reduction and bradyphrenia. Language assessment was likely compatible with the agrammatic non-fluent of primary progressive aphasia (PNFA), mimiking frontotemporal dementia language variant (lvFTD). CSF results allowed us to make a diagnosis of lAD. Phosphorylated tau protein was 66,7 pg/ml; Aβ1-40 was 595 pg/ml; Aβ1-42/Aβ-20 was 0,046. AMY-PET was positive for amyloid plaques. RG is 69 years-old male, who had an onset characterized by anomies which quickly evolved into logopenic aphasia. At neuro-psychological profile semantic and phonological fluency were compromised. 5 years after the onset verbal and visuo-spatial memory were impaired. AMY-PET was positive for amyloid plaques. lAD represents less than 1% of our cases of atypical AD.

Discussion: The differential diagnosis of lAD with others neurodegenerative disease is possible when at least one biomarker of in vivo AD pathology is positive: a CSF profile consisting of decreased Aβ40 together with increased total tau (T-tau) or 181-phosphorylated tau (P-tau) concentrations, or presence of amyloid plaques detected with AMY-PET. Despite the initial symptoms leaded the diagnosis towards other pathologies, the use of CSF biomarkers and PET allowed us a correct diagnosis.

Conclusions: Language disorders may be difficult to classify at onset. Our cases show that CSF biomarkers may be necessary to make a correct diagnosis.

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## POSTERIOR CORTICAL ATROPHY VARIANT OF ALZHEIMER'S DISEASE PHEONOTYPES. A SIX CASES SERIES

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Aims: Alzheimer's disease (AD) starts in the seventh decade of life or later, even if early-onset AD (EOAD at age of 64 or younger) is described in about 15% of the cases. EOAD has a more aggressive course and roughly 25% of subjects shows an atypical clinical onset with preserved episodic memory but with focal cortical symptoms like apraxia, visual, executive or language dysfunctions. Visuospatial variant, also called posterior cortical atrophy (PCA), starts typically with the loss of visual and complex visuospatial functions. Diagnosis is challenging due to the wide range of symptoms at onset and the multiple underling pathologies. Neurological and neuropsychological examination, neuroimaging and pathology biomarkers are important for diagnosis. Here, we describe our case series of 6 patients with PCA and in vivo biomarker positivity for Aβ deposition, with various clinical atypical aspects at onset.

Materials & Methods: We conducted a retrospective study of patients incoming in our clinic between January 21 and December 22, in order to characterize AD visuospatial variants with different onset and underling pathologies. Atypical and EOAD patients underwent neurological and neuropsychological evaluation, assessment of neurodegeneration by brain MRI and 18FDG PET and assessment of pathology by amyloid tracer PET and/or cerebrospinal fluid (CSF) biomarkers.

Results: PCA was identified in 40% of our atypical AD patients. Two of them had acalculia as first symptom, then followed by alexia, agraphia, and difficulty with perception of distance in the first patient, while memory disfunction appeared soon after in the second. A third patient had memory impairment and acalculia at onset followed by unilateral mild extrapyramidal symptoms, agraphia, alexia and digital agnosia like a PCA-Corticobasal degeneration phenotype. The fourth patient had deficits of praxic and numerical abilities at onset followed by spatial disorientation and digital agnosia, while the fifth patienthad memory impairment and anomia at onset and subsequently she developed Gerstman Syndrome The last patient had neuropsychiatric onset with hallucination and subsequently acalculia, praxic and memory disfunctions, and extrapyramidal signs like a PCA-Lewy body dementia phenotype.

Discussion and Conclusions: Diagnosis of PCA is challenging, due to different onset and pathologies that can underlie this syndrome. Most of our patients presented numerical deficits at onset as the only common feature, among a wide range of symptoms and they were all EOAD. Neuropsychiatric symptoms were prominent only in one patient. Our data confirm that PCA spectrum is wide, so neuroradiological imaging and CSF biomarker are crucial for diagnosis.

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## DOES COVID-19 INFECTION REVEAL OLIGOSYMPTOMATIC DEMENTIA?

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We report the case of a 62-year-old man, who was referred to the ER for an episode of loss of consciousness followed by persistent psychomotor slowing down and agitation. Two weeks before he experienced COVID-19 infection. In ER were performed TC scan and MRI with gadolinium that did not show any DWI lesions and showed two hemosiderin microbleeds in the contest of diffuse subcortical white matter lesions. EEG showed diffuse right fronto-temporal slowing. In the cerebrospinal fluid were high protein levels; no cellularity, no oligoclonal bands, no neurotropic viruses' infection signs, no onconeural or autoimmune encephalitis antibodies were detected. In the beginning he was treated with iv Ig 0.4/kg for V days. Neuroleptic treatment and VPA for behavioural symptoms were started. Total body CT scan and total body PET scan were unremarkable. Since few months before, relatives noted some behavioural symptoms: the patient was repetitive and anhedonic. Beta2-amyloid,

TAU, p-TAU levels were normal; RT-QuIC for prion disease was negative. PET-FDG showed hypometabolism in the fronto-lateral and in the fronto-parietal regions bilaterally. Genetic panel for inherited dementia did not show any pathogenetic mutations. During hospitalisation frontal behavioural symptoms persisted. The first neuro-psychological examination showed FAB and trail making B measures compromised. One year later neuro-psychological measures improve except for slight working memory deficits and behavioural symptoms improved. Our case report may suggest that covid-19 infection can worse a slight pre-existing cognitive decline through superimposed transient delirium.

## A CASE OF LEWY BODIES DEMENTIA-ALZHEIMER'S DISEASE TYPE CO-PATHOLOGY ASSOCIATED WITH GBA MUTATION

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Introduction: Glucocerebrosidase (GBA) gene encodes for a lysosomal enzyme involved in the degradation of the complex sphingolipid glucosylceramide. Heterozygous GBA variants lead to a partial enzymatic loss of function, associated with a 5-fold increased risk of developing parkinsonism with early and rapidly progressive cognitive decline. In this report, we describe the case of a patient with GBA variant, dementia with parkinsonism and amyloidopathy.

Case description: A 77 years old man presented since 4 years frequent episodes of time and space disorientation and "mental confusion" with fluctuating course. In the last year, he experienced irritability with verbal aggressivity, unjustified fears and complex visual hallucinations (i.e. people, animals…). Moreover, sleep vocalisation and dream enactment were referred. He take sodium valproate, 600 mg/die, and promazine, 20 mg/die, interrupted because he manifested marked psychomotor slowing, tremor and progressive loss of autonomy. He presented altered mental status with fluctuating course, global aphasia with mutism, difficulty in maintaining upright position, akinetic-rigid parkinsonism, bilateral superior arms myoclonic-like movements, bilateral palm-chin reflex and grasping. At the blood tests, low serum levels of transferrin were detected. Electroencephalogram showed parieto-occipital theta rhythm and presence of sub-continuous diffuse sequences of delta rhythm with triphasic morphology. Brain MRI showed cortical and subcortical atrophy. Positron emission tomography with fluorodeoxyglucose (18F-FDG) revealed diffuse hypometabolism, in particular at the frontal regions. At the cerebrospinal fluid examination, a high level of protein (96.8 mg/dL, n.v. 20-45), IgG (12.3 mg/dL, n.v. 0-3.4), intrathecal synthesis (5.35), hyperphosphorylated tau (73.8 pg/mL, n.v. <56.5), total tau (552 pg/mL, n.v. <404) and low level of β-amiloid (Aβ1-40 3089 pg/mL, Aβ1-42 171 pg/mL, n.v. >599, Aβ1-40/Aβ1-42 0.055, n.v. >0.069) protein, were found. The research of GBA gene variants through Dried Blood Spot (DBS) analysis revealed the presence of the heterozygous mutation c.1224 G>A.

Conclusion: To the best of our knowledge, this is the first case of GBA gene heterozygous mutation presenting as a Lewy Body Parkinsonism and Alzheimer's Disease-type co-pathology.

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## TMS-EEG BIOMARKERS OF MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S AND PARKINSON'S DISEASES

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Background: Transcranial magnetic stimulation (protocols have demonstrated analytical validity in discriminating different forms of MCI, while the role of navigated transcranial magnetic stimulation (in coregistration with electroencephalogram (i e the TMS EEG technique, is still unknown in this field.

Objective: To investigate neurophysiological hallmarks of sensorimotor cortex function in MCI to determine whether the sensorimotor network shows peculiar alterations in different type of MCI.

Methods: We studied several TMS EEG parameters of the sensorimotor cortex in a group of 30 healthy subjects and 30 MCI subjects, including MCI Alzheimer's disease (MCI AD) and MCI Parkinson's Disease (MCI PD)

Results: MCI subjects showed reduced motor cortex (M 1 excitability and disrupted EEG synchronization (decreased intertrial coherence ITC) in alpha, beta and gamma frequency bands compared to Controls (Ferreri et al 2021 The degree of alteration in M 1 excitability and alpha ITC was comparable between MCI AD and MCI PD Importantly, gamma ITC impairment in the stimulated M 1 was greater in MCI AD than MCI PD, while beta ITC showed an opposite trend

Conclusions: Specific cortical changes reflecting deficit of synchronization within the cortico basal ganglia thalamic cortical loop in MCI may reflect pathological processes underlying different type of neurodegeneration.

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## THE DEGENERATION OF LOCUS COERULEUS OCCURRING DURING OF ALZHEIMER'S DISEASE: A NEUROIMAGING FOLLOW-UP STUDY

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Objective: To describe the degeneration of the noradrenergic nucleus Locus Coeruleus occurring during Alzheimer's Disease progression in a group of cognitively impaired patients.

Material and methods: A sub-group of patients belonging to a wider population (N=163) previously submitted to a baseline Locus

Coeruleus MRI, underwent a follow-up assessment after 2.5 years. The integrity of the Locus Coeruleus was evaluated profiting from an already published and standardized template-based approach, and it was expressed through the intensity parameter Locus Coeruleus Contrast Ratio (LCCR) and the volumetric one Locus Coeruleus number of voxels (LCVOX).

Results: The final population which completed the neuroimaging follow-up counted 58 subjects. Forty-six of them had a baseline diagnosis of Mild Cognitive Impairment (MCI), while the other 12 were Alzheimer's Disease Demented patients (ADD). At the end of the follow-up, 19 MCI had converted to dementia (cMCI), while 27 remained stable (ncMCI). LCCR was significantly lower in patients when compared to healthy controls, at the baseline assessment. At the follow-up, a global reduction of LCCR and LCVOX was detected in the whole group ($p<0.001$). Such a reduction was particularly significant in the MCI group and was driven by the cMCI, which had converted to ADD during the follow-up. At baseline, LC parameters were not significantly different between ncMCI and cMCI, while at the follow-up assessment values of the former group were higher than those of the latter one, both in terms of LCCR ($p=0.037$) and LCVOX ($p=0.008$). The percentual reduction of LC volume was significantly higher in cMCI than in ncMCI (67% vs 33%, respectively – $p= 0.039$), and directly correlated with MMSE worsening (Rho=0.277, $p=0.043$).

Discussion: The Locus Coeruleus is the first brain structure involved in Alzheimer's pathology [1] and suffers from a marked degeneration already at the clinical onset of the disease [2]. However, pathological studies show that this nucleus undergoes progressive damage across all the Braak stages [3], with the most severe disruption occurring at the transition from Braak stage III/IV to V/VI [2], which clinically might correspond to the conversion from MCI to dementia. We report, for the first time, this phenomenon in vivo. In our patients, the Locus Coeruleus showed a significant reduction in signal intensity and volume shrinkage that reached their maximum in the group of cMCI, i.e., those who passed from the MCI phase to dementia.

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## RIGHT TEMPORAL VARIANT FRONTOTEMPORAL DEMENTIA: A MULTIMODAL MRI ANALYSIS OF A NEW EMERGING SYNDROME

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Introduction: Right temporal variant frontotemporal dementia (rtvFTD) is emerging as a new entity among the FTD-spectrum, characterized by a predominant neurodegeneration of the right anterior temporal lobe (rATL) and a peculiar clinical presentation, involving face and emotions recognition deficits, behavioral features, memory loss, and naming difficulties. Clinical detection is challenging, since rtvFTD shares features with both the behavioral variant FTD (bvFTD) and the semantic variant primary progressive aphasia (svPPA), and there is no consensus yet on its designation and characterization. Although rATL neurodegeneration is a hallmark of this syndrome, only a few studies investigated patterns of grey matter (GM) atrophy. Even less is known about white matter (WM) involvement. We conducted a preliminary study on the rtvFTD neuroimaging features in a small sample of patients using multimodal magnetic resonance imaging (MRI).

Methods: We compared rtvFTD ($n = 3$) and svPPA ($n = 3$) patients with a group of healthy controls ($n = 27$) in GM volume using voxel-based morphometry (VBM) and WM microstructural integrity using tract-based spatial statistics (TBSS). Age and disease duration were considered as covariates of no interest.

Results: We found that svPPA patients showed GM atrophy on the left temporal structures relative to healthy controls. RtvFTD patients, instead, showed not only GM atrophy in the right frontal and temporal structures, but also in the insula bilaterally, and in the temporal and orbitofrontal cortices of the left side. Direct comparison showed that rtvFTD were more atrophic than svPPA patients in the temporal and frontal regions bilaterally, more so on the right hemisphere. TBSS analysis showed that rtvFTD patients had less WM integrity than controls in the corpus callosum and the right inferior fronto-occipital, inferior longitudinal, and uncinate fasciculi, while svPPA patients had decreased WM integrity in the corpus callosum and the left inferior fronto-occipital fasciculus.

Conclusions: In our study we found that rtvFTD patients present greater atrophy compared to svPPA patients both in the right and left hemisphere, independently of disease duration. This suggests that rtvPPA and svPPA do not mirror each other in GM loss, and that a neurodegenerative process starting in the right hemisphere must be more widespread to become clinically evident. We also first document that rtvFTD patients present WM disruption in fasciculi which have been implicated in face recognition, emotion processing, and language functions, in line with the peculiar clinical features of this syndrome.

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## CLINICAL AND NEUROANATOMICAL CHARACTERIZATION OF THE SEMANTIC BEHAVIOURAL VARIANT OF FRONTOTEMPORAL DEMENTIA IN A MULTICENTRE ITALIAN COHORT

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Objectives: Semantic behavioral variant of frontotemporal dementia (sbvFTD) is a recently recognized entity [1] presenting with specific behavioral and semantic derangements associated with predominant atrophy of right anterior temporal lobe. Our aim was to evaluate clinical, neuropsychological and imaging features of an incident cohort of sbvFTD patients compared to both semantic variant primary progressive aphasia (svPPA) and behavioral variant FTD (bvFTD) patients.

Materials: Fifteen sbvFTD patients were enrolled between June 2017 and January 2023, along with 63 bvFTD and 25 svPPA patients. 40 age- and sex-matched healthy controls were also included. Patients underwent clinical and cognitive evaluations, as well as 3D T1-weighted MRI on a 3 Tesla scanner. Clinical history and emerging symptoms of sbvFTD patients were recorded, based on review of clinical charts.

Methods: Grey matter atrophy was investigated at a whole-brain level using voxel-based morphometry (VBM). Clinical, cognitive and MRI features were compared between groups using ANOVA models corrected for multiple comparisons.

Results: Age at onset and disease duration were comparable among patient groups (p=0.525, p=0.98). Three sbvFTD patients were mutated (n=1 C9orf72, N=1 MAPT, N=1 GRN). 66.7% sbvFTD patients developed person-specific semantic knowledge loss and words/objects semantic loss early in the disease course; 60% presented complex compulsions and rigid thought process; 46.7% developed apathy/inertia. Compared to other groups, bvFTD patients scored higher at CDR-SB (p=0.038), while sbvFTD patients had lower results at an emotion recognition task part of the CATS battery compared to other groups (p=0.025). VBM showed a pattern of prevalent atrophy in the right temporal pole in sbvFTD patients, which was almost specular to the pattern of atrophy of svPPA patients, predominantly left-sided. However, sbvFTD patients also presented a cluster of bilateral orbitofrontal atrophy, which was absent in svPPA. bvFTD patients had a more widespread and bilateral pattern of atrophy in fronto-temporal and parietal regions.

Discussion: We demonstrate that sbvFTD is not merely a right-variant of svPPA, but rather a complex and possibly more extensive disease. The multimodal semantic loss associated with rigidity, compulsiveness and apathy, along with the temporo-frontal pattern of atrophy points towards a disease that unfolds towards frontal networks, which are generally preserved in svPPA.

Conclusions: sbvFTD is a novel and insidious entity that diverges from other forms of FTD. Clinicians should be prompt to recognize early signs of this variant to provide a timely and accurate diagnosis. Funding: European Research Council (StG-2016_714388_NeuroTRACK); Foundation Research on Alzheimer Disease.

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## PLASMA P-TAU181 AS A PROMISING NON-INVASIVE BIOMARKER OF ALZHEIMER'S DISEASE PATHOLOGY IN SUBJECTIVE COGNITIVE DECLINE AND MILD COGNITIVE IMPAIRMENT

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One of the greatest challenges in Alzheimer's Disease (AD) is the discovery of non-invasive, sensitive and specific biomarkers, which might be useful in the early stages of the disease, as Subjective Cognitive Decline (SCD) might be [1]. Plasma phosphorylated tau (p-tau) 181 is becoming increasingly notable in prodromal stages of AD, as a valuable marker for tauopathy, one of the core features of AD [2]. The aim of this study is to investigate the role of plasma p-tau181 as a potential biomarker for AD pathology in early stages of the disease.

Materials and methods: We included 40 SCD, 38 Mild Cognitive Impairment (MCI) and 16 AD demented (AD-d) patients, who underwent clinical evaluation, neuropsychological assessment, Apolipoprotein E (APOE) genotyping, plasma p-tau181 analysis with SiMoA assay. Twenty-six SCD, 32 MCI and 14 AD-d patients underwent CSF biomarkers analysis (Aβ1-42, Aβ1-42/1-40, p-tau, t-tau) and were classified as carriers of AD pathology (AP+) when A+/T+ (regardless of N), or non-carriers (AP-) when they were A- (regardless of T and N), or A+/T-/N-, or A+/T-/N+ according to A/T(N) system. Plasma p-tau181 levels were significantly lower in SCD (2.15±0.88) as compared to MCI (2.91±1.38, p=0.037) and to AD-d (4.03±1.39, p<0.001). MCI had lower plasma p-tau181 levels than AD-d (p=0.015). In SCD plasma p-tau181 levels were correlated with CSF Aβ1-42 (ρ=-0.516, p=0.008), Aβ1-42/1-40 ratio (ρ=-0.748, p<0.001) and p-tau (ρ=0.779, p<0.001). In MCI plasma p-tau181 levels were correlated with all CSF biomarkers (Aβ1-42 ρ=-0.618, p<0.001; Aβ1-42/1-40 ratio ρ=-0.692, p<0.001; p-tau ρ=0.674, p<0.001; t-tau ρ=0.693, p<0.001). Considering AP status, plasma p-tau181 levels were higher in SCD AP+ than in SCD AP- (2.85±0.53 vs 1.73±0.64, p<0.001), and in MCI AP+ than in MCI AP- (4.03±1.07 vs 2.04±0.87, p<0.001). In a multivariate linear regression analysis, AP status was the only variable that significantly influenced plasma p-tau181 concentration (B=1.670 [95% CI 1.097:2.244], p<0.001). A ROC curve analysis showed that plasma p-tau181 was highly accurate for discriminating between AP+ and AP- patients (AUC = 0.910). We identified a cut-off level of 2.69 pg/mL to distinguish between AP+ and AP- (accuracy=84.21%, sensibility=86.36%, specificity=82.50%, PPV=75.00%, NPV=90.32%). Plasma p-tau181 levels were significantly associated with the presence of underlying AD pathology, independently from the cognitive status. Plasma p-tau181 showed a high accuracy in differentiating SCD and MCI patients who were carriers from non-carriers of AD pathology. Our preliminary results suggest that plasma p-tau181 might be a promising noninvasive biomarker of AD pathology at very early stage [3].

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## RAPIDLY PROGRESSIVE DEMENTIA DUE TO HYPOMAGNESEMIA: WHEN RAPIDLY IS NOT IRREVERSIBLE

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Introduction: Rapidly progressive dementia (RPD) is a heterogeneous group of conditions characterized by a swift decline in cognitive abilities and overall functioning that develops faster than the most renowned dementia syndromes. Common causes include Creutzfeldt-Jakob disease (CJD), autoimmune encephalopathies (AE), infectious diseases and toxic/metabolic conditions.

Case presentation: Hereby, we describe a case of an 84 years-old female who came to our attention for the abrupt onset, three months prior, of behavioural symptoms such as irritability, verbal aggressiveness and loss of empathy, associated with mood deflection and loss of appetite. During the first month of symptoms, an episode of tonic-clonic seizure occurred: her CT-scan was irrelevant and levetiracetam was prescribed. Two months later, she developed bradykinesia and gait ataxia, associated with slurred speech and tremor of upper limbs. Therefore, she was admitted to our unit as confusional state and psychomotor agitation abruptly occurred. At examination, the patient was mildly disoriented and displayed severe attention deficit, apathy, constructive apraxia, gait ataxia, horizontal nystagmus, postural tremor in upper limbs, resting tremor in the right arm and dysmetria. She scored 17 out of 30 at mini-mental score examination [MMSE]. No electroencephalographic alterations were found. No instrumental exams suggested the presence of neoplasms, and CSF exams were unremarkable for antibodies associated with AE and biomarkers for neurodegenerative diseases. The only notable findings were undetectable serum magnesium level and multiple pontine hyperintensities visible in the T2-weighted imaging. Therefore, an intravenous supplementation therapy was immediately started and pantoprazole suspended. At discharge she displayed no attention deficit, was fully oriented and highly engaged with her surroundings. Her neurological exam was normal except for minimal horizontal nystagmus. Her MMSE score raised to 21.

Discussion: Our case testifies the broad range of neurological manifestations associated with hypomagnesemia, including mental status changes, seizures, movement disorders, tetany, muscle weakness. Moreover, a reversible cerebellar syndrome induced by hypomagnesemia has been described and associated to MRI specific abnormalities. Our case is unique because of the prominent cognitive decline and the atypical alterations in the pons, rather than the cerebellum. The diagnosis of RPD associated with hypomagnesemia is supported by the exclusion of other causes and the regression of clinical features following magnesium replacement. Notably, the patient's use of levetiracetam and pantoprazole may have contributed to the development of hypomagnesemia through mechanisms involving diarrhea and reduced absorption, respectively. These findings emphasize the importance of considering hypomagnesemia as a potential aetiology for rapidly progressive dementia associated to cerebellar signs.

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## NEUROINFLAMMATION BIOMARKERS AND CLINICAL PROGRESSION IN AMNESTIC MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE


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Introduction: In addition to the core ATN CSF biomarkers for Alzheimer's disease (AD), novel fluid biomarkers related to neuroinflammation have gained attention in recent years. Higher levels of glial biomarkers, such as soluble Triggering-receptor expressed on myeloid-cells-2 (sTREM2), chitinase-3-like-1-protein (YKL-40), and glial-fibrillary-acidic-protein (GFAP) have been found in subjects with mild cognitive impairment (MCI) and AD-dementia. This study aims to investigate the role of CSF neuroinflammation biomarkers in predicting cognitive decline in individuals with prodromal AD.

Methods: Sixty subjects diagnosed with MCI due to ad were enrolled and underwent a comprehensive clinical and neurological evaluation, an extensive neuropsychological assessment, and a lumbar puncture for CSF biomarkers (Aβ42/40 ratio, p-tau, t-tau, NfL, sTREM2, YKL-40 and GFAP) quantification. Participants were retested after a one-year follow-up (n=59) and a two-year follow-up (n=39). Based on their MMSE score reduction after one year, subjects were classified as "fast-decliners" (n=21) or "slow-decliners" (n=38). Additionally, based on their clinical progression to dementia after two years, they were categorized as "converters" (n=18) or "non-converters" (n=21). Comparisons between groups were performed using the Mann Whitney-U test for mean rank, and binomial logistic regression models were utilized to assess whether CSF neuroinflammation biomarkers could predict cognitive decline.

Results: Age, literacy, and baseline MMSE scores did not significantly differ between "fast-decliners" and "slow-decliners", as well as between "converters" and "non-converters". When comparing CSF biomarker levels between these groups, p-tau, t-tau, and YKL-40 showed statistically significant higher concentrations in "fast-decliners" compared to "slow-decliners" and in "converters" compared to "non-converters". To further evaluate the predictive value of these biomarkers, backward stepwise logistic regression analyses were conducted, considering the three biomarkers along with age, literacy, and baseline MMSE score. The best model for predicting MMSE decline after one year included only YKL-40, while the best model for predicting conversion to dementia after two years included p-tau and baseline MMSE score.

Discussion & Conclusion: The elevated levels of p-tau and t-tau in the "fast-decliners" and "converters" groups confirm the importance of tau pathology in AD progression. Importantly, our results contribute to the growing evidence of the involvement of neuroinflammation in AD pathogenesis and reveal the role of YKL-40 as a predictor of cognitive decline in the short term in the early stages of AD. Future research should focus on validating these findings in larger cohorts, exploring the potential of this biomarker in monitoring therapeutic response, and evaluating the efficacy of interventions targeting neuroinflammation in AD.

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## THE IMPORTANCE OF A PROMPT DIAGNOSIS IN COGNITIVE IMPAIRMENT: A CASE REPORT OF CEREBRAL AMYLOID ANGIOPATHY RELATED INFLAMMATION


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Background: Cerebral amyloid angiopathy-related inflammation (CAA-ri) is a distinct and rare clinical manifestation of cerebral amyloid angiopathy (CAA) characterized by an inflammatory response to amyloid deposition in the brain with subacute and progressive neurological symptoms. The clinical presentation of CAA-ri consists in an acute or subacute cognitive decline paired with headache, seizures or behavioural changes. [1]

Case presentation: A sixty-five-year-old patient presented to emergency room after repeated falls due to a progressively worsening motor deficit. He had a fairly unremarkable clinical history except for a minor neurosurgical procedure. Some days before the admission in an outpatient setting, the neurological examination found bilateral hand tremor and worsening cognitive status, attributed to an extrapyramidal disorder. Thus, L-dopa was prescribed. At the time of admission, the patient was alert but disoriented, exhibiting left hemiparesis and dysarthria. He scored 21/30, 1/6 and 0/8 to MMSE, ADL, IADL, respectively. His MRI brain scan showed diffuse vasogenic oedema in the frontal-temporal-parietal-occipital region bilaterally, predominantly expressed in the right hemisphere, shifting the median line structures with diffuse leukoaraiosis and a large number of hemosiderin deposits in the supratentorial region compatible with micro-haemorrhagic foci. A clinical suspicion of CAA-ri was raised and a lumbar puncture was performed. The results were consistent with mild pleocytosis and increased CSF protein with reduced Amyloid Beta42 and ratio of Abeta42/Abeta40, normal total-Tau and p-Tau181. Five grams of methylprednisolone were administered followed by slow tapering with oral prednisone. Over the next two weeks the motor and cognitive functions were ameliorated with the autonomous reaching of the upright stance, disappearance of tremor and better performances with cognitive testing; MRI imaging improved with the partial resolution of the bilateral oedema. The patient was discharged shortly after to a different institution to continue physical therapy where he made a full recovery. At time of discharge his score were: MMSE 24/30 ADL 5/6 IADL 2/8.

Conclusions: Cerebral amyloid angiopathy related inflammation requires an autoptic specimen for a definitive diagnosis, whereas a probable CAA-ri diagnosis may be inferred using clinical and radiological findings. This condition represents one of the few examples of cognitive decline associated with focal neurological symptoms which can be reversible with adequate therapy [2]. As our case highlighted, the identification of asymmetrical lesions by neuroimaging studies was pivotal for an early diagnosis, but the symptomatology may divert the clinician's attention elsewhere, oftentimes delaying treatment, with dire consequences for the patients.

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## APOE GENOTYPE MEDIATES BLOOD-BRAIN BARRIER PERMEABILITY IN DEMENTIA

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Objective: The ε4 isoform of ApoE, a major genetic risk factor for developing Alzheimer's disease (AD), has been shown to be associated with increased blood-brain barrier (BBB) permeability in animal models of AD, while in vivo studies have reported conflicting results. The aim of the present study was to evaluate the effects of ApoE-ε4 genotype on BBB permeability in a large cohort of patients with neurodegenerative disorders.

Methods: Two hundred and thirty patients fulfilling current clinical criteria for AD (n=156), frontotemporal dementia (n=36), dementia with Lewy bodies (n=11), vascular dementia (n=11) and subjective cognitive decline (n=16) were recruited. All subjects underwent a clinical and neuropsychological evaluation, routine laboratory examination, cerebrospinal fluid analysis, ApoE genotyping and brain structural imaging (CT o MRI). BBB permeability was assessed with the CSF/plasma albumin and CSF/plasma light chains ratio. The sample was subdivided into three ApoE subgroups according to the number of ApoE-ε4 polymorphism (0, 1 or 2).

Results: The CSF/plasma albumin ratio, corrected for diagnosis, disease duration and disease severity, was increased in patients with two ApoE-ε4 genes ($p<0.001$). When diagnostic subgroups were considered separately, we observed comparable findings. Increased CSF/plasma kappa light chains were found only in patients with AD.

Conclusions: Our results support the hypothesis that ApoE genotype increases BBB permeability in major dementia disorder, having potential implications for disease pathophysiology and blood-based biomarkers measurements.

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## ASSOCIATION BETWEEN PRESENCE OF ALPHA-SYNUCLEIN IN THE OLFACTORY MUCOSA AND BRAIN METABOLISM IN DEMENTIA WITH LEWY BODIES

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Objectives: Alpha-synucleinopathy encompasses a very complex spectrum of phenotypic presentations, characterized by the presence of abnormal aggregates of alpha-synuclein in the brain, and two ideally distinct models can be identified: a motor form (Parkinson's Disease, PD) and a cognitive form (Lewy Body Dementia, DLB). In vivo pathological confirmation through minimally invasive collection of easily accessible tissue is a key goal for neurodegenerative disease research. The real-time quaking induced conversion assay (RTquIC) is a novel technique that has been tested for alpha-synuclein in olfactory

mucosa brushing (OMB) and cerebrospinal fluid (CSF). This study aim to investigate the symmetry of alterations observed in dopamine transporter SPECT (DaT-SPECT) in a cohort of DLB patients based on OMB results.

Materials: We enrolled 30 patients (21 males, 9 females) from our Memory Clinic with a clinical DLB diagnosis according to McKeith's criteria [1]. The mean age at the time of OMB procedure was 77 +/- 6 years, and the mean MMSE score was 23.4 +/- 5.4.

Methods: All patients underwent OMB and were divided into positive (n=22) and negative (n=8) groups based on RT-quIC alpha-synuclein results. Of these subjects, 27 underwent DaT-SPECT. DaT-SPECT images were post-processed using free BasGanV2 software and compared with a court of normal to obtain Z-scores. Non-parametric statistics were employed to compare the asymmetry in putamen and caudate Z-scores between the two patient groups.

Results: Our data confirm a statistically significant difference in the absolute value of left-right putamen difference between the positive and negative OMB groups (positive group: mean 0.0977 +/- 0.0867, negative group: mean 0.1785 +/- 0.1014; p=0.03). However, no significant difference was found for the caudate (p=0.3).

Discussion: While specific PET tracers for alpha-synuclein are under development, several hypotheses have been proposed regarding disease spread mechanisms. One emerging hypothesis suggests the distinction between brain-first and body-first patterns [2]. The olfactory bulb represents an ambivalent structure, able to be involved in both spreading patterns. However, some murine studies have shown that unilateral injection of alpha-synuclein seeds result in markedly asymmetrical spreading of the pathology [3]. Our results, limited by sample size, confirm a trend toward greater asymmetry in DaT-SPECT metabolism among patients positive for alpha-synuclein pathology on OMB.

Conclusions: The RT-quIC technique for detecting alpha-synuclein in OMB represents a new diagnostic tool in alpha-synucleinopathies. Further studies are needed to characterize its prognostic value and correlations with other biomarkers.

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## METABOLIC AND NEUROCHEMICAL CHARACTERIZATION OF EARLY ONSET VS LATE ONSET BEHAVIORAL FRONTOTEMPORAL DEMENTIA

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Aim: Frontotemporal dementia (FTD) is a highly heterogeneous neurodegenerative disorder, from both the clinical and biological point of view. It is traditionally considered an early onset syndrome, although several epidemiological studies have shown that could also occur later on in life [1]. Currently, whether the early and the late onset might represent different FTD phenotypes is still unclear.

Materials: We enrolled 79 patients with behavioral variant FTD (bvFTD - 34 probable bvFTD, 55 prodromal bvFTD) and 42 Healthy Controls (HC). We acquired brain [18F]FDG-PET images as a marker of neurodegeneration. Patients were divided into three groups based on age at onset, namely early onset-bvFTD (EO-bvFTD, age <70, n = 24, mean age at onset: 62.9±6.4; MMSE: 25.3±2.7; 46% males), late onset-bvFTD (LO-bvFTD, age between 70 and 75, n = 31, mean age at onset: 73.1±1.5; MMSE: 24.2±4.1; 29% males) and very late onset-bvFTD (vLO-bvFTD, age >75, n = 24, mean age at onset: 78.4±1.86; MMSE: 24.2±3.4; 38% males).

Method: We performed a voxel-based analysis between EO-bvFTD, LO-bvFTD, vLO-bvFTD and HC, separately. Using JuSpace toolbox, we explored the correlation between [18F]FDG-PET images and PET maps of dopamine (DAT), serotonin (SERT), noradrenaline (NAT) and choline vesicular (VAChT) transporters cortical distribution.

Results: EO-bvFTD patients showed a typical anterior pattern of cortical hypometabolism, associated with a significant involvement of NAT cortical availability ($p<0.001$) compared to HC. LO-bvFTD and vLO-bvFTD patients showed a similar pattern of hypometabolism, extending to the angular gyrus. LO-bvFTD had a greater involvement of diffuse neurotransmitter pathways, with reduced cortical availability of VAChT ($p < 0.001$).

Discussion: It has been highlighted that cognitive-behavioral profile differs between EO-bvFTD and LO-bvFTD (2). In our work we showed that, in addition to the known anterior pattern well represented in EO-bvFTD patients, a greater involvement of the temporo-parietal junction metabolism is present in LO-bvFTD patients. This is associated with a broader diffuse projection systems involvement. As highlighted in the recent diagnostic criteria [3], this may be related to a more prevalent underlying biological profile of Alzheimer's Disease, either as a single entity or in comorbidity, with subsequent therapeutic implications. Understanding these differences may contribute to improved diagnosis and treatment strategies, particularly in late-onset cases with overlapping features of Alzheimer's Disease.

Conclusion: We highlighted how metabolic and neurochemical patterns differ in bvFTD depending on the age at onset.

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## BRAIN LINEAR MEASUREMENTS FOR DIFFERENTIATING NORMAL PRESSURE HYDROCEPHALUS FROM ALZHEIMER'S DISEASE: AN EXPLORATORY STUDY

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Background: Easy and reliable tools for the differential diagnosis between idiopathic normal pressure hydrocephalus (iNPH) and Alzheimer's disease (AD) are needed.

Material and methods: In this cross-sectional study iNPH and AD referring to the Neurology Unit of the University of Catania from the 1 st of January 2020 to the 1 st of December 2022 were enrolled. The following brain linear measurements were calculated: Evan's

Index (EI), the Parieto-Occipital Ratio (POR) and the Temporal-Ratio (TR). For each index, sensitivity, specificity and area under the curve (AUC) were calculated. Moreover, a cumulative index, i.e. the brain linear measurement (BLM) index was also considered.

Results: Fifty patients (25 iNPH and 25 AD) were enrolled. In differentiating iNPH from AD, EI had the highest AUC (0.956), POR had the highest specificity (100%), while TR had the highest sensitivity (92%). The BLM index differentiated iNPH and AD with a sensitivity of 96%, a specificity of 92% and an AUC of 0.963 with the optimal cut-off value of 0.303.

Conclusion: EI, POR and TR may be useful in the differential diagnosis between iNPH and AD. At an individual level, the BLM index represents a valid and reliable tool to achieve an accurate differentiation between these two conditions.

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## HIGH-DENSITY EEG (HD-EEG) CORRELATES OF CORE CLINICAL FEATURES IN DEMENTIA WITH LEWY BODIES. PRELIMINARY DATA

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Objective: To explore the associations between high-density EEG (HD-EEG) features and the core clinical features of dementia with Lewy bodies (DLB).

Materials: Twenty–nine patients with DLB (20 males, mean age: 78±6 years; mean MMSE score: 22.2±3.9, mean MDS-UPDRS score 17.52±13.7) underwent 64 channels HD-EEG recording and a comprehensive clinical and neuropsychological examination.

Methods: Quantitative EEG analysis was performed, and the following features were extracted: individual alpha peak (IAP), theta-to-alpha transition frequency (TF) computed by the semi-automated tool transfreq, mean frequency (MF), and frequency bands power. Frequency bands were estimated with both standard definition and an individual one (delta=[max(1, TF-4), TF-2], theta=[ TF-2, TF], alpha=[TF, IAP+2 ], beta=[IAP+2, 30]). We tested the associations between HD-EEG features and core clinical DLB features.

Results: The computation of individual bands power highlighted that the posterior dominant rhythm is shifted through standard theta range, with a mean IAP of 7.02±0.94 Hz, a TF of 5.03±0.88 HZ and a MF of 7.83±2.02 Hz. TF positively correlated with IAP ($r = 0.58$, $p<0.001$). MDS-UPDRS-III scores positively correlated with individual theta power ($r = 0.38$, $p = 0.03$) and negatively correlated with both individual beta power ($r = -0.36$, $p=0.04$) and standard beta power ($r = -0.4$, $p=0.02$). Standard alpha power positively correlated with MMSE scores ($r = -0.37$, $p=0.03$).

Discussion: Core clinical features and cognitive decline in DLB may depend on different neurotransmitter pathways that could be reflected in HD-EEG alterations. To avoid misinterpretation of qEEG we estimated TF at individual level with transfreq. In fact, frequency bands may variably overlap across subjects, particularly in DLB patients that present a slowing of background activity. Briefly, transfreq is a method based on the identification of the intersection between the spectral profiles of leads with high alpha activity and the ones of leads with low alpha and high theta activity, with just one resting-state EEG. Individual EEG features estimated with transfreq showed promising results as potential correlates of DLB clinical features. Moreover, TF showed to be independent from MMSE; this could be explained considering that background activity slowing may already begin in mild and prodromal DLB stages.

Conclusions: We showed that individual quantitative EEG analysis implemented with transfreq may better describe cortical functions in DLB patients than standard ones. Moreover, TF was not correlated with global cognitive decline, supporting the hypothesis that posterior rhythm abnormalities may already be present in mild and prodromal stages.

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## HIPPOCAMPAL ATROPHY CAN PREDICT EVOLUTION TO DEMENTIA IN PATIENTS WITH VASCULAR MILD COGNITIVE IMPAIRMENT

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Background and Objectives: Vascular mild cognitive impairment (VMCI) is a transitional condition that may evolve into vascular dementia (VaD) [1]. A deeper understanding of the mechanisms of cognitive impairment in VMCI is crucial to develop markers of disease progression. Studies have suggested hippocampal atrophy as a putative MRI-based marker in early VaD[2]. Our study aims to evaluate (I) differences in hippocampal volume among patients who converted to VaD vs those who did not convert and (II) to what extent hippocampal involvement correlated with cognitive impairment and vascular white matter lesions (WMLs).

Methods: In this longitudinal multicentre study, 110 subjects with VMCI (mean age [±SD]: 74,33 [± 6,63] years, 61 males/49 females) from the vMCI-Tuscany Study database underwent brain MRI and were scored on cognitive tests. Information on whether patients evolved to VaD after 2 years was recorded. For each subject right and left hippocampi were semi-automatically segmented; the hippocampi masks were obtained using FIRST (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) and manually refined where occurs using EADC-ADNI protocol. In addition, vascular WMLs volume in different bundles was assessed by intersecting fibers included in the ICBM-DTI-81 white-matter labels atlas

with lesion masks manually segmented. Linear regression models were used to assess differences in hippocampal volumes between groups and their correlations with cognitive tests and lesions volume, corrected for age, sex, center and education, as appropriate.

Results: In the whole cohort, lower hippocampal volume was associated with worse verbal memory assessment scores, such as ray-auditory-verbal learning test delayed recall (beta coefficient: 101.19, p=0.004). At 2 years of evaluation, 32/110 (29%) of VMCI converted to VaD. Lower whole hippocampal volume was found in VMCI patients who converted to VaD (mean volume [±SD]: 4829 [±897] mm3) with respect to those who did not convert (mean volume [±SD]: 5178 [±819] mm3); (p=0.03). No significant correlation was found between hippocampal volume and lesion volume in any white matter bundle.

Conclusions: Data reported here suggest that hippocampal atrophy can be detected in patients with VMCI, is closely related to subclinical memory impairment and can predict evolution to VaD. In contrast, it does not seem to be influenced by vascular WMLs.

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## AN OLD MAN WANDERING THE STREETS

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Neurosyphilis results from the extension to the central nervous system of an infection caused by Treponema pallidum, leading to consistent heterogeneity in features and time of presentation. Neuroinvasion may resolve spontaneously, given the ability of the immune system to provide full clearance of T. pallidum from CNS, resulting as an asymptomatic stage. Late symptomatic neurosyphilis can manifest decades after primary infection in 10-20% of cases left untreated, and usually presents with tabe dorsalis or general paresis. As the disease can be extremely heterogeneous in presentation, the onset can mimic acute encephalitis, as well as more progressive and subacute encephalopathy, reaching the correct diagnosis might be trickier the more subacute the clinical features become. In our case A 77-year-old patient presented for the sudden occurrence of confusion, memory loss and aggressiveness. The previous medical history was unremarkable, though the patient's daughter had reported similar transient episodes in the previous three months. Neurological examination revealed drowsiness, slight dysarthria, partial disorientation in space and time with short and long-term memory impairment and reiteration. Brain magnetic resonance imaging (MRI) showed mild leukoaraiosis, cortical-subcortical atrophy and bilateral signal change in temporal and insular location, prevalent on the left side, characterized by hypointensity in T1-weighted imaging and hyperintensity in T2-weighted imaging. A total body CT scan revealed a severe dilation of the ascending aorta and aortic arch. CSF analysis revealed unremarkable cell count and proteins, and pattern 3 oligoclonal bands. Acyclovir was started for a possible diagnosis of herpes simplex virus-related encephalitis, but CSF PCR screening turned negative for viruses. VDRL and TPHA serology returned positive. On CSF TPHA was positive, while VDRL was negative, so a final diagnosis of neurosyphilis was made and medical treatment with penicillin G iv was started. This case highlights how non-specific neuroimaging can be in neurosyphilis. Indeed, no brain MRI pattern seems typical, with general atrophy, mesial temporal lobe involvement and diffuse white matter changes have been reported. However, polar temporal white matter changes are rather uncommon, particularly if isolated, and might prompt clinicians to raise suspicion for neurosyphilis in the appropriate clinical context. Reaching the correct diagnosis in patients with a subacute onset of neuropsychiatric symptoms can be complicated and we tend to presume that neuroinfectious diseases represent underdogs. Syphilis cases are rising, and we think that must be considered to avoid missing a potentially treatable cause of cognitive and neuropsychiatric deficit.

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## POSTERIOR CORTICAL ATROPHY MISDIAGNOSED AS NEUROMYELITIS OPTICA SPECTRUM DISORDER: A CASE REPORT

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Background and Aims: Here we report a case of a 62-years-old woman, admitted to our Neurology Unit for the insidious onset unspecified years ago of bilateral visual disturbance. Her medical history was remarkable for an amaurosis in the right eye due to a traumatic retinal detachment at the age of 20 and a bilateral cataract surgery in 2005 and in 2014. In 2019 she was diagnosed with Neuromyelitis optica spectrum disorder, by applying 2015 diagnostic criteria (evidence of bilateral vision loss associated with a right optic nerve hyperintensity at brain MRI and the positivity of AQP4-IgG test (ELISA)). For this diagnosis the patient underwent immunosuppressive treatment without clinical benefit. On admission, neurological examination showed space and objects perception deficit, simultanagnosia, oculomotor apraxia, optic ataxia, left/right disorientation, bilateral positive palmomental reflex and urinary urgency.

Methods: We performed blood tests, ophthalmological examination (including VEP and OCT), brain MRI, neuropsychological evaluation, amyloid PET and AQP4-IgG test with cell-based serum assays (CBA).
Results: Ophthalmological examination confirmed complete vision loss in the right eye (exitus of retinal detachment) and normal findings in left eye. Brain MRI showed marked atrophy in bilateral parietal, posterior temporal and lateral occipital cortex and right optic nerve T2-hyperintensity/atrophy. Neuropsychological assessment revealed significant visual, visuoperceptual, and visuospatial dysfunction and a relatively well-preserved episodic memory. Amyloid PET showed the presence of diffuse cortical beta-amyloid plaques. AQP4- IgG test was negative.

Conclusions: Patient was diagnosed with "Posterior cortical atrophy (PCA) associated with Alzheimer's Disease", a clinico-radiological syndrome characterized by progressive decline in visual processing skills and other functions subserved by parietal, occipital and occipito-temporal regions. PCA is characterized by early prominent visual dysfunction that cannot be explained by ocular causes: patients may have a history of repeated visits to optometrists or ophthalmologists and multiple unsuccessful changes in eyeglasses or surgical procedures in attempt to correct acuity.

Discussion: The present case report show as an incorrect application of diagnostic criteria should lead to an incorrect diagnosis. Adult-onset,

progressive visual disturbance often poses a diagnostic challenge between immunological disorders, infectious causes and also degenerative disease. A thorough medical history and correct interpretation of instrumental examinations are essential in the differential diagnosis of visual disorders. In our case the right optic nerve hyperintensity was due to ascending optic atrophy due to previous retinal detachment and AQP4-IgG test was performed with immunofluorescence assays, that have lower specificity and occasionally yield false-positive results compared with the best available detection method (CBA).

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## THE UTILITY OF CSF BIOMARKERS MEASURED WITH THE LUMIPULSE SYSTEM IN THE DIAGNOSIS AND MANAGEMENT OF ALZHEIMER'S DISEASE

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Objectives: The fundamental biomarkers of cerebrospinal fluid (CSF): total tau (tTau), phospho-tau (pTau), amyloid β1-42 (Aβ 1-42), and the Aβ 1-42/Aβ 1-40 ratio have transformed Alzheimer's disease (AD) research and are now increasingly used in routine. Infact, high levels of tau protein and low levels of amyloid-beta in the cerebrospinal fluid are associated with the presence of amyloid plaques and neurofibrillary tangles in the brain, hallmarks of Alzheimer's disease. Identifying these biomarkers at an early stage can allow doctors to initiate early therapeutic interventions and slow the progression of the disease. [1]

Materials: Seventy-seven CSF samples were collected between December 2019 and May 2023 as part of the subject's routine clinical diagnostic survey. Patients had an average age of 69 years, 58% male and 42% female.

Methods: LUMIPULSE G (Fujirebio) is an automated system for microsphere-based immunoassays, capable of measuring all four AD biomarkers: Aβ 1-42, tTau, pTau and the ratio Aβ 1-42/Aβ 1-40. The four markers were quantified directly from the preservation tubes using Lumipulse G β-amyloid 1-42, β-amyloid 1-40, total Tau, and pTau 181 assays from the automated LUMIPULSE G600 II platform and following the manufacturer's instructions. [2]

Results: The Lumipulse G test showed low intra- and inter-test variability and good agreement with the clinical diagnosis. Quality control was performed at the beginning of each test to ensure that all measured values of each control level (low, medium, and high) were within the target ranges. 11.7% (9/77) of the samples showed low values of Aβ 1-42 with high pTau values which, according to the international bibliography reflect a status of AD. In addition, the clinical diagnosis also confirmed Alzheimer's disease.

Discussion: Fully automated immunoassay instruments with ready-to-use analysis kits and calibrators have simplified their analysis with reproducible, highly specific measurements. Good diagnostic performance was observed for LUMIPULSE G β-amyloid 1-42, β-amyloid 1-40, β-amyloid1-42/40, total Tau and pTau.

Conclusions: The usefulness of CSF biomarkers measured with the Lumipulse system is a valuable resource for the diagnosis and management of neurodegenerative diseases. The accuracy and reliability offered by this technology allows doctors to obtain detailed information about the neurological pathology, facilitating early diagnosis and optimization of treatment.

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## CSF NPTX2 DYNAMIC CHANGES AND TOPOGRAPHIC RELATIONS WITH BRAIN METABOLISM ACROSS MCI DUE TO ALZHEIMER'S DISEASE

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Introduction: Neuronal pentraxin-2 (NPTX2), a protein involved in synaptic function and plasticity, exhibits decreased levels in the cerebrospinal fluid (CSF) and brain tissue as cognition deteriorates in various dementias [1]. The variations of CSF NPTX2 levels across MCI due to Alzheimer's disease (AD) and their association with brain metabolism remain elusive, albeit relevant for patient stratification purpose. We aimed to investigate changes in CSF NPTX2 levels in relation to progression to AD dementia and explored their correlation with regional brain metabolism using [18F]FDG PET imaging.

Materials: We retrospectively selected a cohort of 49 patients with mild cognitive impairment and high-likelihood of AD (MCI-AD, 30 females, mean age 75.2±5.3) based on CSF biomarkers of amyloidosis and tauopathy (AT+)(2), and divided them into two subgroups based on their progression to dementia within a two-year period (late-MCI, LMCI, n=15 versus early-MCI, EMCI, n=34 patients). For comparison, we included a group of age- and sex-matched individuals with other non-dementing conditions (OND).

Methods: We examined demographic variables and cognitive status (MMSE score) in both the EMCI and LMCI groups. We measured the levels of CSF NPTX2 through a commercial ELISA assay to be compared among the EMCI, LMCI, and OND groups. Through a voxel-based analysis of [18F]FDG PET scans (SPM12 software), we investigated the topographical correlation between brain metabolism and CSF NPTX2 levels, using age as a nuisance.

Results: CSF NPTX2 differed among groups ($p=0.003$), and at post-hoc analysis, EMCI had significantly higher values than either LMCI ($p=0.028$) and OND ($p=0.006$). We found a significant positive correlation between NPTX2 values and metabolism of bilateral precuneus in MCI-AD patients ($p<0.005$ at voxel level, $p<0.05$ with FWE correction at the cluster level, cluster extension 364 voxels).

Discussion: Higher CSF NPTX2 levels in early MCI compared to controls and late MCI may indicate synaptic compensation in response to initial AD pathology. However, as the disease progresses, these mechanisms may become overwhelmed, resulting in decreased NPTX2 levels approaching dementia. Additionally, the positive correlation between NPTX2 and glucose metabolism in the precuneus, an area that is commonly affected early in AD and associated with

cognitive decline [3], highlights a strong relationship between NPTX2 and the metabolic changes related to AD throughout the disease course.

Conclusions: Our study provides valuable insights into the dynamics of CSF NPTX2 and its intricate relationship with metabolic changes across MCI with AD etiology, highlighting its potential as a biomarker for patient staging and stratification of progression risk.

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## MACHINE LEARNING PREDICTIVE MODEL OF PROGRESSION FROM SUBJECTIVE TO OBJECTIVE COGNITIVE DECLINE: A 12-YEAR FOLLOW-UP STUDY

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Background and aims: Subjective cognitive decline (SCD) represents a target population to be screened for dementia. Previous studies identified demographic, cognitive and genetic features associated with a higher risk of progression to mild cognitive impairment (MCI) and Alzheimer's disease (AD) [1,2]. We aim to test the accuracy of a machine learning (ML) model, trained on features derived from non-invasive and easily accessible techniques, in predicting conversion from SCD to MCI and AD.

Materials and Methods: We included 150 SCD patients who underwent neuropsychological examination, assessment of cognitive complaint, mood disorders and cognitive reserve, and APOE genotyping at baseline. All the patients underwent clinical-neuropsychological follow-up every 12-24 months for a mean time of 12 years.

Results: During follow-up, 63 patients were classified as progressive SCD (p-SCD, 42.0% [95% C.I.=34.1:49.9], including 41 MCI (27.3% [95%C.I.=20.2:34.5]) and 22 AD (14.7% [95%C.I.=9.0:20.3]). 87 patients were classified as non-progressive SCD (np-SCD, 58.0% [95%C.I.=50.1:65.9]). We split the whole sample into a training (80%) and a test group (20%). A gradient-boosted trees algorithm was trained on 15 selected features including: age, APOE, education, test assessing for global cognition, immediate and delayed verbal, ecological memory and working memory, language, visuospatial abilities, phonemic fluency and cognitive reserve. This model showed a good accuracy (0.83, AUC=0.78) in distinguishing p-SCD and np-SCD in the test group.

Discussion: Previous studies demonstrated that ML algorithms are able to classify images from AD, MCI, and healthy participants with very high accuracy levels but only a few studies focused on predicting the progression of cognitive decline [3]. To the best of our knowledge, this is one of the first longitudinal studies applying ML to an SCD population.

Conclusions: Our machine learning models, including demographic, neuropsychological and genetic features, might represent a reliable, cost-effective and globally scalable tool for a first-step screening of SCD patients before confirmation of AD pathology via more invasive and expensive tests.

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## SUBJECTIVE COGNITIVE DECLINE: A PROPOSAL FOR A MANAGEMENT PROTOCOL BASED ON REVIEW OF LITERATURE AND 15 YEARS' EXPERIENCE FROM A MEMORY CLINIC

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Background and aims: Increasing evidence suggests that subjective cognitive decline (SCD) is a risk factor for dementia [1]. For this reason, the National Institute of Aging-Alzheimer's Association (NIA-AA) included SCD as a first manifestation of the symptomatic stages of AD, preceding MCI [2]. On the other hand, SCD has also been related to non-degenerative diseases [3]. Nevertheless, a consensus is lacking about how to manage patients with SCD. We aimed to: i) describe our experience with SCD; ii) review the literature about the impact and causes of SCD; iii) propose a practical approach for the management of SCD.

Methods: From a sample of 445 SCD patients self-referred to our center, we considered 119 patients followed-up for at least 10 years. All the patients underwent neurological and neuropsychological examination at baseline. A subsample of 78 patients underwent Alzheimer's disease biomarker assessment (CSF or amyloid-PET), rated according to the AT(N) system.

Results: During the follow-up, 55 patients (47.0%) were diagnosed with MCI and 22 (18.8%) with dementia. A patient developed Parkinson's disease and a patient had a brain tumor. Mean progression time was 7.9(5.2) years to MCI and 10.39(4.7) to dementia. Thirty-eight (32.5%) patients still were SCD at the end of the follow-up (15.2[5.4] years). In this group nine patients were diagnosed with depression, six had vascular leukoencephalopathy and two were diagnosed with obstructive sleep apnea syndrome (OSAS). Among 78 patients who

underwent AD biomarker assessment 10 (12.8%[5.4-20.2]) were A+ (seven A+/T+/N- and five A+/T+/N+). The review of the literature allow us to identify other potential causes of SCD including: mood disorder, sleep disorders, use of sleep medication, vitamin B12 deficit and cerebrovascular disease.

Discussion: We elaborated a management protocol to be applied both in clinical and in research settings: at the baseline evaluation, all the conditions possibly associated with SCD should be considered. If none of the baseline exams shows a possible explanation for the SCD, we classify patients as "SCD of unknown cause". We suggest stratifying patients according to age at onset and APOE genotype. Regarding patients who undergo AD biomarker analysis, we suggest applying the ATN classification to classify patients as affected by "SCD not due to AD", "Alzheimer's pathologic changes with SCD" or "AD with SCD".

Conclusions: Our proposal may assist clinicians in managing patients with SCD, enabling them to identify underlying conditions suitable for therapeutic approaches and select patients to participate in clinical trials and upcoming disease-modifying therapies at the earliest stages of the disease.

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## COMORBIDITIES IN MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE: EFFECTS ON NEUROPSYCHIATRIC SYMPTOMS AND THERAPY

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Background: Mild cognitive impairment (MCI) is a heterogeneous condition with high variabilities in clinical outcomes related to patient demographics, genetic, fluid biomarker alterations, and concomitant comorbidities (CBs). Although previous studies reported a crucial role for CBs in favouring cognitive decline and conversion from MCI to dementia [1], the individual weight of these potentially modifiable risk factors is not yet established.

Aim: This study aimed to investigate the presence of CBs in a cohort of MCI participants and longitudinally evaluate their impact on global cognition, development of neuropsychiatric symptoms, risk of conversion to dementia, and therapeutic management.

Methods: We retrospectively included n=93 participants with amnestic MCI [2], evaluated between 2018 and 2020 at the Centre for Cognitive Disorders and Dementia of "Sant'Andrea Hospital", Vercelli, Italy. We included only subjects with at least six months of available follow-up. As CBs, we considered: hypertension, coronary artery disease, chronic heart failure, diabetes, respiratory illness, chronic kidney disease, hypothyroidism, hypercholesterolemia, cancer, depression, parkinsonism, visual impairment, stroke, hip fracture, peripheral artery disease, osteoporosis, arthritis. We evaluated: the baseline and follow-up Mini-Mental State Examination (MMSE) as an index of global cognition; the index of progression (calculated as MMSE point loss per year); the conversion to dementia; prescription of anticholinesterases, memantine, antidepressants and antipsychotics.

Results: In the whole cohort, the mean follow-up was 2,5±1,6 years, 68% of subjects converted to Alzheimer's disease (MCI-co), and the mean progression index was 2,2±3,5. Overall, CBs did not impact conversion to dementia. However, by analysing MCI-co, CBs influenced therapeutic management. Prescription of memantine was more frequent in subjects with two or more CBs than in those with no or one CB (p=0,02). Moreover, depression was significantly associated with two or more additional CBs, and consistently a higher number of CBs was associated with a larger use of antidepressant therapy (p=0,03).

Discussion: In our study, CBs in MCI-co subjects were associated with the presence of depression and a consequent larger use of antidepressant therapy. These findings are consistent with previous studies, reporting a higher rate of depression in patients with cognitive decline and concomitant chronic diseases [3]. In addition, we showed a higher prescription of memantine in patients with two or more CBs, probably due to a better safety profile.

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## CO-OCCURRENCE OF NPC1 MUTATION AND C9ORF72 REPEAT EXPANSION IN A CASE OF FRONTOTEMPORAL DEMENTIA WITH MILD PHENOTYPE

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Introduction: Frontotemporal lobar degeneration (FTLD) is a progressive neurodegenerative disorder, typically classified into behavioural

variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA). At least 30% of patients with FTLD have a positive family history. Intronic GGGGCC hexanucleotide repeat expansion in chromosome 9 open reading frame 72 (C9ORF72) is the most common cause of familial and sporadic MND and FTLD. Furthermore, it has been described in patients with other dementias, parkinsonism or psychosis, as well as in healthy subjects. Previous report described FTLD patients carrying two mutations. Interestingly, in all cases one of them was the C9ORF72 expansion. Here we report a new association leading to a milder form of FTLD.

Case Report: The proband was a 70-year old man with a 5-year history of slowly progressive cognitive disturbances. His father was affected by dementia, clinically diagnosed as Alzheimer's disease (AD). Neurological examination of the proband was normal. Neuropsychological assessment showed impaired attention, memory, speech production, and executive functions, in absence of significant behavioural alterations. A previous brain MRI showed temporoparietal cortical atrophy. Initially, AD was suspected. However, CSF biomarkers profile (A-,T-,N+) suggested a non-AD dementia. Amyloid-PET confirmed absence of brain amyloid deposit. FDG-PET showed frontotemporal hypometabolism. We performed a diagnosis of FTLD. Overlap with MND was clinically and electrophysiologically excluded. Disease-causing expansion in the first exon of the C9ORF72 gene was found. Also, an NGS panel of 31 genes associated to dementia was analysed: we found the heterozygous c.2761C>T (p.Gln921Ter) mutation in NPC1, already described as pathogenic and reported in Italian patients with Niemann-Pick type C disease. Serum oxysterol analysis showed significant increase of 7-Ketocholesterol (7KC) and cholestan-3β,5α,6β-triol (triol), strongly supporting the pathogenicity of the NPC1 mutation.

Discussion: Our case report further supports the hypothesis that co-occurrence of two pathogenic mutations could contribute to the clinical heterogeneity that is detected in subjects with C9ORF72 repeat expansions. Sometimes C9ORF72 repeat expansion is probably not sufficient to develop disease, and an additional mutation or environmental exposure may be needed. Such being the case, FTLD patients carrying C9ORF72 expansion should not be excluded from further genetic studies: both clinicians and genetic counsellors should be aware of this phenomenon when advising patients and their family members. In our patient, the pathogenic variant in the NPC1 gene might have modified the phenotype which was milder than expected in "classical" FTLD and required a thorough differential diagnosis with a frontal variant of AD.

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## EARLY-PHASE AMY-PET VERSUS FDG PET IN ATYPICAL VARIANTS OF ALZHEIMER DISEASE: PRELIMINARY DATA FROM A MULTICENTER STUDY (AMY-ITA)

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Introduction: Amyloid PET and [18F]FDG PET scans are commonly used in patients with uncertain diagnosis of AD. A few studies showed that early frames of amyloid PET correlate well with FDG PET images, providing perfusion-like information, thus being a potential surrogate for FDG-PET. We investigated whether the early frames of the florbetaben-PET (FBB-PET) scan are comparable to the FDG-PET in terms of regional uptake deficits in patients with a clinical suspicion of atypical Alzheimer's disease.

Materials and Methods: AMY-ITA is a still ongoing prospective multicenter study conducted in 9 Italian centres. Until now, 84 patients have been enrolled, collecting FDG-PET and FBB-PET images. The brain was divided into 8 different regions in both FDG and early-frames FBB-PET scans. Each region was visually and blindly analysed in both PET scans, defining the tracer uptake abnormality, using a scale of 0 to 3. A statistical analysis was then performed using Spearman and Wilcoxon tests. Clinical data were collected by neurologist, who estimated the suspicion of AD for all patients before AMY-PET result and then confirmed or not the initial diagnosis. For 18 patients CSF analysis was available. In 50% of cases the neurologist rejected the initial diagnosis and changed the clinical management. AMY-PET resulted useful to confirm AD in case of uninformative CSF.

Results: The most frequent clinical variants of AD were primary progressive aphasia andposterior cortical atrophy. Visual analysis of the brain revealed similar patterns between early-frame FBB-PET and FDGPET images in atypical AD; however, the scores of abnormal uptake were globally higher in FDG-PET. The Spearman test showed a statistically significant correlation in all brain regions (ρ from 0.798 to 0.927, $P < 0.0001$). and clinicians changed baseline clinical diagnosis in 27% of cases after the result of AMY-PET.

Conclusions: Early-phase FBB-PET acquisitions correlated well with FDG-PET scans in atypical forms of dementia, offering a surrogate marker of brain metabolism. As a consequence, AMY-PET with analysis of early frames may convey added information on metabolism thus reducing patient radiation exposure and health costs by avoiding FDG-PET. AMY-PET is a valid biomarker also in detecting amyloid deposition in atypical variants of AD.

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## UTILITY OF FIVE-WORD TEST AS A SCREENING TOOL IN CLINICAL PRACTICE TO IDENTIFY MEMORY DEFICIT SPECIFIC OF ALZHEIMER'S DISEASE

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Introduction: Alzheimer's disease (AD) is the most common form of dementia, usually characterized by progressive memory deficit of hippocampal type, defined by difficulties on coding, storage and retrieval of the informations without benefit by cueing. While there is a validated second level test to investigate these deficits, (Free and Cued Selective Reminding Test, FCSRT), we lack of screening tools specific for this type of memory deficit uniformely used in Italy. The Five Words Test (FWT) by Dubois [1] is a screening memory tool specifically built to discriminate the hippocampal memory deficit typical of AD and it was recently adapted in Italian language [2]. The aim of our study is to evaluate the diagnostic power of the FWT in the detection of memory deficit of the hyppocampal type.

Materials and Methods: We recruited 13 patients (7 men and 6 women) aged between 68 and 87 years consecutively visited in our

CDCD complaining memory deficits. Patients underwent FWT as a screening during the first assessment and, later a second level battery including: FCSRT, Rey figure test, attentive matrixes, verbal digit span, stroop test, fonemic and semantic fluency, copy of simple figures.

Results: In the cohort there were 3 patients with mild AD (clinical dementia rating scale 0.5-1), 1 patient with vascular dementia, 5 affected by psychiatric disorders, 3 amnestic mci, 1 patient with logopenic PPA. Among patients with AD, 3 out 3 scored pathologically both on FWT and FCSRT. Of the 5 psychiatric patients 4 scored in the normal range for FWT but all the patients had normal scores on the FCSRT. The patient with vascular dementia, performed well on the FWT but was pathological on the FCSRT; Among the 3 patients with amnestic MCI two of them were pathologic on the screening test but only one on the FCSRT; the patient with MCI who performed well on the FWT resulted impaired on the FCSRT. The patient with logopenic variant of PPA scored well in both tests.

Conclusions: Our data show that the FWT is a valid screening tool in distinguishing memory deficit between psychiatric disorders and Alzheimer dementia even in early phases. Results on amnestic MCI cases in our cohort were unconclusive suggesting the heterogeinity of patients in this group and probably the necessity to use a specific and sensitive second level test in this type of patients to identify a real hyppocampal memory deficit. Our data need further validation in bigger cohorts.

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## A CASE OF CNS VASCULITIS PRESENTING WITH ACUTE-SUBACUTE ONSET DEMENTIA

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Vasculitis is a group of diseases characterized by infiltration of inflammatory cells with reactive damage to blood vessel walls of different size. Almost all forms of vasculitis can involve the vessels feeding the brain parenchyma and central nervous system involvement usually manifests with an insidious onset with slow progression. The multifocal characteristic of the lesions determines the absence of pathognomonic signs and symptoms, although headache, focal neurological deficits (mostly stroke or hemorrhage) and seizures are more frequently reported. In the case below, we illustrate a case of vasculitis that presented atypically with an acute-subacute onset dementia. A 61-year-old male with a recent severe trivasal coronary artery disease treated with PCI and a history of hematuria presented to ER for altered mental status, spatial-temporal disorientation, ideomotor slowing and mnestic deficits with a subacute onset. To assess the patient's cognitive status, MMSE and MoCa tests were performed with raw scores of 23/30 and 18/30 respectively; a thorough neuropsychological testing showed a moderate cognitive impairment involving executive and mnestic functions. The brain MRI with contrast showed T2-FLAIR hyperintense lesions in the left corona radiata and right thalamo-capsular region with contrast enhancement in T1-gd images and restriction in DWI scans. Also, SWI scans showed diffuse biemispheric microhemorrhages, black-blood imaging showed enhancement of the terminal portion of both internal carotid arteries and middle cerebral arteries compatible with a possible vasculitis of medium-caliber vessels. In the hypothesis of vasculitis an autoimmune panel was performed on serum, which was negative. A cerebral angio-CT was normal. A lumbar puncture was performed showing hyperproteinorrachia with a normal white blood cells count, but the CSF immunophenotype was suggestive of neutrophilia and monocytosis. Steroid therapy with methylprednisolone 500 mg/day for 4 days was started with mild clinical improvement. The patient was discharged with the indication to continue oral steroid therapy with prednisone 50 mg/day and to start azathioprine 50 mg/day. At follow-up neurological examination after one month, the patient reported a marked improvement in cognitive performance and memory, gaining a score of 28 at the MMSE test. Rarely, vasculitis affecting the central nervous system can manifest as acute-subacute onset dementia and treatment with steroid and cytotoxic therapy can play an important role in improving the patient's cognitive performance.

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## TRAILBLAZER-ALZ 4: DIRECTLY COMPARING DONANEMAB TO ADUCANUMAB ON AMYLOID LOWERING IN EARLY, SYMPTOMATIC ALZHEIMER'S DISEASE - RESULTS FROM 12-MONTHS

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Objectives: The primary outcome of TRAILBLAZER-ALZ-4 (NCT05108922) evaluated the potential superiority of donanemab treatment compared to aducanumab on the percentage of participants with amyloid plaque clearance (≤24.1 Centiloids (CL)) at 6 months in the overall study population and subpopulation of participants with intermediate tau deposition [1]. This abstract presents the secondary analyses of 12-month results of the ongoing study.

Material and Methods: Participants (n=148) were randomized 1:1 to receive donanemab (titration: 700mg IV Q4W [first 3 doses], then 1400mg IV Q4W [subsequent doses]) or aducanumab (titration per USPI: 1mg/kg IV Q4W [first 2 doses], 3mg/kg IV Q4W [next 2 doses], 6mg/kg IV Q4W [next 2 doses] and 10mg/kg IV Q4W [subsequent doses]). The study is ongoing with a total duration of 18 months.

Results and Discussion: Baseline demographics and characteristics were well-balanced across treatment arms (donanemab [N=71], aducanumab [N=69]). Twenty-seven donanemab-treated and 28 aducanumab-treated participants had low/medium (intermediate) tau levels based on screening tau PET scans. In all participants at 12 months, 70.3%±6.2% (least square [LS] mean ± standard error [SE]) donanemab-treated vs. 21.4%±5.8% aducanumab-treated participants achieved amyloid plaque clearance ($p<0.001$) assessed by florbetapir

F18 PET scans. In the low/medium tau subpopulation, 80.0%±9.9% donanemab-treated vs. 9.6%±5.4% aducanumab-treated participants achieved amyloid clearance (p<0.001). The percent change (LS mean ± SE) in brain amyloid levels were -82.8%±3.1% (baseline [LS mean ± standard deviation]: 97.59±28.20 CL) and -56.6%±3.1% (baseline: 102.71±35.30 CL) in donanemab and aducanumab arms, respectively (p<0.001). In the low/medium tau subpopulation, percent change in brain amyloid levels were -82.7%±4.6% (baseline: 104.97±25.68 CL) and -57.0%±4.5% (baseline: 102.99±27.87 CL) in donanemab and aducanumab arms, respectively (p<0.001). The 6-month brain amyloid reduction with donanemab treatment is superior to aducanumab at 12 months (LS mean change ± SE, -63.9±2.8 CL; -55.6±3.0 CL, respectively, p=0.044). Adverse events occurred in 78.9% of donanemab-treated and 82.6% of aducanumab-treated participants, respectively. Amyloid-related imaging abnormalities occurred in 29.6% (1.4% serious [n=1]) and 40.6% (2.9% serious [n=2]) of participants in the donanemab and aducanumab arms, respectively, with higher rates in ApoE4 carriers.

Conclusions: TRAILBLAZER-ALZ 4 provides the first active comparator data on amyloid plaque clearance in patients with early symptomatic Alzheimer's Disease and demonstrates the higher brain amyloid reduction of donanemab compared to aducanumab at 12 months when drug titration has been completed and the treatment regime has stabilized.

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## DEMENTIA WITH LEWY BODIES ASSOCIATED WITH PROGRESSIVE APHASIA: SUGGESTIONS FROM MOLECULAR IMAGING IN A CASE-SERIES

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Introduction: Primary progressive aphasia (PPA) is a dementing disorder characterized by predominant language impairment, primarily associated with frontotemporal lobar degeneration (FTLD) or Alzheimer's disease (AD) pathology [1]. Language impairment in dementia with Lewy bodies (DLB) is not the among the more typical symptoms but can occur in the disease course. However, recent evidence on pathological samples suggests that a PPA may rarely be attributed to Lewy-body pathology [2]. Differentiating the etiologies of PPA can be challenging, and molecular imaging biomarkers may assist in the differential diagnosis in vivo. However, the insights that cerebral metabolism evaluation can provide about the alterations in DLB-PPA remain elusive.

Case-series: We describe seven patients (age 72.7±5.5, 2 females, MMSE score 24.4±4.6, education 12.3±3.5, CDR range 0.5-1) who, at their initial evaluation at our Memory Clinic, presented with language impairment as their chief complaint, significantly impacting their lives. Two of the patients met the diagnostic criteria for PPA3 and were initially diagnosed as either non-fluent PPA or logopenic-PPA, within the spectrum of FTLD or AD pathology based on the results of CSF biomarkers for amyloidosis. However, within a 2-year period, they developed parkinsonism and core features consistent with a probable DLB diagnosis. The others revealed slight disturbances in other cognitive domains, and the core clinical features of DLB were already evident during the diagnostic workup. [18F]FDG PET imaging consistently showed a decrease in glucose metabolism in the lateral temporal region of the dominant hemisphere (left) in all patients. Specifically, the hypometabolism was confined to this region in the two patients diagnosed with PPA, while in the remaining patients, it was observed alongside the typical parieto-occipital hypometabolism seen in DLB. In-depth investigation revealed reduced dopamine transporter uptake in the basal ganglia in all patients, and [123]iodine-MIBG cardiac scintigraphy was abnormal in 4 (2/2 of patients with PPA).

Discussion: These findings suggest that a Lewy-body disorder may underlie PPA. Specifically, the integration of clinical and imaging biomarkers provided an in vivo diagnosis of probable DLB in patients with predominant speech impairment at onset. The specific involvement of the left temporal lateral region may explain language disorders in DLB and indicate a distinct spread of Lewy-body pathology.

Conclusions: The diagnostic work-up of PPA should also incorporate an investigation of the core symptoms of DLB to guide the use of biomarkers, taking also into account that hypometabolism may deviate from the typical parieto-occipital pattern.

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## CREUTZFELDT-JAKOB DISEASE (CJD) IN A MAN SURVIVING COVID-19: A CASUAL OR CAUSAL LINK?

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Objectives: To describe the rare case of a man surviving COVID-19, presenting with ataxia, subsequently associated with a rapidly progressive dementia, eventually diagnosed to have a sporadic Creutzfeldt-Jakob disease (CJD).

Materials: A 54-year-old man came to our observation for a subacute onset of ataxia, gait disturbance, dizziness, headache, anosmia and hallucinations, followed by rapid cognitive decline, reduced verbal fluency, apathy and urinary incontinence. His past medical history included only hypertension. Two months before, he had contracted SARS-CoV2 infection, and had remained in home isolation for about 40 days.

Methods: Diagnostic assessment included blood and cerebrospinal fluid (CSF) microbiological testing, onconeural antibodies and neural surface antigens antibodies, brain MRI, EEG studies, chest CT scan, CSF prion real-time quaking-induced conversion (RT-QuIC) and 14-3-3 protein analysis, and PRNP sequencing.

Results: Blood and CSF screening and microbiological tests resulted all negative. Chest CT scan documented a mild hypodiafania. Brain MRI showed multiple DWI/FLAIR hyperintensities of caudate and globus pallidus, putamina and thalami. EEG showed short sequences of periodic polyphasic delta waves. Treatment with intravenous steroids and immunoglobulins was promptly tried without any clinical

improvement. In the suspicion of CJD, CSF resulted positive for the 14-3-3 protein, and prion seeding activity was demonstrated by the RT-QuIC assay. PRNP sequencing revealed valine homozygosity (VV) at codon 129 and no pathogenic mutations. Our patient progressed up to mutism, akinetic and fully dependent state, and died two months after the discharge. A brain autopsy was performed. The neuropathologic examination revealed spongiform change, gliosis and neuronal loss, predominantly involving the cerebellum, striatum and thalamus. Immunoblotting detected the abnormal, proteinase-K resistant prion protein (type 2 according with Parchi's classification). There were no findings suggesting for COVID-19 related encephalitis.

Discussion: Before the COVID-19 outbreak, the principal cause of rapidly progressive dementia was certainly prion disease, excluding infectious, metabolic, vascular, neoplastic, and autoimmune disorders. Some recent studies demonstrated that patients surviving COVID-19 can show neuroinflammatory activation of microglia and astrocytes, that might favor the fast development of neurodegenerative diseases, such as CJD. In our case, the neuropathological examination allowed the definite diagnosis of CJD and ruled out a specific neuroinflammatory "phenotype" related to COVID-19 infection. Further studies will address whether SARS-CoV-2 infection could trigger or enhance susceptibility in individuals already at risk for neurological syndromes.

Conclusions: This case expands the spectrum of differential diagnosis of rapidly progressive dementia. Whether COVID-19-related neuroinflammation can accelerate neurodegeneration in CJD still remains elusive.

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## IDENTIFICATION OF A NOVEL PSEN1 VARIANT ASSOCIATED WITH POSTERIOR CORTICAL ATROPHY: A CASE REPORT


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Introduction and Objective: Posterior cortical atrophy (PCA) is a rare variant of Alzheimer's Disease (AD) that mainly affects the posterior regions of the brain, causing visuospatial and visuoperceptual deficits, alexia and apraxia. While most AD cases occur sporadically, a small percentage (<0.5%) are inherited with an autosomal dominant pattern, due to mutations in three main genes (APP, PSEN1, PSEN2). [1] In this study, we describe the case of a 52-year-old female patient with a clinic-neuroradiological diagnosis of PCA due to AD, and we identified a novel mutation in the PSEN1 gene c.1301 C>T p. (Ala434Val) affecting a critical protein domain.

Materials and Methods: Due to progressive difficulties at work, a 52-year-old woman presented to our Cognitive Disorders Centre. The patient underwent neurological and neuropsychological assessment, neuroimaging investigations (brain CT-scan, MRI, 18FDG-PET and Amyloid PET) and lumbar puncture. Furthermore, considering the presence of dementia in the family history, genotyping of the APOE gene and analysis of 25 dementia-associated genes was obtained using next-generation sequencing (NGS).

Results: The neurological and neuropsychological evaluation revealed mild amnestic and attentional deficit, accompanied by constructive apraxia and diminished visual-spatial abilities. Brain MRI showed predominantly posterior pattern atrophy. 18FDG-PET evidenced marked left predominant hypometabolism in the occipital, parietal, and temporal regions. A clinical-radiological diagnosis of PCA was then made. Cerebrospinal fluid analysis showed a reduction of Aβ42 concentration and Aβ42/40 ratio, and increased t-tau level. The presence of cerebral amyloidosis was confirmed through a PET scan with Flutemetamol. The genotype of the APOE gene was ε3/ε4. NGS sequencing identified the c.1301C>T p.(Ala434Val) variant in the exon 12 of Presenilin-1 (PSEN1; NM_000021.4) gene, confirmed by Sanger sequencing. Based on the American College of Medical Genetics (ACMG) criteria, the variant was classified as likely pathogenic.

Discussion and conclusions: We report the case of a patient with PCA associated with a novel likely pathogenic variant p.(Ala434Val) in the PSEN1 gene. The production of Aβ from the amyloid precursor protein requires a series of proteolytic processes. The point mutation identified in this case introduces a variation in a highly conserved motif, which is recognized as critical for the catalytic activity of γ-secretase. This study corroborates the importance of genetic analysis in patients with early-onset AD and expands the clinical phenotype associated with PSEN1 mutations.

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## LUMIPULSE AND SIMOA PLASMA P-TAU AND AMYLOID MARKERS TO DETECT ALZHEIMER'S DISEASE CSF-RELATED PATTERN IN CLINICAL SETTING


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Objective: Plasma p-tau and amyloid markers have been validated in large clinical studies for the diagnosis of Alzheimer's disease (AD). Still, the sensitivity of different techniques and the diagnostic utility at single subject level in predicting CSF AD-related pattern is theme of debate. Objective of this study was to evaluate the ability of lumipulse and SIMOA markers assessment to detect Alzheimer's disease related pathology in clinical setting.

Materials: Consecutive patients with AD and other neurodegenerative disorders underwent CSF analyses and plasma collection.
Methods: Plasma p-tau181, T-tau abeta 1-42, Abeta 1-40, were performed using Lumipulse and SIMOA analyses. The ability of different biomarkers to distinguish AD related pattern in neurodegenerative conditions was evaluated using ROC analyses.

Results: Fifty A+T+N+ AD and 40 other neurodegenerative disorders (NDD) and 40 HC were included in the analyses. P-tau181 were elevated in AD and NDD compared to controls. Plasma p-tau181 assessed by Lumipulse exhibited a strong correlation with CSF pattern and high correlation with SIMOA-plasma detection. The combination of p-tau181 and abeta42 exhibited high diagnostic accuracy for identifying CSF AD pattern (ROC AUC 0.78-0.83).

Conclusions: This study confirmed the construct validity of both Lumipulse and SIMOA techniques for the identification of CSF AD pattern in clinical setting.
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## THE ATN FRAMEWORK IN ALZHEIMER'S DISEASE. IS IT TIME TO INCLUDE (F)UNCTIONAL CONNECTIVITY MARKERS?

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Introduction: Different neurodegenerative diseases might mimic Alzheimer's disease (AD) behavioral syndrome. Limbic-predominant age-related TAR DNA binding protein 43 (TDP-43) encephalopathy (LATE) account for 15-20% of all clinically diagnosed AD cases. AD and LATE also share temporal atrophy. Therefore, it is crucial the development of effective model of AD pathophysiology. Recently, the ATN framework (A: amyloid; T: tau; N: temporal lobe neurodegeneration) allowed to shift from a clinical to a biological AD perspective. By applying the ATN framework, we can unravel the similarities between AD and LATE. Brain atrophy without amyloid (A-) and tau (T-) pathology but with temporal neurodegeneration (N+) may indicate LATE with no comorbid AD. Based on these assumptions, we investigated the ATN framework in a large dataset of patients within the AD continuum to identify individuals with typical/atypical profile. Dynamic patterns of brain functional connectivity (dFC) were evaluated, as we hypothesize dFC can provide relevant insights to complement the ATN biological fingerprints due to its close association with protein propagation.

Methods: Data were included from the Alzheimer's Disease Neuroimaging Initiative. Patients were included whether ATN information (biochemical markers, and molecular/structural imaging) and resting state functional imaging (rsfMRI) were collected. Patients were categorized into different groups based on a data-driven approach on ATN features. Concerning rsfMRI, dFC was derived by means of co-activation patterns of the posterior cingulate cortex (PCC), a key region linked with memory. Biological, clinical, cognitive, and dFC measures were compared between sub-cohorts. Finally, we investigated whether dFC could predict patient classification computed with ATN features.

Results: A total of 152 controls and 334 patients were included. Three clusters were identified. The first group exhibited mild pathological alterations in the ATN markers. The second cluster showed evidence of clinical/cognitive impairment and AD pathology. The third cluster displayed similar behavioral impairment but more severe temporal atrophy without tau accumulation, suggestive of a LATE-like profile. Different PCC-dFC patterns were observed among these two latter clusters, particularly in the temporo-occipital regions. PCC-dFC states showed an accuracy around 80% in predicting typical/atypical ATN groups.

Discussion: We identified patients with atypical ATN trajectories within the clinical continuum of AD. These findings suggest the presence of different pathophysiological profiles associated with distinct patterns of dFC between the PCC and the rest of the brain.

Conclusion: Functional connectivity (F) markers can complement the ATN framework and aid in identifying patients with AD-like clinical profiles but with separate underlying pathologies.
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## BREAKING DIAGNOSTIC BARRIERS: NODDI-MACHINE LEARNING FUSION FOR FTLD DIFFERENTIAL DIAGNOSIS

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Objective: To investigate microstructural gray matter (GM) and white matter (WM) alterations in patients with frontotemporal lobe degeneration (FTLD) and to develop a machine learning (ML) algorithm that classifies patients according to NODDI metrics and neuropsychological data.

Materials: Thirty-five behavioral-variant frontotemporal dementia (bvFTD), 20 semantic variant primary progressive aphasia (svPPA),

14 nonfluent variant primary progressive aphasia (nfvPPA), 9 semantic bvFTD (sbvFTD) and 48 controls were enrolled and performed multi-shell diffusion brain MRI and neuropsychological assessment.

Methods: Fractional anisotropy (FA) maps were computed on diffusion-tensor imaging (DTI); the NODDI multi-compartment model was used to estimate Intra-cellular Volume Fraction (ICVF) and Orientation Dispersion Index (ODI) maps, providing information about neurite morphology and integrity. GM and WM voxel-wise comparisons between FTLD groups were performed using, respectively, tract-based spatial statistics (TBSS) and GM-based spatial statistics (GBSS) in FA, ICVF and ODI maps. Support vector machine (SVM), ML algorithm used for classification of different syndrome, was trained on (i) mean GM and WM values of FA, ICVF and ODI maps subdivided in different regions of interest (brain lobes) and (ii) neuropsychological data.

Results: TBSS and GBSS showed significant differences in different groups relative to controls. FA maps showed widespread WM damage in FTLD patients relative to controls, while no significant differences were found in GM maps. Intriguingly, ICVF maps showed specific damage in FTLD patients relative to controls in the areas considered the epicenter of the neurodegeneration process (bilateral frontotemporal for bvFTD, left temporal-frontal for svPPA and nfvPPA, right temporal for sbvFTD). Moreover, ODI maps showed a GM reduction with a similar, but wider, ICVF-GM pattern. WM alterations in patients relative to controls was also observed: (i) WM reduction in corpus callosum and corona radiata (bvFTD, svPPA, nfvPPA) and right corona radiata (sbvFTD) and (ii) WM increase in temporo-occipital WM bundles (bvFTD) and stria-terminalis (svPPA). SVM model (ICVF+ODI+neuropsychological data) showed a 95.9% accuracy in the correct classification of each patient syndrome.

Discussion: NODDI capture subtle microstructural alterations in GM and WM, demonstrating advantages over standard DTI in FTLD. By combining the rich information from NODDI with cognitive data, ML models can learn complex patterns and relationships to differentiate between different FTLD clinical subtypes.

Conclusions: NODDI and ML algorithm hold potential for advancing our understanding of FTLD pathology and facilitating diagnosis, personalized management and treatment strategies at individual level.

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## INFLAMMATORY RESPONSE AND NEUROAXONAL DAMAGE IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE

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Objectives: Alzheimer's disease (AD) pathology has been associated with an activation of the immune response. From this perspective, the study of proinflammatory cytokines has gained increasing interest. Several studies have investigated the cytokine levels in AD holding inconclusive results. Thus, their clinical significance is still uncertain. Neurofilament light chain (NfL) is a well-established biomarker that indicates neuroaxonal injury and is gaining increasing interest in neurodegenerative diseases. The aim of this study is to assess the CSF concentrations of NfL, and 13 different cytokines in a cohort of AD patients in the early phases of the disease.

Materials and Methods: CSF samples were collected and stored at -80°C until assay. We used the commercially available immunoassay kits for NfL run on the ultrasensitive SR-X Biomarker Detection System (Quanterix). Concentrations of selected cytokines in the CSF were determined by multiplex bead-based flow cytometry assay (LEGENDplex HU Essential Immune Response Panel – 13plex, BioLegend, San Diego, CA, USA) that allows simultaneous quantification of 13 cytokines. The cytokine panel included IL-4, IL-2, CXCL10 (IP-10), IL-1β, TNF-α, CCL2 (MCP-1), IL-17A, IL-6, IL-10, IFN-γ, IL-12p70, CXCL8 (IL-8), TGF-β1 (Free Active Form).

Results: 24 patients were enrolled in this ongoing study. Patient median age (IQR) was 74 years (71.5-77) and 25% were males. Patients were grouped for disease severity, into those with a MMSE<26 (n=14) and those with a MMSE>27. The first group showed higher CSF concentrations of NfL (median, IQR 201.8 pg/ml, 172.1- 322.5 vs 73.2 pg/ml, 35.8-193.8; p= 0.0068) and IL-6 (median, IQR 2.9 pg/ml, 1.5-4.6 vs 1.5 pg/ml, 0.3-3.7; p= 0.0376) than the second. Interestingly, IL-8 tended to be increased in those patients with a MMSE<26 (median, IQR 24.3, 17.1-33.5 vs 18.1, 7.4-26.4; p= 0.0677).

Discussion and conclusion: The findings of this ongoing study, support the notion of a link between neuroinflammatory processes and dementia and further strengthen the hypothesis that IL-6 may be involved in dementia pathology and cognitive decline.

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## EXPLORING THE DIFFERENT PATHWAYS OF ALZHEIMER'S DISEASE AND LEWY BODY DEMENTIA: TRANSCRIPTOMIC ANALYSIS IN DIFFERENT AREAS OF THE HUMAN BRAIN

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Introduction and Aims: Senescence is often characterized by a progressive loss of cognitive abilities that may lead to major neurocognitive disorders, whose pathogenesis is largely obscure. Alzheimer's Disease (AD) and Lewy Body Dementia (LBD) are the most frequent forms of degenerative dementia. Our aim is to shed light on their pathogenesis, and generate new attractive hypothesis about it, by the use of novel approaches such asomic sciences.

Material and Methods: In this study, a whole transcriptome analysis and a Gene Set Enrichment Analysis (GSEA) have been carried out on brain samples from hippocampus (HI), temporal and parietal

cortex (TC, PC), cingulate cortex (CG), and substantia nigra (SN). All brains have been characterized according to the Abbiategrasso Brain Bank Protocol, including all the main proteinopathies and vascular scoring [1]. The brains belonged to subjects with a clinical and neuropathological diagnosis of AD and LBD (6 per pathology), and to 3 healthy age-matched controls in duplicate.

Results: Transcriptomic results showed major differences in the number of differentially expressed genes (DEGs) between the two pathologies. In particular, the number of DEGs is strongly higher and more heterogeneous in AD brains compared to LBD brains (DEGsAD=3156; DEGsLBD=278). The GSEA showed that in AD it is possible to cluster the analysed areas by biological processes (HI and TC: DEGs primarily related to synaptic transmission; PC, CG and SN: DEGs primarily related to proper protein folding and inflammation). In LBD there is only a strong and peculiar involvement of SN (DEGs primarily related to proper protein folding and inflammation) and PC (DEGs primarily related to myelination and glial system activation). Conclusions and

Discussion: Although AD and LBD are often coexisting and present a clinical overlap due to the same topography of the lesions, they show a completely different pathogenesis, characterized by the involvement of very different pathways according to a specific pattern that is time- and severity-related. Moreover, AD appears as a more heterogeneous disease than LBD. For both diseases it is possible to draw a molecular map that comes before pathology and spreads inside the brain following a specific and individual trajectory, which could unveil unexplored roads and possible shortcuts leading to a better understanding of their pathogenesis. This approach might help to discover novel biological targets in order to develop effective and personalized therapeutical approaches.

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## DYNAMICS OF THE 'COGNITIVE' BRAIN WAVE P3B AT REST FOR AD PREDICTION IN MCI

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Objective: Alzheimer's disease (AD) is the most common cause of dementia that involves a progressive and irrevocable decline in cognitive abilities and social behaviour, thus annihilating the patient's autonomy. The theoretical assumption that disease-modifying drugs are most effective in the early stages hopefully in the prodromal stage called mild cognitive impairment (MCI) urgently pushes toward the identification of robust and individualized markers of cognitive decline to establish an early pharmacological intervention [1, 2, 3].

Materials: Several studies have reliably shown that changes in the amplitude and latency of the P3b are strongly related to cognitive decline and ageing both healthy and pathological. Here, we used a P3b spatial filter to enhance the electroencephalographic (EEG) characteristics underlying 175 subjects divided into 135 MCI subjects, 20 elderly controls (EC), and 20 young volunteers (Y). The Y group served to extract the P3b spatial filter from EEG data, which was later applied to the other groups during resting conditions with eyes open and without being asked to perform any task. The group of 135 MCI subjects could be divided into two subgroups at the end of a month's follow-up: 75 with stable MCI (MCI-S, not converted to AD), 60 converted to AD (MCI C).

Methods: The P3b spatial filter was built by means of a signal processing method called Functional Source Separation (FSS), which increases the signal-to-noise ratio by using a weighted sum of all EEG recording channels rather than relying on a single, or a small sub-set, of channels.

Results: A clear difference was observed for the P3b dynamics at rest between groups. Moreover, a machine learning approach showed that P3b at rest could correctly distinguish MCI from EC (80.6% accuracy) and MCI-S from MCI-C (74.1% accuracy), with an accuracy as high as 93.8% in discriminating between MCI-C and EC.

Discussion: Finally, a comparison of the Bayes factor revealed that the group differences among MCI-S and MCI-C were 138 times more likely to be detected using the P3b dynamics compared with the best performing single electrode (Pz) approach.

Conclusions: We propose that P3b as measured through spatial filters can be safely regarded as a simple and sensitive marker to predict the conversion from an MCI to AD status eventually combined with other non-neurophysiological biomarkers for a more precise definition of dementia having neuropathological Alzheimer's characteristics.

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## TRADITIONAL BOARD GAMES AND PREVENTION OF DEMENTIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Traditional board games can entail significant skills encompassing several cognitive functions across different domains. Therefore, they may represent a potentially effective intervention to slow down cognitive decline in the aging population. To verify this hypothesis, we performed a systematic review of the literature on traditional board games and dementia.

Methods: We searched five databases with tailored search strings, including studies on elderly subjects at risk of or suffering from cognitive impairment. Studies in which the effect of board games was not separated by cards or other games were excluded. A meta-analysis was performed for specific cognitive and non-cognitive outcomes with enough data available.

Results: Board games improved general cognition compared to controls, as measured by MoCA (I2=75%, MD=2.89, 95%CI 0.96-4.82, p=0.003) and MMSE (I2=92%, MD=2.61, 95%CI 0.45-4.76, p=0.02). Ska and go, but not chess, seem to improve Trail Making Test – part A scores. Mahjong, but not go or chess, seems to improve executive functions, measured with the Shape Trail Test – part B. Board games did not improve Digit Span performance. Mahjong improved categorical fluency, while go did not. Chess significantly improved quality of life measured with the WHO-QoL-OLD scale (I2=63%, MD=7.69, 95% CI 4.84-10.54, p<0.00001), while mahjong temporarily improved depressive symptoms. Go practice

increased BDNF levels and metabolic activity in the left middle temporal gyrus and bilateral putamen.

Conclusions: Traditional board games may slow down cognitive decline and improve quality of life in elderly subjects. Specific games have different impacts on different cognitive domains, possibly mediated by peculiar functional and biological factors.

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## DELIRIUM MANAGEMENT (BPSD) IN ALZHEIMER'S DISEASE. COGNITIVE OVERLOAD?

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Definition: BPSD (Behavioral and Psychological Symptoms of Dementia) identifies the psychic and behavioral symptoms that can accompany the cognitive disorders of people suffering from dementia. It includes symptoms such as hallucinations, depression, apathy, agitation, aggression, wandering, busyness. The prevalence of BPSD is very high in patients with Alzheimer's disease. This symptomatology represents the main cause of the "burden of the caregiver" syndrome which, to a greater extent than the decline in cognitive abilities, is reflected in a decrease in the patient's abilities and causes long hospitalizations and consequent increase in costs.

Burden of Caregiver: "Burden of caregiver" refers to a particular response to chronic stress that is perceived by caregivers, due to their caring actions towards sick family members. It's a syndrome with psychophysical manifestations similar to burnout, with an increasing feeling of tiredness and emotional exhaustion and a general worsening of the quality of life.

Purpose of the Study: The study tries to answer an ethical dilemma: is it more correct to try to obtain an improvement in cognitive abilities and motor skills, with an increased onset of BPSD, or to try to control these symptoms by facing a global cognitive deterioration?

Materials and Methods: We analyzed 4 clinical cases (3 males and one female), median age (75.6+9.7 range 63-79) who had been diagnosed with delirium. Evaluated by psychiatrists and stabilized with major tranquilizers, neuroleptics and anesthetics. The short-term result was an increasing onset of BPSD leading to a need for patient containment and caregiver burden syndrome. Patients then were transferred to the Alzheimer Nucleus of the ASP Santa Margherita di Pavia where pharmacological treatment was set up with atypical (low-dose) antipsychotics, antiepileptics and antidepressants. As reference parameters were detected: MMSE, ADL, IADL and BARTHEL at admission and at discharge.

Results: After 4 weeks there was a compensation of the BPSD with improvement or stationarity of the MMSE and partial recovery of autonomy (ADL/IADL/BARTHEL). Consequently, the risk of burden of the care giver syndrome was also reduced.

Conclusions: The restoration of the sleep-wake cycle represents the starting point for the effective continuation of the treatments. The cooperative effect of drugs with different receptor targets can be exploited to achieve this goal. The polyfactoriality, age and complexity of the receptor interactions within a damaged synaptic network in the course of Alzheimer Disease do not allow us to suggest a unique therapeutic algorithm.

## EARLY STAGE COGNITIVE DISORDER CONTROL (PREMCI/MCI) USING QUEEN CHARLOTTE® (OMEGA3/ASTAXANTHIN ASSOCIATION): PRELIMINARY DATA

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Introduction: QUEEN CHARLOTTE is a food supplement consisting exclusively of oil obtained from the sole head of wild Pacific Sockeye salmon. It is rich in biologically essential substances (which our body is unable to produce) among these, the fatty principles of the omega3 series (EPA) and docohexaenoic acid (DHA) and Astaxanthin, to which the unmistakable red-orange colour. Astaxanthin optimizes the biological effects of omega3 through its antioxidant action.

Objectives of the study: The proposed observational study is aimed at determining the efficacy of Queen Charlotte on cognitive disorders in a selected patient population and, furthermore, establishing the most correct dosage.

Materials and Methods: Cognitive status assessment was determined using test tools (neuropsychological tests: MMSE and SF12 Questionnaire). Blood chemistry parameters were examined such as: Cholesterol, Triglycerides, Folate dosage, Vit.12 and Homocysteine. First administration of the tests at the time of the nosographic classification, after specialist neurogeriatric visit, second administration after 90 days. Subjects attending CDCD clinics of the ASP IDR S. Margherita di Pavia - University of Pavia with cognitive disorders (MCI - Pre-MCI) were recruited.

Results: Between January and April 2023, 28 (16F, 12M) patients with MCI/PreMCI with a mean age of 67 (range: 55-74 years) were treated with Queen Charlotte 3 cp/day for 90 days. MMSE (T0): 25.1; (T1): 27.4, ADL and IADL unchanged. Improved quality of life (SF12) and asthenia.

Conclusion: The correct analysis of the cognitive disorders (MCI and Pre-MCI) treated with Queen Charlotte 3 cp/day for 90 days showed a slight improvement in the MMSE, a stability of the ADL and IADL; good tolerability and no reported side effects.

## USE OF VORTIOXETINE AS A POSSIBLE INTEGRATION OF SEROTONERGIC AND DOPAMINERGIC SIGNALING IN THE CONTEXT OF VASCULAR DEMENTIA: CASE-REPORT

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Introduction: An 82-year-old male patient comes to our observation for rehabilitation hospitalization in the course of cerebrovascular dementia with behavioral disorders and psychomotor agitation (BPSD), with non-executable MMSE, ADL (0/6) and IADL (0/8); classified as CDR4. Describe Investigate Create Evaluate (DICE) protocol applied. Finding of vascular parkinsonism.

Brain CT: Bilateral ischemic lacunar nucleocapsular outcomes, hypodense patches of the periventricular white matter, radiated crowns and semioval centers due to chronic vascular disease. Start therapy with vortioxetine and levodopa. Already in therapy with anticholinesterases (Rivastigmine 4.6 mg patch/24 h), atypical antipsychotics (Quetiapine 75 mg/day), aceinhibitors (Lisinopril 20 mg/day), calcium channel blockers (Amlodipine 5 mg/day), statin (Simvastatin 10 mg/day) 24 hours after admission and taking the therapy, the patient resumed spontaneous movement and continued with increasing doses of levodopa up to (levodopa/carbidopa 100/25 mgx3/day) and vortioxetine (10 mg/day). At 21 days improvement in MMSE (8.1>12.1) and NPI (34>0) and in CDR functional class (4>3). We wondered whether there could be a correlation between damage to specific subcortical regions and the evolution towards dementia, ie whether the administration of multimodal antidepressants could operate in a protective key or induce a recovery of function. In support of this intuition we cite the effects that certain polymodal antidepressants (Vortioxetine) exert on populations of interneurons expressed in the parahippocampal regions and responsible for movement control, which could perform an action on the limbic-emotional sphere and on mnemonic processes, through the modulation of the bioavailability of dopamine. Thus it can be deduced that the multimodal antidepressant (Vortioxetine) has an action on the serotonergic, noradrenergic, dopaminergic and cholinergic systems.

Conclusion: The therapeutic treatment of cognitive impairment associated with behavioral disorders (BPSD) represents an important therapeutic target; the management of BPSD associated with an improvement in humoral and behavioral disorders and in this case-report, also motor disorders, could allow the patient to return home and reduce the caregiver's emotional and care burden. Very important is the restoration of sleep homeostasis.

## VALIDATION OF A STUDY PROTOCOL FOR THE CONTROL OF EARLY STAGE COGNITIVE DISORDERS (PREMCI/MCI) USING QUEEN CHARLOTTE® (OMEGA3/ASTAXANTHIN ASSOCIATION)

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Introduction: QUEEN CHARLOTTE is a food supplement consisting exclusively of oil obtained from the sole head of wild Pacific Sockeye salmon. It is rich in biologically essential substances (which our body is unable to produce) among these, the fatty principles of the omega3 series (EPA) and docohexaenoic acid (DHA) and Astaxanthin, to which the unmistakable red-orange colour. Astaxanthin optimizes the biological effects of omega3 through its antioxidant action.

Study Objectives: The proposed observational study is aimed at determining the efficacy of Queen Charlotte on cognitive disorders in a selected patient population and, furthermore, at establishing the most appropriate dosage.

Materials and Methods: The evaluation of the cognitive state will be determined using test tools (Neuropsychological Tests: MMSE and SF12 Questionnaire). On the basis of the clinical data collected in a special data collection form, it will also be evaluated whether within this selected population of patients it will be possible to witness a reduction in blood chemistry parameters such as: Cholesterol, Triglycerides, Folate dosage, Vit.12 and homocysteine. First administration of the tests at the time of the nosographic classification, after specialist neurogeriatric visit, second administration after 90 days. Subjects belonging to CDCD clinics of the ASP IDR S. Margherita di Pavia - University of Pavia will be recruited.

Inclusion criteria: patients with cognitive disorders (MCI – Pre-MCI). Exclusion criteria: patients already in therapy with anticholisterases, anti-NMDAs and other therapies with food supplements.

Conclusions: At the end of the protocol, the data will be analyzed for a correct analysis of the cognitive disorders (MCI and Pre-MCI) of the possible response to treatment with Queen Charlotte 3 cp/day for 90 days.

## PLASMA AND CSF AMINO ACID PROFILE OF ALZHEIMER'S DISEASE: A METABOLIC SIGNATURE OF DISEASE

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Objective: Biochemical alterations linked to the neuronal/astroglial dysfunction affect the molecular composition of the interstitial fluid and of the cerebrospinal fluid (CSF). Pathology and nutritional status can influence the amino acids (AA) levels in the CSF compartment and plasma in subjects with Alzheimer's disease (AD). The aim is to search for a distinct AA profile in AD patients taking into account the nutritional status.

Materials and Methods: In 54 patients with AD (69% males, 74.4 ± 8.2 years) and 17 age-matched control (CTRL) subjects, CSF and venous blood samples were taken for AA measurements. Patients were stratified according to the nutritional status (Mini Nutritional Assessment, MNA, scores).

Results: Compared to CTRL, AD patients showed reduced levels of aspartic acid, and increased levels of taurine and 3-methyl-histidine ($p<0.001$). In addition, amyloid correlated inversely with histidine ($p < 0.05$), while p-tau correlated positively with levels of serine and glycine ($p < 0.05$). In the combined group (CG) including malnourished AD (16.7%; MNA < 17) and AD at risk for malnutrition (36.6%, MNA 17−24), essential amino acids (EAAs)/Total AA (TAA) ratio and Branched-Chain AA (BCAA)/TAA ratio were lower compared to normo-nourished AD ($p<0.05$). As for the subjects with available CSF, CG had lower levels of all CSF essential amino acids (EAAs) and 30% of non-EAAs compared to the CTRL ($p < 0.018$ to 0.0001), whereas normo-nourished AD (46.7%, MNA > 24) had lower levels of 10% of EAAs and 25% of non-EAAs ($p < 0.05$ to 0.00021). Finally, compared to normo-nourished AD, CG had lower CSF levels of aspartic acid, glutamic acid and BCAA (all, $p < 0.05$ to 0.003).

Discussion: Low levels of aspartic acid are related to a mitochondrial energetic dysfunction, increased levels of taurine are associated with neuroinflammation, while high histidine and low leucine and glutamic acid with the impairment of the leucine-glutamate shuttle. After deamination, EAAs in particular BCAAs provide carbon skeletons useful for replenishing the Krebs cycle and maintaining an adequate neuronal energy balance.

Conclusion: AD patients had low levels of some AA in plasma and CSF, particularly EAA and BCAA. The amino acid profile is an expression partly of the metabolic signature of the disease, partly of the ongoing nutritional status.

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## PLASMA GFAP LEVELS CORRELATE WITH PHYSICAL ACTIVITY AND BODY COMPOSITION: A BIOELECTRIC IMPEDANCE ANALYSIS STUDY ON HEALTHY ELDERLY POPULATION

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Introduction and Aim: Glial fibrillary acidic protein (GFAP) is a key player in astrocyte functions, thus modulating regeneration, synaptic plasticity and reactive gliosis. Several studies show a strong relationship between CSF GFAP and plasma levels detected by newly developed SIMOA detection methods. Physical activity (PA) enhances the production of neurotrophic factors, neurotransmitters, and hormones but no data about the relationship between PA and GFAP exist yet. The aim of the study is to evaluate the complex interaction between body composition and the plasma biomarker in neurologically healthy population.

Materials and methods: The prospective study included ninety healthy elderly individuals neurologically intact (65.9±7.1 years). Each individual underwent a multidimensional assessment including evaluation of physical activity, cognitive status and comorbidities. All individuals underwent a body composition assessment using bioelectric impedance analysis (BIA) and a blood sample was collected. Plasma GFAP levels were evaluated using SIMOA technique.
Results: According to International Physical Active questionnaire (IPAQ), very active subjects (VA, n=33) showed lower GFAP level in blood ($p<0.02$) than inactive (IN) and active (AC) subjects (n=57). No differences were founded between IN and AC. BIA showed a negative correlation between skeletal muscle index (SMI) ($r= -0.224$, $p<0.05$) and fat free mass index (FFMI) ($r= -0.235$, $p<0.05$) with GFAP levels in plasma.

Discussion and conclusions: This prospective study suggested that high levels of PA and body composition indexes might be neuroprotective trough their indirect action on astrocytes activation. Further on-going studies evaluating subtle inflammatory mediators and longitudinal changes of biomarkers are warranted to understand the predictive value of GFAP in healthy ageing.

## CEREBRAL AMYLOID ANGIOPATHY-RELATED INFLAMMATION: A SINGLE CENTER LONGITUDINAL STUDY ON SURVIVAL AND INCIDENT DEMENTIA

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Introduction: Cerebral amyloid angiopathy-related inflammation (CAA-ri) is characterized by an anti-amyloid immune response towards cerebrovascular-deposited amyloid-beta protein (Aβ) and the radiographic appearance of amyloid-related imaging abnormalities due to edema (ARIA-E), often associated with ARIA-H micro-hemorrhagic markers of CAA on magnetic resonance imaging (MRI). Clinically, the condition may present with focal neurological signs, epilepsy and acute and rapidly progressive cognitive impairment. Little is known about the natural history or predictive factors of relapse or clinical worsening, apart from a heightened haemorrhagic risk associated with sulcal siderosis and clinical improvement after immune-suppressive therapy. Aim: To longitudinally assess a cohort of patients with a diagnosis of probable CAA-ri describing clinical presentation, instrumental findings and long-term outcomes.

Methods: Patients with a diagnosis of probable CAA-ri according to current clinical-radiological criteria were recruited at a single center at the Department of Neuroscience in Padova (part of ICAB and SINdem CAA Study Group) from August 2013 to May 2023. Inclusion criteria were: MRI images of good quality on T2*/SWI and FLAIR sequences and clinical and cognitive findings collected both at (sub)acute presentation and at least one follow up visit. ApoE genotyping and CSF chemical-physical and AD-related biomarkers.

Results: Twenty-one patients (mean age 72 years, 57% male) were recruited and followed for a mean time of 2,6 years +/- 2,7 (minimum 0,05, maximum 8,6 years). At presentation, 76% of patients had focal neurological signs (sensitive/motor signs, visual disturbances, aphasia), 38% cognitive deficits, 29% seizures (10% status epilepticus), and 19% alteration of consciousness or headache. CSF analysis was abnormal in 48% patients (mean 12 WBC +/- 31, QAlb at higher normal value). At first 81% had multifocal ARIA-E, 61% with a diameter less than 5 cm. At follow up, 3 patients had a CAA-ri relapse, 14% did not improve after steroid therapy. Kaplan Meier analysis showed a 30% of mortality after 2 years and occurrence of dementia in 55% of cases. Survival was not associated with presence and length of steroid therapy. 75% of patients developing dementia met the biomarker criteria for Alzheimer's disease continuum pathological changes.

Discussion: CAA-ri is an increasingly recognized and diagnosed autoimmune encephalopathy which presents with a wide range of symptoms and may have a poor long-term outcome both for survival and for development of dementia, mainly of AD-type. Early diagnosis and treatments with immune-suppressive therapy and strict surveillance to intercept evolving cognitive decline or inflammatory relapses should be considered.

## A FUNCTIONAL VARIANT IN GRIN2C IDENTIFIED IN AN ITALIAN FAMILY WITH LATE-ONSET ALZHEIMER'S DISEASE

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Background: Alzheimer's disease (AD) is the most common type of neurodegenerative dementia, but the cause of AD remained poorly understood. In early-onset Alzheimer disease, positional cloning led to the identification of rare, disease-causing variants in APP, PSEN1, and PSEN2 gene. Late-onset AD represents the most common form of the disease and is associated with several confirmed Alzheimer's

disease loci [1, 2]. The aim of this study is to describe the clinical, genetic and functional studies of an Italian, autosomal-dominant late-onset Alzheimer's disease pedigree carrying a new rare variant in the glutamate ionotropic receptor NMDA type subunit 2C (GRIN2C).

Methods: We describe a targeted exome sequencing analysis of a large Italian kindred with late-onset AD with a typical clinical presentation, negative for APP, PSEN1, and PSEN2 variants. Previous analysis using NeuroX array excluded further mutations linked to neurodegenerative disorders. Whole Exome Sequencing (WES) on the three affected subjects and two healthy relatives was performed. Bioinformatic analysis of WES data followed a general pipeline previously described to identify single nucleotide variants and small insertions and deletions. Functional analysis was performed using neuronal cells cultures, immunocytochemistry, and electrophysiology.

Results: The c.3215 C>T (p.Ala1072Val) in GRIN2C (NM_000835) was identified and validated by Sanger sequencing. The segregation of the variant with the disease in the family was confirmed in a total of 8 affected subjects and in 6 healthy relatives. Primary hippocampal neurons overexpressing GluN2C A1072V showed significantly increased NMDAR-induced currents associated with an increase surface level of the mutant subunit. Furthermore, GluN2C A1072V change is close to the binding motif of 14-3-3 scaffolding proteins, and an impaired colocalization of the mutant GluN2C with 14-3-3 was detected.

Discussion: GRIN2C mRNA is widely expressed in the brain, and the Ala1072Val variant was considered of interest based on DANN pathogenicity scoring, allele frequency in the general population (GnomAD database). Functional whole-cell voltage clamp recording on GluN2C A1072V overexpressing hippocampal neurons clearly showed an increase of NMDAR-induced currents. Moreover, we demonstrated that GluN2C A1072V change impaired GluN2C colocalization with 14-3-3 scaffolding proteins which could result from the fact that the site of the mutated aminoacid is close to the binding motif of these proteins.

Conclusion: In this study, we report for the first time a rare missense variant in GRIN2C causing late-onset Alzheimer's disease, and our study provides interesting data supporting a role for the GluN2C-containing NMDARs and 14-3-3 proteins in Alzheimer's disease pathogenesis.

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## REAL-WORLD APPLICATION OF THE AT(N) CLASSIFICATION FOR ALZHEIMER'S DISEASE: A COMPREHENSIVE STUDY OF A HOSPITAL-BASED POPULATION

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Objective: Alzheimer's disease (AD) is a significant global health concern with an increasing social and economic burden. The AT(N) classification system was created to stratify patients based on biomarker profiles, including amyloid-beta deposition (A), tau pathology (T), and neurodegeneration (N), providing a research framework for understanding disease heterogeneity. This study aims to apply the AT(N) classification to a hospital-based cohort of patients with cognitive decline and/or dementia, within and outside the AD continuum, to enhance our understanding of the multidimensional aspects of AD and related disorders.

Materials: We conducted a retrospective evaluation of 429 patients referred to the Memory Center of IRCCS San Raffaele Hospital in Milan. Clinical, neuropsychological, and neurobehavioral assessments were performed, along with lumbar puncture, structural imaging with magnetic resonance imaging (MRI) or computed tomography (CT) scans, and functional imaging using positron emission tomography (FDG-PET).

Methods: The cohort was stratified according to the AT(N) classification, and comparisons were performed between groups. The number of eligible cases for anti-β amyloid monoclonal antibodies was also calculated.

Results: Sociodemographic and clinical features were similar across groups. Although the clinical presentation was similar, the A+T+N+ group showed more severe cognitive impairments in memory, language, attention, executive, and visuospatial functions compared to other AT(N) groups. FDG-PET outperformed MRI and CT scan in distinguishing amyloid-positive from amyloid-negative patients. Among the observed cases, only 6% were eligible for amyloid-targeting clinical trials.

Discussion: The findings support the applicability of the AT(N) classification in a real-world clinical setting. The classification system provided insights into clinical management and treatment strategies. Differences in neuropsychological performance and imaging features among the AT(N) groups further contribute to our understanding of the disease. This work provides also a realistic picture of the low proportion of AD patients eligible for disease modifying treatments.

Conclusions: This study emphasizes the need for early detection and personalized treatment approaches to address the challenges of AD.

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## APPLICATION OF ARTIFICIAL INTELLIGENCE TO STANDARD CLINICAL DATA IN PRODROMAL ALZHEIMER'S DISEASE: HOW FAR ARE WE?

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Background and Aim: Machine Learning (ML) techniques are increasingly employed to support research from a data-driven point of view in neurodegenerative conditions, like the Mild Cognitive Impairment-Alzheimer's Disease (MCI-AD) continuum. To achieve optimal accuracy, the algorithms are typically fed with a wealth of data unavailable in the standard clinical practice (e.g., cortical thickness, metabolomics). Thus, their routinary application is debatable and limited. We assessed the feasibility of ML application to standard and readily available clinical data in cognitively normal and Mild Cognitive Impairment (CN, MCI) subjects to predict a 3-year change in their cognitive status.

Methods: CN and MCI were selected from the ADNI dataset according to the availability of demographic, CSF, neuropsychological

measures, and a 3-year follow-up. Subjects were divided into CSF-positive and CSF-negative according to t-tau/abeta ratios (from Hansson et al.). A gradient boosting algorithm was combined with Random Forest's variables ranking and applied to the two cohorts. The goal was to predict the 3-year conversion, assess the model's accuracy, and identify differences in the predictors according to the CSF status. SHAP analysis was then applied to analyze the decisional processes of the algorithm.

Results: Our model achieved 90.0% prediction accuracy in patients with negative CSF, while 87.5% accuracy was obtained in patients with a positive CSF ratio. We also found differences between CSF-positive and negative patients regarding the most valuable predictors and suggested cut-offs.

Conclusions: Our approach yielded remarkable prediction accuracy only using standard clinical data and could be easily implemented.

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## VALIDATION AND NORMATIVE VALUE STUDY OF COGNISTAT IN THE ITALIAN POPULATION

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Background: Early detection of neurocognitive disorders frequently relies on the Mini Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA) for screening purposes. Unfortunately, both tests have low sensitivity in detecting mild cognitive impairment (MCI) or mild dementia. COGNISTAT is an international test designed to assess intellectual functioning in the five major ability areas: Language, Spatial Skills, Memory, Calculations, and Reasoning. Level of Consciousness, Attention, Memory Registration, and Orientation are assessed independently. In each area, the patient is first presented with a screen test, that is failed by approximately 20% of normal individuals. If the patient passes the screen, no further testing is done in that section. If the screen is failed, the examiner administers the metric, a series of test items of increasing difficulty. In this way, intact areas of functioning are tested briefly, while areas of disability are studied in detail.

Methods: We translated and then tested an Italian version of the COGNISTAT in a population of healthy volunteers enrolled at our outpatient clinic. After signing the informed consent, volunteers underwent a socio-demographic data collection (Age, sex, education, medical history, medication use, employment status, family medical history), and two neuropsychological evaluations with the MoCA and the MMSE, and then the computer based COGNISTAT test. For the aim of this study, COGNISTAT was administered using both the screen and metrics part of the test, even if volunteers passed the screening questions.

Results: We enrolled 210 healthy volunteers aged 18-84 years, and stratified them in 7 age groups, 30 patients for each group: 18-40, 41-59, 60-64, 65-69, 70-74, 75-79, >79. Mean ± Sandard Deviation of the COGNISTAT scores for every age group were: 79.9±2.8 (18-29 years), 79.2±4.5 (30-49 years), 76.1±5 (50-59 years), 76.3±3.2 (60-69 years), 72.3±5.0 (70-79 years), 65.9±3.8 (>79 years). COGNISTAT scores correlated with MoCA (0.656; $p<0.001$) and less with MMSE (0.391; $p<0.001$). Age had a significant impact on all sub scores of COGNISTAT, except for orientation, attention, and registration. Gender had a significant impact on attention ($f = 7.668$; $p=0.007$). We found no impact of the interaction between age and gender. We also calculated normative values corrected for gender, age and education.

Conclusion: COGNISTAT is a reliable and useful tool that can aid in the diagnosis of cognitive disorders in the Italian population. Compared to other screening tools, it combines reduced administration time with a defined output that allows for a neuropsychological diagnosis.

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## ENLARGED PERIVASCULAR SPACES ARE ASSOCIATED WITH CEREBROSPINAL FLUID AQUAPORIN-4 AND TAU LEVELS IN PATIENTS WITH NEURODEGENERATIVE DEMENTIA

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Background: Perivascular spaces (PVS) are fluid-filled compartments that dilate in response to many different conditions. A high burden of enlarged PVS (EPVS) in the centrum semiovale (CSO) has been linked to neurodegeneration. Moreover, an increase in cerebrospinal fluid (CSF) levels of aquaporin-4 (AQP4), a water channel expressed on PVS-bounding astrocytes, has been described in patients with neurodegenerative dementia. Our aim was to investigate the relationship between neurodegenerative diseases and two putative glymphatic system biomarkers: AQP4 and EPVS.

Methods: We included 70 individuals, 54 patients with neurodegenerative diseases and 16 subjects with non-degenerative conditions. EPVS were visually quantified on MRI-scans according to Paradise et al. All subjects underwent lumbar puncture for the measurement of AQP4 levels in the cerebrospinal fluid (CSF). CSF levels of

amyloid-β-1-42, phosphorylated and total tau (tTau) were also measured. Linear regression analyses were adjusted for age, sex, education and disease duration.

Results: CSF-AQP4 levels were independent predictors of total (β = 0.33, standard error [SE] = 0.09, p < 0.001), basal ganglia (β = 0.29, SE = 0.08, p = 0.006) and centrum semiovale EPVS (β = 0.53, SE = 0.17, p = 0.002). tTau levels predicted CSO-EPVS (β = 0.40, SE = 0.19, p = 0.046). Moreover, increased levels of AQP4 were strongly associated with higher levels of tTau in the CSF (β = 0.36, SE = 0.13, p = 0.006).

Conclusions: We provide evidence that CSO-EPVS and CSF-AQP4 might be clinically meaningful biomarkers of neurodegeneration secondary to glymphatic dysfunction.

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## ASSOCIATION BETWEEN FRAILTY AND NEUROPHYSIOLOGICAL MEASURES OF PERIPHERAL NERVE CONDUCTION


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Introduction: Frailty is a marker of biological age and has been associated with a higher risk of adverse neurological outcomes. Specifically, frailty has been shown to increase the risk of for diverse illnesses affecting the central nervous system and to predict unfavourable disease courses. To date, no studies explored its impact on the pathophysiological mechanisms and neurophysiological measures of the peripheral nervous system. The present study aimed at investigating the association between frailty and quantitative neurophysiological parameters in patients with no peripheral nervous system disorders.

Materials: Patients who were subjected to a nerve conduction study at the Department of Human Neuroscience, Sapienza University of Rome were considered for the present analysis. Data about age, date of birth, sex, medical history, current therapies, and diagnostic question were collected.

Methods: Frailty was assessed through a Frailty Index (FI), designed on the model of deficit accumulation. A total of 36 items constituted by symptoms, signs, diseases, disabilities, and laboratory findings were included in the index. For each participant, the FI score was obtained by dividing the number of deficits presented by the subject and the total number of items (i.e., 36). Spearman's correlations were conducted to explore the association between FI and the SNAP amplitude of the right sural and ulnar nerve expressed in mV.

Results: Overall, 25 participants (mean age 59.9, standard deviation [SD] 16.1; 64.7 % women) were recruited. The mean FI score was 0.20, SD 0.13. SNAP amplitudes were significantly, inversely correlated with age (ulnar: rho = -0.48, p = 0.03; sural: rho = -0.73, p < 0.001). A negative correlation was also observed between SNAP amplitudes and FI scores, although not statistically significant (ulnar: rho = -0.09, p = 0.03; sural: rho = -0.73, p = 0.06). In partial correlations adjusted by FI, age was no longer correlated with the SNAP amplitude of the ulnar nerve (rho = -0.35, p = 0.18); the correlation coefficient between age and the SNAP amplitude of the sural nerve decreased to -0.54, p = 0.03.

Discussion: The negative correlation between increasing age and measures of SNAP amplitudes seems to be partly moderated by frailty. The FI may be useful to explore the impact of the ageing process on peripheral nerve conduction, beyond chronological age.

Conclusions: Future studies are needed to clarify how frailty the pathophysiology of the peripheral nervous system and the clinical expression of its disorders.

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## DEMENTIA WITH LEWY BODIES FOLLOWING NORMAL PRESSURE HYDROCEPHALUS: COMORBIDITIES OR CAUSAL LINK? CASE REPORTS AND A COMPREHENSIVE REVIEW OF THE LITERATURE


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Objectives: Reports about comorbidity between idiopathic Normal Pressure Hydrocephalus (iNPH) and neurodegenerative diseases have been recently increased in literature, but mechanism underlying their causal link has not yet fully defined. Many cases of iNPH have been proven to be synucleinopathies such as Dementia with Lewy Bodies (DLB), after several years of follow-up[1].

Materials: Herein we report two our recent clinical cases of DLB patients started as iNPH, and we review literature focusing on potential clinical or fluid biomarkers that could help clinicians to distinguish these two nosological entities.

Methods: We described two male patients that were admitted to our department due to impaired gait and cognitive issues presenting with a NPH radiologic pattern. We also reported all clinical case series that we have found in literature focusing on patients initially described as iNPH who developed clinically or pathologically proven DLB. Motor and non-motor symptoms as well as cerebrospinal fluid (CSF) and serum biomarkers were tested as potential red flags for the diagnosis of DLB.

Results: Among all symptoms and clinical signs, early or late-onset axial parkinsonism together with postural impairment and repeated falls should mostly lead us towards DLB diagnosis, along with an early cognitive involvement and alertness fluctuations. However, visual hallucinations remain the most representative of synucleinopathy. Additionally, transient motor or non-motor improvement after shunt placement does not exclude the possibility of an underlying neurodegenerative process [2]. CSF total-Tau levels of our first patient remained high (>1000 pg/ml) from the prodromal until the dementia stage of DLB history. Both (123I) FP-CIT SPECT with DAT-scan and (123)I-meta-iodobenzylguanidine (MIBG) cardiac scintigraphy tested positive in both patients.

Discussion: Having total-tau levels increased by one standard deviation was 2.5 times more frequent in LBDs relative to iNPH [1]. CSF Alpha-synuclein assay could also be useful for diagnosis, although not always available in routinary clinical practice.

Considering that symmetrically reduced DaT uptakes in the caudate nucleus could be a common finding in the locomotor iNPH subtype [3], MIBG can help in differential diagnosis, being altered only in DLB and not in iNPH.

Conclusions: Hydrocephalus should be considered not only as a single pathology but also as a prodromic pattern of several degenerative diseases. Relying on its link with alpha synuclein, CSF value of tau protein could probably be considered as an early predictive biomarker of motor and non-motor impairment in prodromal DLB patients, allowing clinicians to make a correct differential diagnosis against iNPH.

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## CSF BIOMARKERS FOR ALZHEIMER'S DISEASE ON FUJIREBIO'S LUMIPULSE AND ROCHE'S ELECSYS FULLY AUTOMATED PLATFORMS IN CLINICAL PRACTICE: DIAGNOSTIC ACCURACY AND CONCORDANCE

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Background: In the last decades the implementation of cerebrospinal fluid (CSF) biomarkers of amyloidopathy (Aβ42 and Aβ42/40), tauopathy (p-tau) and neurodegeneration (t-tau) in clinical practice has significantly enhanced the identification of Alzheimer's disease (AD) pathological processes in vivo, leading to improved diagnostic accuracy and better selection for clinical trials. CSF biomarkers can be measured using various methods, among which the most widely used in clinical practice are two fully automated platforms: Lumipulse by Fujirebio (based on a chemiluminescent enzyme immunoassay) and Elecsys by Roche (based on an electrochemiluminescence immunoassay). This study aimed to assess the concordance between CSF biomarker measurements obtained from these two methods and evaluate their diagnostic performance in comparison to clinical diagnosis.

Methods: We consecutively recruited 60 subjects who were candidates for CSF biomarker analysis from our Memory Clinic. CSF biomarkers were quantified using both Lumipulse and Elecsys instruments and ratios were calculated. Correlations between CSF biomarkers were performed by the means of Spearman's correlation coefficient and ROC analyses were carried out.

Results: Our results revealed a high correlation between biomarker measurements obtained from the two methods ($\rho$=0.918 for Aβ42; $\rho$=0.984 for p-tau; $\rho$=0.943 for t-tau; $\rho$=0.937 for p-tau/Aβ42; all p values <0.001). When considering the three possible biomarkers of amyloidopathy (Aβ42 and Aβ42/40 ratio for Lumipulse and Aβ42 for Elecsys), we found that 11 subjects tested negative for all amyloidopathy biomarkers, 22 subjects tested positive for all of them, and 27 subjects tested positive for only one or two biomarkers, indicating a low concordance between the manufacturer cut-offs. The p-tau/Aβ42 ratio measured by both instruments showed the highest accuracy in distinguishing AD subjects.

Discussion & Conclusion: Our study demonstrated a strong correlation between CSF biomarkers measured using Lumipulse and Elecsys. However, when considering individual measures of amyloidopathy, the sensitivity and specificity of manufacturer cut-offs differed, leading to relevant false positive and false negative rates. The p-tau/Aβ42 ratio emerged as the most accurate measure, compensating subjects misclassified by individual measures of amyloidopathy. Relying solely on a single biomarker of amyloidopathy can lead to inconsistent results and potentially misclassify individuals, while the use of the p-tau/Aβ42 ratio may enhance the identification of AD. This could be particularly relevant for clinical trials, where subjects are typically selected on the amyloidopathy criteria alone. According to the ATN classification AD is better defined by the presence of both amyloidopathy and tauopathy and our results on the p-tau/Aβ42 ratio support this evidence.

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## THE FREQUENCY OF APOLIPOPROTEIN E EPSILON4 ALLELE ACCORDING TO NIA-AA RESEARCH FRAMEWORK: A RETROSPECTIVE COHORT STUDY FROM TOR VERGATA HOSPITAL

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Background and Objectives: According to NIA-AA research framework, based on biomarkers accounting for Amyloid-Beta deposition (A), presence of fibrillar tau tangles (T), and neurodegeneration (N), it is possible to stratify patients in the AD continuum (ADc) [1]. Apolipoprotein E (APOE) is the strongest genetic risk factor for AD, and we know that the epsilon4 allele increases the AD risk compared to epsilon3 and epsilon2 allele [2]. In the NIA-AA research framework genetics is included only as a risk factor for the development of the disease, mainly due to the fact that it is not representative of neuropathologic changes. Nevertheless, it has been demonstrated that APOE epsilon4 is associated to both higher amyloid-beta accumulation and Tau iper-phosphorylation. To our knowledge a report on the prevalence of the APOE epsilon4 according to a biological classification of AD is lacking. The aim of this study is to analyse the frequency of APOE epsilon4 in AD patients, stratified according to NIA-AA, and in subjects with negative AD biomarker.

Materials and methods: We enrolled 1201 patients from Tor Vergata Hospital, which underwent blood screening for APOE genotype and measurement of amyloid-beta, total tau and phosphorylated tau in the Cerebrospinal Fluid (CSF) for diagnostic purpose. According to AD biomarkers all enrolled subjects were stratified in A+T+ (AD, n=263), A+T- ("Alzheimer's pathologic change", n=398), and A-T- (non-AD pathology, n=540).

Results: We observed that the frequency of APOE epsilon4 allele was significantly different in the three groups, in particular the ε4 allele was expressed in the 45.7% of A+T+ patients, 30.4% of A+T- and 15.6% of A-T- ($\chi 2$ test p<0.05).

Discussion and conclusions: APOE epsilon4 allele was significantly more expressed in A+T+ patients than in A+T- group, and in the latter respect to A-T- subjects. The A+T- group represents, in terms of APOE genotype distribution, a population in its own, different from both AD and non-AD subjects. Our data support the necessity to further investigate in the pathophysiological process underlying "Alzheimer's pathologic change" to clarify whether this category is considerable as a stage of AD or a distinct nosological entity.

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## INHIBITION AND FACILITATION EFFECTS ALONG THE AD SPECTRUM: A VOXEL-BASED MORPHOMETRY STUDY

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Objective: In the context of episodic memory, it was proposed that remembering an item implies forgetting for other related items (i.e., retrieval-induced forgetting-RIF) (1), while practicing a certain item induces facilitation for its subsequent retrieval (i.e., facilitation effect-FAC) [1]. However, this paradigm and its underlying mechanisms remain controversial in healthy as well as in pathological aging [1-2]. We aimed here to investigate RIF and FAC and their putative neural correlates in the Alzheimer disease (AD) continuum.

Methods: 28 AD and 29 amnestic mild cognitive impairment (aMCI) patients, 23 individuals with subjective memory complaint (SCD), and 20 healthy subjects (HS) underwent a recognition memory task to assess RIF and FAC effects using verbal/visual material. They also underwent a 3T-MRI scan including a T1-weighthed volume to assess through voxel-based morphometry (VBM) [3] potential associations between regional grey matter (GM) volumetrics and RIF and FAC measures. MANOVAs were used to assess RIF and FAC effects, while One-sample t-test models were used to investigate associations between RIF/FC effects and GM volumes.

Results: The FAC effect was present in all groups when using both, verbal and visual material, while the RIF effect remained undetected. VBM analysis showed associations between verbal RIF effects and regional GM volumes in the AD (i.e., left medio-temporal lobe) and HS group (i.e., bilateral precuneus/posterior cingulate, left parietal lobe). In the aMCI group, when using the visual task, VBM revealed associations for both RIF and FAC with regional GM volumes (i.e., RIF: right fusiform gyrus and cerebellar lobules; FAC: bilateral pre/post central gyri, and right inferior frontal gyrus). Finally, in the SCD group associations were found between GM volumes in the parahippocampal/fusiform gyrus bilaterally and both RIF and FAC effect.

Conclusions: The FAC effect was observed along the AD spectrum independently from the material used. Conversely, the RIF effect was not elicitable. This is probably due to the yes/no recognition paradigm employed here which is unable to induce a significant inhibition. The brain areas involved are those typically related to memory processes. Overall, this study suggests that facilitation/consolidation processes, although at different levels of accuracy, are relatively preserved across AD stages.

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## MORE RESERVE HELPS EVERY INDIVIDUAL ACROSS EITHER NORMAL OR PATHOLOGICAL AGING: THE ROLE OF LEISURE'S ACTIVITIES

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Background: Brain, cognitive, and neural reserves hypotheses have been introduced to account for the apparent inconsistencies between accumulation of neuropathological damage and clinical manifestations [1]. Leisure's activities pursued during life are theoretically considered as reserves' builders, although their association with actual cognitive efficiency remains to be clarified [2]. We aimed here to assess whether cognitive, social and physical leisure's activities pursued in different life-periods predict the present cognitive functioning during normal and pathological aging.

Methods: Twenty patients with Alzheimer's disease (AD), 19 patients with single domain amnestic mild cognitive impairment (a-MCI), 12 individuals with subjective cognitive decline (SCD), and 17 healthy elderly subjects (HE) underwent an extensive questionnaire to quantify cognitive, social and physical activities pursued during their youth (age range 20-40 years), middle age (age range 40-65 years) and old age (age >65 years) [3]. Neuropsychological assessment was performed using the Addenbrooke's cognitive examination (ACE-R). Categorial principal component analyses (cPCA) were used to extract the main component in the three life-periods for cognitive (C1, C2, C3), social (S1, S2, S3) and physical (P1, P2, P3) activities. CPCA scores were summarised to obtain three scores of the whole leisure's activity (LA1, LA2, LA3) alongside a total score (LAtot). CPCA scores were entered as independent variables, while the ACE-R total score, the MMSE score and different ACE-R subscores (representing different

domains) were entered as dependent variables in a series of regression models for each diagnostic group taken in isolation.

Results: In the a-MCI group C1, C2, and C3 predicted the general cognitive efficiency and cognition (attention, memory and language abilities); in the SCD group, L2 and L3 predicted the general cognitive efficiency and memory and language functioning; in the AD group S2 only predicted attention abilities; in the HE group, S3, P1 and C1 predicted general cognitive efficiency and memory functioning.

Discussion: Cognitive activities pursued during the middle- and old age account for the cognitive efficiency in patients with a-MCI only; in the SCD and HE groups, all recreational activities account for cognitive functioning, while in patients with AD current social interactions predict the cognitive level. These findings may be useful to address tailored interventions during normal and pathological aging.

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## SEX DIFFERENCES IN THE SEVERITY AND PROGRESSION OF NEUROPSYCHIATRIC SYMPTOMS ACROSS DIFFERENT DEMENTIA TYPES: A CROSS-SECTIONAL AND LONGITUDINAL STUDY

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Introduction: Neuropsychiatric symptoms manifest variably across common dementia types, such as Alzheimer's disease (AD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), vascular dementia (VaD), mixed dementia (MD), and in the stage of subjective cognitive decline (SCD), often a precursor to clinical dementia. Despite the pronounced impact of NPS on patient quality of life and caregiver burden, the influence of sex on the prevalence and severity of these symptoms remains largely uncharted territory.

Objective: This study seeks to bridge the gap in our understanding of sex differences in the prevalence, severity and progression of NPS across various forms of cognitive impairment assessed retrospectively in a single-center cohort.

Methods: A thousand sixty-eight patients were included (AD n=650, FTD n=166, DLB n=77 and SCD n=175). Hierarchical generalized linear mixed models were utilized to model neuropsychiatric symptoms as a function of disease severity (CDR-SoB), sex, and clinical phenotypes.

Results: We observed significant differences in neuropsychiatric symptoms' prevalence between men and women in AD, FTD, DLB and SCD. In particular, in AD, women reported symptoms more frequently than men (86.3% vs 80.7%), particularly in the early stages of the disease. Apathy was the most common symptom reported by men (53.0%), whereas depression/dysphoria was most common in women (52.3%). In FTD, 97.0% of patients reported experiencing at least one NP, with apathy being the most common. Delusions, hallucinations and depression/dysphoria were more frequently reported by women, while men reported higher instances of agitation/aggression, apathy/indifference and irritability/lability. In DLB, as in FTD, patients exhibited a notably high frequency of NPS on average. The frequency of experiencing any NPS were similar for both sexes (90.9% in men, 94.9% in women). Anxiety was significantly more common in women (60.3%), than in men (44.4%). In patients with SCD, the frequency of NPS was notably lower than in other neurodegenerative disorders (60.3% in men and 64.7% in women). The most commonly reported symptoms were depression, anxiety, and irritability.

Discussion: Critically, NPS can fluctuate and evolve over the disease course, adding a layer of complexity to patient management. Despite this dynamic nature of NPS, longitudinal studies systematically tracking these changes across different dementia types remain exiguous. Although the pathophysiological contribution of sex in neurodegeneration is not characterized yet, our findings highlight its role as possible biological variable in dementias.

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## TRANSCRANIAL PULSE STIMULATION (TPS) FOR MILD COGNITIVE IMPAIRMENT: A PRELIMINARY STUDY

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Objective: The aim of the present study was to verify the effectiveness and safety of Transcranial Pulse Stimulation (TPS) in improving cognitive performances in Mild Cognitive Impairment (MCI).

Material: A consecutive series of patients treated with TPS at the Neurological Unit of the San Salvatore Hospital of L'Aquila was included in the study. Inclusion criteria were: diagnosis of MCI, no contraindication to Magnetic Resonance Imaging (MRI) preliminary assessment and availability to return for longitudinal follow-up visits.

Methods: All patients performed the stimulation sessions according to the following schedule: six initial stimulations (three times a week for two weeks) followed by a one-week break and four maintenance stimulations (once a week), for a total of ten stimulation sessions. The TPS system consists of a mobile single transducer and an infrared camera system for MR based neuronavigation (NEUROLITH, Storz Medical AG). All patients were assessed through the Mini Mental State Examination (MMSE), the Rey Auditory Verbal Learning Test (RAVLT), Raven's Progressive Matrices, the Verbal and Semantic Fluency Test, the Constructive Apraxia Test, the Immediate Visual Memory Test and the Beck Depression Inventory- II (BDI-II) at baseline (t0), at 15 days (t1) and at one and a half months after the start of the treatment (t2). Data were analyzed by paired t-test or Wilcoxon signed-rank tests. A p-value $<0.05$ was considered statistically significant.

Results: Fourteen patients (mean age$\pm$SD 73.4$\pm$6.73; mean education 10.6$\pm$4.83) completed the 10 stimulation sessions and were assessed through the neuropsychological and behavioral battery at time t0, t1 and t2. No statistically significant changes were found between

the scores obtained at baseline and at the 15 days follow-up. Conversely, a significant improvement was observed in global cognitive function (MMSE 21.80±4.12 Vs 23.49±3.89; p= 0.002), mnestic function (RAVLT: immediate recall 19.21±6.88 Vs 23.86±7.08; p= 0.012) and in visual memory test (15.27±4.47 Vs 17.06±3.99; p= 0.018) at one and a half months after the start of treatment as compared to baseline. No side effects were detected in the managed patients.

Discussion: TPS is a safe and effective brain stimulation technique that may be used as an add-on therapy in MCI.

Conclusions: Future studies are needed to evaluate the long-term effectiveness of TPS in patients with MCI and other clinical populations.

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## INTERCEPTING FATIGUE: AN ALERT FOR NEURODEGENERATION AND FRAILTY IN AGING


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Introduction: Fatigue is usually defined as a subjective feeling of extreme and persistent mental and physical tiredness, weakness, or exhaustion. It represents a common and distressing symptom in older people and has been associated with poor health outcomes. Nevertheless, its pathophysiological underpinnings and clinical correlates have been scarcely characterized.

Objective: The present study aimed to explore the clinical manifestations and biomarker abnormalities associated with fatigue in a population of older, cognitively unimpaired individuals.

Materials and Methods: Cognitively normal participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) 2 study were considered for the present analysis. The study sample was divided into two groups according to the presence or absence of fatigue based on self-reported "low energy" at baseline. Univariate analyses were conducted to compare the sociodemographic and clinical characteristics of the two groups and identify possible differences in CSF and neuroimaging biomarkers. A logistic regression analysis was then performed to identify clinical and biological determinants significantly associated with fatigue (bivariate dependent variable of interest). A sensitivity analysis was undertaken to ascertain the influence of sex.

Results: Overall, 291 subjects (mean age 73.0 ± 6.0 years; 54.0% women) were considered. Among them, 44 (15.1%) complained of fatigue. Participants reporting fatigue were more frequently women, more severely frail and depressed, and exhibited lower hippocampus volumes at the MRI relative to their non-fatigue counterparts. At the logistic regression, female sex, increasing frailty index scores, depression, ApoEε4 genotype, and lower hippocampus volume resulted as significantly associated with the presence of fatigue (all $p<0.05$). Relevant sex differences were observed in sensitivity analyses.

Conclusion: Fatigue is a complex symptom in older people, potentially resulting from the interplay between diverse determinants such as genetic traits, frailty, and mood. Moreover, it may represent an early manifestation of incipient neurodegeneration. A comprehensive and multidimensional approach is therefore needed to investigate the nature and role of this common manifestation.

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## BRAIN FDG-PET DIFFERENTIATES TYPICAL AND ATYPICAL ALZHEIMER'S DISEASE WITH NEUROPSYCHIATRIC SYMPTOMS: CLINICAL CLASSIFICATION AND PROGNOSTIC PREDICTION


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Background: The amnestic syndrome represents the most common presentation of Alzheimer's disease (AD), named typical (tAD). Atypical AD variants have been increasingly recognized, including the frontal variant (fvAD), described in patients with predominant behavioral/dysexecutive deficits [1]. Neuropsychiatric symptoms (NPS) are common in typical and atypical AD variants, associated with a steeper cognitive decline [2]. NPS may already be present in the early stage of dementia, making diagnosis challenging and meaning prognostic shortcomings. Our study aimed to investigate the brain metabolism pattern in patients with both memory and behavioral/dysexecutive disturbances to provide an early-stage accurate clinical and prognostic classification.

Methods: Based on the clinical evaluation, n=30 patients with memory and behavioral/dysexecutive deficits were included in the study. All patients had neuropathological or biomarker evidence of AD pathology (amyloid-PET or CSF analysis). All patients underwent baseline cognitive and neuropsychological evaluation and FDG-PET. FDG-PET was analyzed following a validated voxel-based SPM procedure, obtaining hypometabolism maps at the single-subject level. Based on previously validated literature, patients were classified according to the adherence of the hypometabolism maps to pre-defined disease-specific anatomical templates in tAD (temporoparietal and posterior cingulate cortex hypometabolism) and fvAD patients (both typical and prefrontal cortex hypometabolism) [3]. Baseline and follow-up cognitive evaluation was carried out by the Mini-Mental State Examination (MMSE), while NPS were investigated through the Neuropsychiatric Inventory (NPI).

Results: According to the single-subject SPM analysis, n=14 patients were classified as fvAD, n=10 as tAD, n=6 patients showed other hypometabolism patterns (limbic, unclassifiable) and were excluded from the analysis. Both fvAD and tAD groups showed baseline mild-to-moderate cognitive impairment. Patients in the fvAD group showed a higher rate of NPS as evaluated by the NPI (including the sum of scores, several NPI sub-scores, and caregiver distress), with a significant longitudinal increase in NPI scores. At follow-up (16.5 ± 7.1 months) mean MMSE score did not differ between groups, but fvAD showed a steeper cognitive decline than tAD as evaluated by the MMSE points lost per year (p=0.03). Prefrontal cortex hypometabolism (especially orbitofrontal cortex and dorsolateral cortex hypometabolism) correlated with NPI global score and sub-scores.

Discussion: In our study, fvAD patients showed higher NPS at onset and a steeper global cognitive and neuropsychiatric decline at follow-up than tAD. Hypometabolism in the prefrontal cortex correlated with the severity of NPS. Brain hypometabolism maps aided differential diagnosis between typical and atypical AD forms at the first evaluation, supporting a more accurate prognostic prediction than clinical evaluation.
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## NEUROPSYCHIATRIC SYMPTOMS IN PEOPLE WITH MILD COGNITIVE IMPAIRMENT AND MILD ALZHEIMER'S DISEASE ARE ASSOCIATED WITH ALTERATIONS IN DOPAMINE-ENRICHED FUNCTIONAL CONNECTIVITY PATHWAYS

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Objectives: Alterations in neurotransmission and brain functioning are likely to be among the first neuropathological changes occurring in Alzheimer' disease (AD). However, how such alterations are associated with neuropsychiatric symptoms still remain elusive. The aim of this study is to investigate resting-state functional connectivity based on a priori knowledge of dopamine receptor distribution in the brain as a potential marker of AD-related behavioural problems.

Material and Methods: Clinical, Neuropsychiatric Inventory (NPI) and structural and resting-state functional MRI data were collected for people with either mild cognitive impairment or mild dementia due to AD. Functional MRI data were pre-processed by using the Receptor-Enriched Analysis of functional connectivity by targets (REACT) procedure to obtain functional connectivity (FC) maps informed by dopamine D1 (D1r) and D2 receptor (D2r) PET atlases. The association between NPI total scores and dopamine-enriched FC was tested with multiple regression models in SPM12 by including age, education, sex, MMSE scores and total intracranial volume as covariates. An exploratory analysis was carried out to compare dopamine-enriched FC maps between 10 patients with and 10 without psychotic symptoms.

Results: The total NPI score was negatively correlated with D1r-enriched FC in the brainstem, thalamus, medial and inferior temporal cortices and in the precuneus and with D2r-enriched FC in fronto-parietal and superior temporal areas. Psychotic patients showed primarily lower D1r-enriched FC than non-psychotic patients in occipito- and medio-temporal areas and lateral fronto-parietal areas and lower D2r-enriched FC in occipito-parietal areas. However, psychotic patients also had higher D1r-enriched FC in dorsolateral prefrontal cortices and D2r-enriched FC in the basal ganglia, thalamus and hypothalamus than non-psychotic patients.

Discussion and Conclusions: A widespread decrease in FC influenced by the distribution density of different dopamine receptors, especially in fronto-parietal, occipito-temporal and brainstem areas, may represent the neural process driving behavioural alterations in people with mild AD. Such alterations may be particularly predisposing to psychotic symptoms, although a combination of both downregulation and upregulations in specific dopamine-informed FC pathways may play a pivotal role.
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## ELECTROPHYSIOLOGY OF EARLY STAGES OF VISUAL PROCESSING DYNAMICS IN SUBJECT COGNITIVE DECLINE AND MILD COGNITIVE IMPAIRMENT

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Objectives: This study aims to identify Electroencephalography (EEG) markers associated with early processing of visual stimuli in patients with Subjective Cognitive Decline and Mild Cognitive Impairment [1].
Materials: We analyzed event-related EEG potentials in 144 subjects (85 SCD, 41 MCI and 18 age-matched healthy HS subjects) while performing a sustained visual attention task. We measured the information carried about both group and performance by N1 integrals in occipital channels and computed the percentage of extraoccipital channels recruitment (EOR) via Spearman correlation metrics.

Results: N1 integral showed significative differences between HS and patients, i.e., SCD+MCI (KW test=5.838, pvalue=1.568e-02) and, specifically, while comparing HS and SCD (KW test=6.970, pvalue=2.487e-02). Moreover, we found N1 nonmonotonic values associated with dementia progression: HS (247.58[μV*ms]±38.79), SCD (146.50[μV*ms]±11.86) and MCI (171.29[μV*ms]±72, KW test=6.97, p=2.487e-02). EOR measures displayed significative differences between SCD and MCI (KW test=5.808, p value=4.785e-02) with higher values for MCI (25%±0.08) than SCD (21%±0.09).

Discussion: N1 Previous studies associated N1 decrease with dementia [2], but here we report that such decrease is non-monotonous in early stages. EOR is a visual functional connectivity proxy that could indicate specialized reorganization [3] due to worsening pathology, as the transition from SCD to MCI.

Conclusion: The continuum of neurodegeneration associated with loss of cognitive abilities appears to show a discontinuity in visual EEG correlates. Follow-up of patients could indicate the extent to which early dynamics in visual processing could help suggest dementia-related risk factors.
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## CHCHD2 AND DNAJC6 GENE MUTATION IN AN ITALIAN PATIENT WITH EARLY-ONSET ALZHEIMER'S DISEASE

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Objectives: We report for the first time a case of a Caucasian woman with a concomitant mutation in CHCHD2 and DNAJC6 genes who developed early-onset Alzheimer's disease (AD). To date, CHCHD2 mutations in AD patients has been described only in Chinese populations.

Materials and Method: A 52 years-old Caucasian woman was evaluated in the Centre for Dementia and Cognitive Disorders at S. Andrea Hospital in Vercelli, Italy. Her disturbances had started one year and a half before and were characterized by memory, concentration, and attention deficits, progressively worsening. Initial disturbances in visuospatial abilities and writing were also present. The patient was admitted to the Neurology Unit for further evaluation. During hospitalization, she underwent neurological and neuropsychological examinations, blood tests, magnetic resonance imaging (MRI), fluorodeoxyglucose-positron emission tomography (FDG-PET), cerebrospinal fluid (CSF) samples, and blood sampling for genotyping.

Results: The neuropsychological assessment revealed severe deficits in memory, language and executive functions. The brain MRI showed a diffuse cortical atrophy. FDG-PET imaging revealed a pattern of marked hypometabolism in the bilateral postero-parietal and temporo-parietal regions, and moderate hypometabolism in frontal left regions. The CSF analysis showed increased total tau and phosphorylated tau and reduction of amyloid β levels. In light of the clinical presentation, laboratory and imaging data a diagnosis of AD was made. Genotyping revealed two rare different heterozygous mutations: c.235 G>A, p.A79T (rs200784526) c.1331A>G, p.D444G (rs761459753) in CHCHD2 and DNAJC6 genes, respectively. Both variants have been classified as of uncertain significance according to the 2015 ACMG criteria.

Conclusions and discussion: The CHCHD2 gene encodes for a multifunctional protein that takes part in the regulation of mitochondrial metabolism. CHCHD2 mutations have been previously associated with familial and sporadic Parkinson's disease (PD). Additionally, CHCHD2 variants were identified in other neurodegenerative diseases including fronto-temporal dementia, amyotrophic lateral sclerosis and AD. To date, CHCHD2 variants in AD patients have been described only in Chinese populations [1] [2]. DNAJC6 encodes for a co-chaperone protein that belongs to the endo-lysosomal pathway. DNAJC6 mutations have been reported in early-onset PD patients. Regarding AD, only one report described a possible association between AD and DNAJC6 mutations [3]. In conclusion, our report described for the first time a concomitant mutation in CHCHD2 and DNAJC6 genes in a Caucasian AD case, with early-onset and rapid disease course.

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## LATE-ONSET ALZHEIMER'S DISEASE (AD) WITH PROGRESSIVE BULBAR MOTOR INVOLVEMENT: A COINCIDENTAL ASSOCIATION?

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Aims: To describe the unusual occurrence of progressive bulbar impairment in a patient with late-onset cognitive decline.

Materials and methods: The patient underwent clinical, neurophysiological and laboratory examination, neuropsychological assessment, and brain MRI and FDG-PET.

Results: An 83-year-old woman with a 4-year-history of cognitive decline with predominant memory impairment consistent with amnestic mild cognitive impairment (MCI) developed progressive dysarthria and dysphagia over the previous 2 years. At admission, her speech was nearly unintelligible, and neurological assessment showed frontal release with disinhibition and pseudobulbar signs, brisk deep tendon reflexes, diffuse muscle wasting and tongue fasciculations. Needle electromyography confirmed the presence of widespread chronic and active denervation of the tongue and motor evoked potentials revealed alterations in both cortico-bulbar and cortico-spinal tracts. The neuropsychological assessment revealed severe deficits of verbal and visuo-spatial memory. Brain MRI showed severe atrophy of mesial temporal lobes and hippocampi and mild posterior parietal atrophy. Brain FDG-PET showed fronto-temporo-parietal, cingular and precuneal hypometabolism. Cerebrospinal fluid analysis revealed increased total tau and p-tau with reduced amyloid beta42, consistent with Alzheimer's disease (AD). Single gene analysis tested negative for pathologic C9orf72 gene expansion.

Discussion: Up to 50% of patients with amyotrophic lateral sclerosis (ALS) show neuropsychological abnormalities, with nearly 10-15% of them fulfilling criteria for behavioral frontotemporal dementia (FTD). Moreover, bulbar involvement is more frequently associated with cognitive disfunction. Our patient showed the unusual association between Alzheimer and bulbar ALS. Increasing evidence suggests that hippocampal volume loss in ALS patients could correlate with amnestic dysfunction, providing clues for a widespread involvement of non-motor cortical areas in ALS. Although patient's advanced age could explain the presence of AD biomarkers, the association with bulbar ALS might be caused by pathogenetic TDP43/tau interactions [1]. The co-occurrence of AD with TDP-43 pathology [2], and the existence of ALS cases that fulfill pathological criteria for AD [3] support the latter hypothesis.

Conclusions: Our findings suggest that further studies are warranted to investigate the association between ALS/FTD and AD.

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## DATA-DRIVEN APPROACH REVEALS DIFFERENT PATTERN OF HYPOMETABOLISM IN BEHAVIORAL FRONTOTEMPORAL DEMENTIA AND LATE-ONSET PRIMARY PSYCHIATRIC DISEASES

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Background: Late-onset primary psychiatric diseases (PPD) and behavioural variant frontotemporal dementia (bvFTD) present both with a frontal lobe syndrome Neuroimaging of brain metabolism may have a crucial role among the investigations that could help in the differential diagnosis.

Objective: To compare brain glucose metabolism in bvFTD and late onset PPD mimicking bvFTD and study metabolic correlates of cognitive and behavioural disturbances Methods: Fifty-seven subjects with late-onset frontal lobe syndrome, 37 bvFTD (n= 37) and 20 PPD, were studied with brain FDG-PET/MRI: the variance of regional FDG standard uptake values ratio (SUVr) was evaluated with PCA and correlation analysis between SUVr data and cognitive/behavioural variables was performed.

Results: The degree of metabolism in the frontal regions and caudate explained 44.8% of the variance. 32% of bvFTD showed a spatial pattern of FDG uptake with relative sparing of frontal metabolism and these patients were genetic variants of bvFTD and/or had signs of motor neuron disease. Nearly half of PPD patients showed low-grade FDG hypometabolism in the anterior cingulate and/or parietal regions. In bvFTD lower metabolism of the caudate correlated with severity of compulsive symptoms while higher metabolism on the primary visual cortex correlated with higher disinhibition. There were not metabolic correlates of cognitive or neuropsychiatric symptoms in PPD.

Conclusion: hypometabolism of frontal regions and caudate, but not the cingulate cortex could help in distinguishing bvFTD from PPD, except cases with motor neuron signs and/or genetic forms which mimic PPD patients. No metabolic correlates of clinical features were found in PPD.

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## MULTIPLE GENE VARIANTS ASSOCIATED WITH DEMENTIA IN A LARGE COHORT OF ITALIAN PATIENTS WITH COGNITIVE DECLINE

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Background: Alzheimer's disease (AD) is related to genetic and environmental factors. Approximately 10% of patients with AD have an early onset presentation (<65 years, EOAD) with 5-10% of cases linked to genetic autosomal dominant variants. Conversely, sporadic late onset AD (LOAD) is genetically more complex and approximately 40 disease associated genes/loci have been reported. Fronto-temporal-dementia (FTD) is probably the most common form of dementia affecting people under the age of 60, and 5 to 10% of all FTD are caused by a genetic mutation. Although many genes have been classified as causative of dementia, there are many other whose prevalence and role in the pathogenesis of dementia remain uncertain.

Aim: To investigate common and uncertain dementia genetic variants of candidate genes in a large cohort of Italian young onset dementia patients or LOAD showing a familial presentation.

Methods: 152 outpatients and inpatients from 2002-to-2022 referred to the Research-Center-for-the-Aging-Brain (CRIC) of the Padua University Hospital were recruited. The cohort consisted of 108 patients with a diagnosis of AD (89 EOAD and 19 familial-LOAD, female 55%) according to 2011-NIA-AA and International-Working-Group-2 criteria and based on the evidence of beta-amyloid (CSF or amyloid PET) and 44 patients with a diagnosis of FTD (female 67%) according to recent FTD-consensus. The genetic analysis was performed using probes (13000) build with the Agilent SureDesign tool (Agilent Technologies Santa Clara, California, USA), binding coding exons and closest regions involving approximately 492.244 Kbp. NGS analysis was performed using NextSeq System e MiniSeq (Illumina, San Diego,CA,USA), and a total of 148 genes were analysed.

Results: We identified a genetic variant in 21/108 (19%) patients with AD. In the EOAD subgroup we found a variant in 18/89(20%) patients: 10PS2, 3PS1, 1APP, 1SPG11(compound heterozygous), 1misGRN, 1SPAST, 1TUBA4a. In the LOAD subgroup we found variants in 3/19(15%) patients: 1GRN, 1SOD1, 1TARDBP. Overall, we found a pathogenetic variant (evidence class 4/5) in 16/21(76%) and uncertain role (evidence class3) in 5/21(23%). In the FTD group we identified a variant in 13/44(29%) patients: 5GRN, 2MAPT, 2C9ORF72, 3TREM2, 1CSF1R. Overall, we found a pathogenetic variant (evidence class 4/5) in 10/13(76%) and uncertain role (evidence class3) in 3/13(23%).

Conclusions: The proportion of patients with a related genetic variant is relevant in familial and young onset cases. However, variants with uncertain role have been found in about 20% of patients. With our work we confirmed that disentangling the genetic contribution in the pathogenesis of dementia is critical to improve screening and therapy.

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## DIGITAL NEUROLOGY

### USABILITY OF TELE-MEDICINE PLATFORM AND TELE-REHABILITATION APPLICATIONS AND RELATED DEVICES IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT/EARLY ALZHEIMER'S DEMENTIA AND THEIR CAREGIVERS

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Objectives: Tele-medicine and tele-rehabilitation systems are increasingly proposed as useful approaches to improve or stabilize cognitive functions and increase the quality of life of patients with mild or moderate cognitive decline. [1] The aim of the present project was to investigate the usability of tele-medicine and tele-rehabilitation systems designed for remote assistance and treatment of patients with mild cognitive impairment or early Alzheimer's dementia (MCI/early AD) and in their caregivers. This project was founded by the Alzheimer's and Dementia Fund 2021-2023 of the Italian Ministry of Health (Project Line #4) and coordinated by the Italian National Institute of Health.

Methods: The project included two lines of intervention for which usability is analyzed: 1) a program of tele-rehabilitation for the MCI/early AD patients, using at home a dedicated software installed on a tablet, for 4 consecutive weeks, under the supervision of a neuropsychologist; 2) a program of visits in Tele-Medicine, with a neuropsychologist and a social assistant, for educational and psychological support, for patients and caregivers, for 4 consecutive weeks. Ten Cognitive Disorders and Dementia Centers (CDCD), distributed throughout the Calabria territory, participated to the project. Each center was committed to recruit consecutive patients with MCI/early AD and their caregivers, with a minimum of 15 patients and 15 caregivers for center, for a total of an expected number of 150 patients and 150 caregivers recruited at the end of recruitment period (lasting from April to October 2023).

Results: The digital platform of Tele-Medicine of the University of Catanzaro (Pohema Platform) was implemented for the present project, creating a dedicated domain and a related portal. Furthermore, the devices specifically dedicated to tele-rehabilitation (Neurotablets) were integrated into this platform. All operators of the CDCDs, after a training on the use of the Pohema platform and of related devices, started the recruitment of patients and caregivers to consecutively include in the telemedicine and cognitive telerehabilitation interventions. Data on the usability of the platform and of the related devices are currently collected and the analyses results will be available at the end of the project (October 31, 2023).

Conclusions: The results of this project will allow to analyze the strengths and the limitations of the use of tele-medicine and tele-rehabilitation systems in patients with MCI/early AD and in their caregivers. These data are going to be of value in view of the growing diffusion of these technologies and of the increasing needs that the health system has to address.

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### VALIDITY OF THE MANCHESTER TRIAGE SYSTEM IN THE PRIORITISATION OF PATIENTS WITH TRANSIENT GLOBAL AMNESIA IN THE EMERGENCY DEPARTMENT

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Background: The Manchester Triage System is one of the most widely used and studied triage systems in Emergency Departments (ED). MTS does not have a specific presentational flow chart for patients with transient global amnesia (TGA). The goal of this study was to determine the adequacy of priority code assignment for patients with TGA presenting at the ED and triaged using the MTS. In addition, the correct application of MTS by triage nurses was assessed through the audit method.

Methods: This is a single-center observational retrospective study from 1 January 2013 to 31 June 2020. All patients with a medical diagnosis of TGA were considered. An audit was conducted on these triages to assess the correct application of MTS by the triage nurses. Correct triage was considered as a patient classified as yellow.

Results: During the study period, 216 patients with a diagnosis of TGA were considered. Of these 49.5% were classified as yellow, 13.0% were undertriage and classified as green or blue and 37.5% were overtriaged and classified as orange or red. The audit demonstrated that 98.8% of overtriaged patients were triaged incorrectly and 57.1% of undertriage patients were triaged incorrectly. In addition, in 38 patients the triage nurse confused TGA with an acute neurological deficit suggestive of Stroke or transient ischaemic attack.

Conclusion: The present study demonstrates an inability of MTS to correctly stratify patients with TGA. The results of the present study indicate the need for a specific flow chart for patients with neurological problems to improve the performance of MTS.

### EXPLORING THE KNOWLEDGE, ATTITUDES AND PRACTICES ON SEXUAL AND GENDER MINORITIES PATIENTS: A SURVEY ON ITALIAN NEUROLOGISTS

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Background: Sexual and gender minorities (SGM) is an umbrella term including the population identifying themselves as part of the lesbian, gay, bisexual, transgender and queer (LGBTQ+) spectrum. In Europe, an estimated 5% of the population identifies itself as belonging to a sexual minority, whereas preliminary the prevalence of transgender persons is estimated between 0.5-1% of the general population. SGM patients experience difficulties in access to care and might face discrimination, impacting their health outcomes.

Improving knowledge is the first step to reduce barriers. While few data are available on knowledge, attitudes and practices of Italian health providers, no information is available for Italian neurologists' preparedness to treat SGM patients.

Aim: To describe the knowledge, attitudes and practices on SGM patients of Italian neurologists.

Materials and Methods: The study has been conducted on the neurologist of the Italian society of neurology (SIN) using a survey instrument comprising 5 multiple choice questions on gender medicine and 24 Likert type questions divided into three sections exploring the knowledge, attitudes and practices towards sexual minorities and gender minorities. Members of the society have been sent an email asking to complete the survey anonymously followed by a reminder one-month after the original email. Likert scales have been analyzed considering scores 1 and 2 as negative response, score 3 as neutral and scores 4 and 5 as positive responses.

Results: Overall 177 neurologists (5.2%) out of the 3.410 neurologists members of the Italian Society of Neurology participated at the survey. The mean age of the respondents was 44.3 ± 14.6 years; 103(58.2%) were female and the majority (106, 59.9%) worked at a University-Hospital or a Hospital. More than half of the respondents identified sexual and gender orientation as social determinants of health, whereas only a minority was aware of a higher burden of physical and mental health problems in SGM populations. Almost all respondents were confident in examining a sexual minority patient, while only half of them was confident when examining a transgender patient. The vast majority of neurologist reported insufficient training and supervision in treating SGM patients.

Conclusion: In order to improve the quality of healthcare for the SGM population, healthcare professionals should receive proper training in how to approach, investigate and treat patients belonging to a SGM.

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## ACCESS TO HEALTHCARE IN A HEADACHE/HIV+ POPULATION IN MALAWI AND THE WHO-INTERSECTORAL GLOBAL ACTION PLAN


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Objectives: Providing access to care is the main goal of the WHO-Intersectoral Global Action Plan (IGAP), yet many in the developing world as sub-Saharan Africa (SSA) have poor access to treatment due to lack of resources. A major issue are costs of transportation. About half of SSA population (1.1 billions) live with less than 2 EUR per day with no public transportation; the fuel costs almost as in Europe so that some patients stop seeking healthcare because they can't afford transportation [1]. We investigated access to healthcare in a HIV+/headache population focusing on transportation issues.

Materials: The study was conducted in Blantyre, Malawi, in collaboration with the DREAM (Disease Relief through Excellent and Advanced Means) program, active in 10 SSA countries providing care for HIV/AIDS and non-communicable diseases (NCDs). Due to the high level of poverty, all services including drugs are free.
Methods: Trained personnel at the Blantyre DREAM centre administered a structured questionnaire about access to the centre to 500 consecutive HIV+ patients who had been followed for at least 1 year under antiretroviral treatment (ART). This represents the extension of a previously published study on headache among HIV+ patients [2].

Results: Among the 495 respondents, 79.8% needed less than 1 hour to reach the centre, 15.8% between 1 and 2 hours, and 4.4% were more than 2 hours (some even more than 3 hours) away. Most of the subjects reached the centre by private minibus (86%) or by foot (11%). The mean expense for reaching the centre was 1933MWK (=1.76EUR; range 0-36'000), compared to a mean yearly national income of 360'000MWK (328EUR). Considering the high cost of transportation, the repeated number of visits per year for each patient and the illness duration (>1year HIV+), the observed percentage of patients who missed one appointment was very low: 28.7%. Main characteristics among the participants were: mean age 41.3±9.9 years, [range 13-65], 1% minors, 75.6% female, viral load undetectable in 92.2%. The overall 1-year prevalence of any headache was 76.6%. In the month preceding interview 56.6% subjects had at least one headache, analgesics were used by 54.5%.

Discussion: In previous studies on HIV+ patients, cost for transportation was a main cause for missing appointments and treatment failure [3]. DREAM offers free services to facilitate access to care. This can explain the limited number of missed appointments compared to other facilities. IGAP requires strategies to improve access, key to retention in care.

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## VALIDATION OF EXPANDED NEUROLOGICAL IMPAIRMENT SCALE (ENIS) IN ACUTE SETTING


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Objectives: The use of standardised neurological assessment is still lacking in clinical setting and is an important unmet need for both the research and the clinical communities. The Neurological Impairment

Scale (NIS) has been originally developed in neurorehabilitation and might need implementation to be applied in other neurological settings. Aim of this study was to examine the construct validity and inter-rater reliability of an expanded version of the NIS (eNIS) with the inclusion of specific items for cranial nerves, involuntary movements, coordination, and gait disturbances in a clinical acute neurological setting. We also developed a eNIS severity index (SI) to address the validity of the eNIS as a measure of an individual specific and overall neurological impairment.

Materials: In this prospective single-center cohort study, we included all adult inpatients admitted to the Neurology Unit of Spedali Civili, Brescia, in 2022.

Methods: All the subjects underwent a standardised evaluation including premorbid clinical frailty, cognitive function, functional dependency and admission/discharge severity of neurological impairment using the eNIS. Inter-rater reliability was tested by two independent raters in a subset of 40 patients. Construct validity of the eNIS total score and subscores was evaluated in the subset of patients with diagnosis of cerebrovascular disease and other acute neurological conditions.

Results: One thousand -eighty-one patients entered the study, including 675 patients with acute cerebrovascular disease, 72 with encephalitis/encephalopathies, 58 with epilepsy, 46 with brain tumor, 43 with headache, 83 with medically unexplained symptoms, and other disorders. The inter-rater reliability was excellent for eNIS total score and subscores between the different raters (ICC 0.90, 95% CI 0.82-0.95). The eNIS showed a strong construct validity for total score and subscores compared to other severity clinical scales (r 0.47-0.97, $p<0.001$). The new items identified patients with cranial nerves, coordination, gait impairment and abnormal involuntary movements with clinical impact across different diseases in a range of 25 to 65% of cases. eNIS total score and SI exhibited a relevant correlation with both dependency and disability scores independently from premorbid frailty and comorbidity status.

Discussion: These findings demonstrate the eNIS to be a valid and reliable measure of neurological impairment. The four items added to the NIS and the evaluation of both the eNIS total score and SI are pivotal to make the eNIS suitable for use across different neurological conditions.

Conclusions: the eNIS is a valid instrument for the standardisation and stratification of neurological impairment in acute neurological patients.

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## PREDICTORS OF OUTCOMES IN ACUTE NEUROLOGICAL SETTING: THE COMPLEXITY MULTIDIMENSIONAL ACUTE NEUROLOGICAL (MAN) MODEL


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Objectives: Clinical complexity is a key issue for healthcare providers and define subjects at higher risk of mortality, in-hospital complications and short-term as well as long-term disability [1]. Clinical complexity might depend on a combination between premorbid vulnerability and resilience and severity of acute vs chronic diseases. No combined scores integrating premorbid vulnerability and disease severity able to stratify patients with different progression is still available. Aim of this study was to define factors related to short-term outcomes in acute neurological setting by adopting a multidimensional assessment evaluating a) premorbid conditions b) acute neurological and c) non-neurological severity.

Material: In this prospective cohort study, we included all adult inpatients hospitalized in a Neurological department.

Methods: All the subjects underwent a standardized assessment evaluating premorbid comorbidities, clinical and multidimensional frailty, cognitive function, functional dependency and the admission/discharge severity of neurological impairment using the Expanded version of NIS scale. Predictors of in-hospital mortality, severe disability and duration of stay were evaluated by both AUC ROC and multivariate logistic and linear regression models.

Results: One thousand -three hundred fifty patients entered the study, including 700 patients with acute cerebrovascular disease, 85 with epilepsy, 80with encephalitis/encephalopathies with very wide range of age, premorbid and acute severity at admission. In -hospital mortality was predicted by a combination of age, acute neurological and non-neurological severity (MAN global score AUC 0.85 IC-0.80-0.89). Duration of stay was related by both neurological severity and premorbid vulnerability, with only fair predictive value (ROAC AUC 0.66 IC 0.61-0.70) MAN score. Premorbid vulnerability impacted on final disability and improvement during hospitalization in logistic regression models adjusted for baseline severity.

Discussion: The MAN complexity model including premorbid vulnerability, acute neurological and non-neurological severity is a valid instrument of stratification of risk of deterioration for neurological patients.

Conclusions: Further ongoing longitudinal studies are warranted to evaluate the impact of MAN stratification of general management of acute and chronic neurological patients in different healthcare settings.

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# EPILEPSY

## IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME (ICANS): A NEW CAUSE OF STATUS EPILEPTICUS


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Introduction: Immune effector cell-associated neurotoxicity syndrome (ICANS) is a clinical and neuropsychiatric syndrome that may occur in the days or weeks following administration of certain immunotherapies, especially CAR-T cell therapies, available for treatment of relapsed and refractory hematologic malignancies. The

clinical presentation of ICANS includes encephalopathy with confusion and behavioral changes, visual and auditory hallucinations, language dysfunction, apraxia, dysgraphia, headache, seizures, and, in severe cases, cerebral edema with coma.

Case report: We describe the case of a 68-year-old woman with refractory diffuse large-B-cell lymphoma who received CAR-T cell therapy. The day after she presented a cytokine release syndrome (CRS) with fever and hypotension. She complained also headache, confusion and aphasia, symptoms compatible with ICANS. The woman was treated by tocilizumab and dexamethasone. On day 5 she developed spatial and temporal disorientation and sudden deterioration in consciousness level, necessitating admission to the neurological ICU. EEG showed fast and diffuse polyspikes and wave discharges, compatible with generalized non-convulsive status epilepticus (NCSE). Cerebrospinal fluid analysis showed increased protein level, without evidence of infection. Cerebral MRI showed T2 hyperintensity within the left inferior frontal gyrus with signs of impaired blood-brain barrier (BBB), compatible with focal cerebral edema. NCSE was treated with midazolam, levetiracetam, lacosamide and fenobarbital. On day 10, the patient mental status improved, even persisting mild aphasia. MRI findings of the brain resulted completely normalized by day 20 with a total regression of language dysfunction.

Discussion: Despite the clinical features of ICANS could be readily recognizable, its pathophysiology remains poorly understood. A possible hypothesis is that high levels of circulating cytokines result in endothelial-cell activation and BBB disruption, which in turn cause an inflammatory cascade within the CNS, subsequent alterations in cortical-subcortical functions, and cerebral edema in some cases. Treatment is supportive and consists of glucocorticoids, antiepileptics and tocilizumab if a concurrent CRS is present. While neurologic deficits are usually reversible with appropriate management, fatal outcomes have been reported secondary to malignant cerebral edema. Since CAR-T cell-therapy rapidly entering in clinical practice, a profound knowledge of the clinical presentation, early identification and prompt therapeutic action is an essential requisite for neurologists. From our experience, EEG is a fundamental diagnostic tool to identify status epilepticus, a rare but relevant manifestation of ICANS. It can be possible that the rate of NCSE is under-diagnosed for the EEG underutilization, yet its identification is crucial to the management of ICANS.

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## A NEXT GENERATION SEQUENCING STUDY OF A FAMILIAL EPILEPSY WITH PHENOTYPIC VARIABILITY EVIDENCES A NEW MUTATION IN KCNQ2 GENE

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Objective: Epilepsy is a neurological disorder that can have different aetiologies including genetics. In recent years, numerous genes associated with various forms of epilepsy have been highlighted with the advent of techniques such as next generation sequencing. One of the most involved genes in epilepsy is KCNQ2, encoding for voltage-dependent potassium channel subunits.

Materials and methods: We describe a 21-year-old woman who, at the age of 17, presented episodes of seizures characterized by throbbing headache followed by loss of consciousness. In addition, she presented some episodes of loss of consciousness, preceded by pallor and algid sweating. The family history was positive for epilepsy: her 11-year-old brother suffered of nocturnal epilepsy since the age of 4 and her 38-year-old mother had episodes of parasomnia from adolescence to adulthood. Her paternal grandfather suffered from late epilepsy after a stroke. The proband was studied by medical history, neurological examination, blood tests, magnetic resonance imaging, angiographic magnetic resonance, electroencephalogram, Head Up Tilt test and NGS.

Results: Neurological examination of the proband was negative. Extensive biochemical, immunological, and hormonal tests were not pathological. The HUTT was positive for neurogenic syncope: therefore, some episodes of loss of consciousness were diagnosed as syncope. EEG documented the bilateral presence of some irritative activities in the occipital derivations. Brain MRI and angio-MRI were not pathological. Due to the family history positive for epilepsy, extensive genetic analysis was performed in the proband by NGS. The results showed a mutation of KCNQ2 gene in heterozygosis: p. Leu425ValfsTer9, a deletion of a cysteine which causes a frameshift and termination. The genetic analysis was carried out to the other members of the family. The same mutation was present in her brother and in her mother.

Discussion: The NGS has redefined the genetic landscape of the epilepsies: the high-definition molecular genetic diagnosis is important to inform patients and healthcare professionals about the prognosis of the disease, the clinical management and the creation of new target therapies.

Conclusions: To date, 296 KCNQ2 variants are known: the variant p. Leu425ValfsTer9 has been discovered for the first time in a familial epilepsy with phenotypic variability within the same family in several generational lines. This feature completely reflects the already known phenotypic variability associated with KCNQ2.

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## RESILIENCE PREDICTS AND MODULATES ANXIETY SEVERITY IN PEOPLE WITH EPILEPSY

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Background: Anxiety is one of the most relevant psychiatric comorbidity in people with epilepsy (PwE). [1-2] The role of resilience (RES) in the development of anxiety is not well understood. [3] We purposed to better characterize RES impact on anxiety severity in PwE.

Materials and Methods: 176 PwE underwent online surveys including a collection of socio-demographic, seizure-related and psychological variables. PwE were grouped according to the data collected; anxiety levels were compared through non-parametric statistics. Hierarchical regression analysis (HRA) and logistic regression were performed to characterize RES contribute in predicting the presence and the severity of anxiety. Mediation/moderation analysis was performed to evaluate causal effects among RES, depression and anxiety.

Results: Anxiety did not differ according to socio-demographic and seizure-related variables, exemption for the presence of drug-related adverse effects. Depression, RES and sleep quality provided the major contribute on anxiety variance. The addiction of RES level in HRA and logistic regression provided a significant increase of R-squared value (p-value=.02) and of Area Under the Curve (p-value=.03), respectively. RES modulated depression/anxiety relationship (p-value<.001), while depression did not mediate RES/anxiety correlation (p-value=.68).

Conclusions and discussion: We demonstrated that RES is a significant independent predictor of anxiety in PwE, able to modulate depression impact on anxiety. Moreover, we confirmed the relevance of depression and sleep quality on anxiety severity.

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## CLINICAL-INSTRUMENTAL-RADIOLOGICAL PROGRESSION OF AN EARLY CEREBRITIS PRESENTING WITH FIRST SEIZURE IN AN OTHERWISE HEALTHY MAN: A CASE REPORT

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Introduction: A 63-year-old man comes to E.R. for secondary generalized seizure, preceded by motor automatism. He is on home antihypertensive therapy. He denies fever and previous seizure. Clinical examination shows mild expressive aphasia. Brain CT and angio-CT are normal. EEG demonstrates frequent left F-C-T irritative waves with contralateral diffusion. Brain MRI-Gd shows small left mesial-frontal T2-FLAIR hyperintensity, T1 isointense, not capturing gadolinium. MRI appears compatible with low-grade glioma. Neurological conditions worsen in 5 days with confabulation and confusion. Thus, MRI with spectroscopy and perfusion studies is repeated. The known lesion has grown with extension to the left orbital gyrus, becoming hypointense at T1 and with peripheral gadolinium impregnation. Perfusion study is normal. Peak of NAA is observed. Given the abrupt change, lumbar puncture is executed. 18 WBCs (neutrophils) and 90 proteins are found in CSF. CSF virological and bacteriological tests are negative. Tests for HIV, VDRL, THPA, Toxoplasma, Cryptococcus Neoformans on blood and CSF are negative. On blood exams anticardiolipin IgM are increased (48 mg/dl N.V. < 10 mg/dl). Given the CSF and clinical-radiological condition, suspicion of infectious early cerebritis is raised. Broad-spectrum antibiotic and antimycotic therapy are started. After about 2 weeks, neurological examination is normal, EEG documents sporadic left F-C-T sharp-theta potentials. At 3 weeks of treatment, MRI-Gd illustrates significant reduction of T2-FLAIR hyperintensity, with absent contrastographic impregnation. EEG shows slow potentials in absence of irritative abnormalities. The patient continues treatment for a total of 5 weeks with complete clinical-instrumental-radiological recovery.

Discussion: Early Cerebritis is a rare condition, caused by fungi or bacteria. It precedes the development of brain abscesses. It is often indistinguishable from a glioma, so the rare case reports, have been diagnosed following cerebral biopsy. It may present with seizures and blurred/absent neurologic signs, without fever or elevation of inflammatory markers; only in 25% of cases the responsible microorganism is identified. In our case, the elevation of anticardiolipin antibodies, which often cross-react with viruses, bacteria and fungi, together with CSF exams and rapid clinical-instrumental-radiological change allowed prompt diagnosis and treatment without brain biopsy.

Conclusion: In case of new, unclear brain lesions, even without infectious markers, Early Cerebritis should be taken into account. In selected cases, a short-distance MRI may be useful to distinguish between cerebritis and neoplasia, without invasive procedures like brain biopsy. Progression to potentially life-threatening infections, which develops in about 2 weeks, can be blocked by tempestive antibiotic therapy, with complete recovery.

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## ROLE OF NEW GENERATION WISE CORTICAL STRIP (WCS) IN BOTTOM-OF-THE-SULCUS FOCAL CORTICAL DYSPLASIA: A CASE REPORT.

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Background: In epilepsy surgery, intraoperative electrocorticography (iECoG) can add information to identify the epileptogenic zone and guide the surgical resection. Bottom-Of-Sulcus-focal cortical Dysplasia (BOSD) are often difficult to detect with iECoG due to their deep localization. We describe a patient with drug-resistant frontal lobe epilepsy due to BOSD who underwent an iECoG-guided cortectomy using next-generation cortical strips (Wise Cortical strip, WCS) capable of easily adapting to cortical gyri.

Methods: We performed serial iECoG recordings with WCS (4-contact, length: 62 mm; thickness: 0.25 mm; Material: platinum; exposed electrode diameter: 2.3 mm; inter-electrode distance: 10 mm). Strip were placed on the suspected epileptogenic lesion, then on the resection border. Both bipolar and referential electrode montages were

reviewed to identify epileptiform activity (ranked through Palimini's classification).

Results: A right-handed 20-years-old male presented with frontal lobe seizures since he was 8 years-old. Longterm monitoring (LTM) recorded numerous interictal epileptiform discharges (IEDs) and several seizures without loss of consciousness arising from right frontal scalp eletcrotes. A 3T brain MRI showed a FCD on the bottom of inferior frontal sulcus. IECoG, performed on the convexities of the investigated frontal cortex, recorded sporadic spikes (Class. Palmini A). Then WCS was placed on the floor of the sulcus (between precentralis girus and parsoperculari girus) and showed a 3-4 Hz continuous/subcontinuous rhythmic spikes activity from the deepest electrode (Palmini D). Registration after resection of the BOSD didn't show any epileptiform activity. Pathology showed dysmorphic neuron and gliosis. No surgical complications occurred. Patient is seizure free after 6 months.

Conclusions: iECoG can be a useful tool in epilepsy surgery to define epileptogenic zone, especially in lesion-negative patient. However, it's not always easy perform optimal registration on the suspected cortex. This case report showed that WCS features allowed to perform high-quality registration from the bottom of the sulcus, leading to surgical resection of highly epileptogenic cortex.

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## ANTISEIZURE MEDICATIONS FOR PRIMARY PREVENTION OF ACUTE SYMPTOMATIC SEIZURES AFTER STROKE: A SYSTEMATIC REVIEW


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Aims: To evaluate the efficacy of antiseizure medications (ASMs) in primary prevention of acute symptomatic seizures (ASS) after stroke (ischemic or haemorrhagic).

Material and methods: Systematic search of the literature (CENTRAL; MEDLINE; ClinicalTrials.gov) to identify randomized controlled trials (RCTs). Critical appraisal and qualitative synthesis of study results.

Results: We included two placebo-controlled trials (total 114 participants) conducted in haemorrhagic stroke [1,2]. In one RCT, ASS occurred in 1/ 36 patients (2.7%) with valproate and in 4/36 patients (7%) with placebo (p=0.4) [1]. In the other RCT, ASS were electrographic only and occurred in 3/19 (16%) with levetiracetam and in 10/23 (43%) with placebo (p=0.043) [2]. Both RCTs were stopped prematurely, including a lower number than initially planned. In the levetiracetam trial, there was an imbalance of baseline characteristics, with higher prevalence of factors possibly associated with ASS [2].

Discussion: The evidence on ASMs for primary prevention of post-stroke ASS is limited to intracerebral haemorrhage, of low quality, imprecise, and not enough informative to guide clinical practice. The statistically significant result favouring levetiracetam could reflect imbalance of prognostic factors across groups at baseline. Performing studies with a number of patients lower than initially planned increases the risk of covariate imbalance at baseline and imprecise results.

Conclusions: Additional studies are required to evaluate the role of ASMs in preventing post-stroke ASS. It should be clarified whether brief electrographic seizures without any clinical correlate affect functional outcomes and mortality in stroke patients. Finally, it should be evaluated if preventing ASS may have antiepileptogenic effects modifying the risk of post-stroke epilepsy.

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## EPILEPTIC SEIZURES PROBABLY ARISING FROM THE CEREBELLUM: A CHALLENGE TO THE TRADITIONAL CORTICOCENTRIC VIEW OF EPILEPSY


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Objective: To describe a patient with an epileptic seizure whose epileptogenic zone was probably located in the cerebellum.

Methods: Case report.

Results: A 51 years-old healthy male experienced a first-ever apparently generalized tonic-clonic seizure. Seven years earlier he underwent a surgical removal of a cerebellar metastasis (right cerebellar hemisphere) of a renal carcinoma, through a surgical access in the nearby region. His medical history was otherwise perfectly unremarkable. The oncological follow-up was normal. Despite a thorough diagnostic work-up no further explanations for the epileptic seizure were found. Brain magnetic resonance imaging showed only a gliotic area in the right cerebellar hemisphere and the small skull section in the region of prior craniotomy. The EEG recording, including a prolonged sleep-deprived recording, was normal. A treatment with levetiracetam 1000 mg/day was started and the patient did not experience any further epileptic seizure.

Discussion: Traditionally, it is widely believed that epileptic seizures originate in the cerebral cortex, although with some interplay with subcortical structures like the thalamus. However, in recent years evidence has been accumulated for an initiation of epileptic seizures within subcortical structures. In the literature there are few cases of seizures thought to have arisen from the cerebellum [1]. Furthermore, animal studies have shown that it is possible to induce seizures by cerebellar electrical stimulation [2].

Conclusions: The present case adds to the available literature and contributes to challenging the traditional corticocentric concept of epilepsy, suggesting that a cerebellar lesion could have an intrinsic seizure-generating (i.e., epileptogenic) potential leading to epileptic seizures. This hypothesis is supported by the extensive cortico–subcortical anatomical and functional connections between the cerebral cortex and the cerebellum. Further studies are required to confirm this hypothesis.

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## "IS IT STRUCTURAL EPILEPSY?" CRITICAL APPRAISAL OF THE ILAE DEFINITION OF EPILEPSY

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Objective: To critically evaluate the accuracy of the current ILAE practical definition in the setting of a first unprovoked seizure following an acquired static brain lesion.

Methods: Critical appraisal of the Case example n. 2 of the ILAE official report on the practical clinical definition of epilepsy [1] and of the study therein quoted [2] reporting the risk of a subsequent unprovoked seizure after a first seizure following stroke, brain injury or cerebral infection.

Results: According to ILAE definition, epilepsy can be diagnosed after a first unprovoked seizure following stroke, brain injury or cerebral infection due to the "high (>70%) risk of another unprovoked seizure". In the single study used to substantiate this statement, only the risk of recurrence after a first unprovoked post-stroke seizure was ≥60% over the next 10 years. For seizures due to trauma or infection, the values within the 95% confidence intervals do not rule out a long-term risk of recurrence <60%.

Discussion: The application of the current practical definition of acquired structural epilepsy as reported in the ILAE official report is inaccurate. The estimates for risk of seizure recurrence after a first unprovoked seizure due to brain trauma or infection are imprecise and do not automatically support a diagnosis of epilepsy. The current definition carries the risk of overdiagnosing epilepsy, with possible negative psychosocial consequences and unnecessary use of antiseizure medications.

Conclusions: There is an unmet need to clarify which factors modify the risk of seizure recurrence in various clinical situations.

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## OCCIPITAL LOBE EPILEPSY AND AN EEG PATTERN SUGGESTIVE OF PROLONGED EYE-CLOSURE SENSITIVITY: A CASE REPORT

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Objective: Description of an adult patient with occipital-onset epilepsy with visual seizures and possible prolonged eye-closure sensitivity.

Methods: Case report

Results: A 35-year-old woman with seizures with simple visual hallucinations ("white dots") in both visual fields since the age of 3 years. They were followed by altered consciousness, and occasionally by occipital headache with nausea. Initially the frequency was weekly, but in adulthood it has become very rare. There are no clear triggering factors, and seizures occur in various light conditions. The neurological examination is normal. Visual field: normal. EEG: diffuse rhythmic (epileptiform?) abnormalities of long duration, constantly present at the closing of the eyes, disappearing at complete darkness and at open eyes with Frenzel glasses. No photosensitivity. Brain MRI: Pineal cyst, nodular heterotopia in mesial occipital cortex links. Therapy: Lamotrigine 150 mg X 2; Levetiracetam 1500 mg X 2; Clobazam 10 mg.

Discussion: In posterior occipital evisual epilepsy of children seizures starting from the occipital lobe can be associated with epileptiform abnormalities on eye closure, mostly attributable to fixation-off phenomenon, scotosensitivity or eye closure sensitivity. However, these are self-limiting forms. Our patient has epilepsy with visual seizures, and with a peculiar EEG pattern that is difficult to classify, not resembling fixation-off or scotosensitivity. Instead it might be interpreted as eye-closure sensitivity, with markedly prolonged and persistent EEG abnormalities lasting as long as the patient keeps her eyes closed. The phenomenon is intriguing due to the possible relationship with the cortical mechanisms of genesis of the posterior dominant rhythm.

## P-GLYCOPROTEIN INHIBITORS AS ADJUNCTIVE TREATMENT FOR REFRACTORY SEIZURES: A SYSTEMATIC REVIEW OF THE LITERATURE WITH SOME METHODOLOGICAL CONSIDERATIONS

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Objectives: To evaluate the efficacy of the P-glycoprotein inhibitors tariquidar, elacridar or verapamil as adjunctive treatment for refractory seizures.

Method: Systematic search of the literature (CENTRAL; MEDLINE; ClinicalTrials.gov) to identify randomized controlled trials (RCTs) evaluating the efficacy of tariquidar, elacridar or verapamil as add-on treatment for refractory seizures. Critical appraisal and qualitative synthesis of study results.

Results: No RCT on tariquidar or elacridar was found. We identified two pilot RCTs on verapamil (31 patients included) [1,2]. One was an open-label trial comparing two different doses of verapamil (120 mg/day, 13 patients versus 240 mg/day, 6 patients) [1] and the other was a double-blind RCT comparing verapamil (240 mg/day, 7 completers) versus placebo (5 completers) [2]. In the former RCT, 7 patients (36.84%) experienced a > 50% reduction in seizure frequency (3/6, 50% in the 240 mg/day and 4/13, 30.7% in the 120 mg/day) [1]. In the latter, no patient achieved 50% reduction in seizure frequency [2].

Discussion: The lack of a placebo control prevented the RCT that compared two different doses of verapamil from revealing the efficacy of this drug by subtracting and controlling for the variables that can influence clinical outcomes (regression to the mean, changes in seizure frequency due to the natural course of the disease, and placebo effect). Both RCTs were conducted in a small number of patients, with risk of imbalance of prognostic factors at baseline due to random fluctuations in known and/or unknown variables. The small sample size prevented both RCTs from reaching an adequate statistical power to identify a difference in efficacy between the treatment arms.

Conclusions: The evidence on verapamil as an adjunctive treatment for refractory seizures remains preliminary. Enrichment strategies (e.g., based on results of [11C]-verapamil PET scan) could identify patients

with P-glycoprotein overexpression in the brain, possibly increasing the informative value of future RCTs.

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## THE INFLUENCE OF PATIENT'S AGE AT FIRST EPILEPTIC SEIZURE ON SEIZURE RECURRENCE: A PRELIMINARY ANALYSIS

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Objective: To evaluate whether the patient's age at first epileptic seizure affects the risk of seizure recurrence.

Methods: This is a preliminary retrospective analysis of a large database of all patients accessing the emergency department of our hospital for epileptic seizures from 2001 to 2021. We included data on a randomly chosen subset of patients with a first-ever seizure. We stratified patients according to their age at first seizure: <15 years, 15-65 years, and >65 years. We compared the risk of a first seizure recurrence in different time intervals (30 days, 90 days, 6 months, 1 year after the first seizure) with a Kaplan-Meier survival analysis.

Results: We included data on 377 patients (135 with seizure recurrence, 35.8%). Overall, the risk of seizure recurrence after a first-ever epileptic seizure was highest in patients aged >65 years and lowest in those aged 15-65 years. A significant difference in risk of seizure recurrence was observed in the 30 days (p=0.017), 90 days (p=0.014), and 6 months (p=0.009) after the first seizure; the difference was not significant at 1 year (p=0.09).

Discussion: Our preliminary analysis shows that the patient's age at first seizure affects the risk of recurrence up to 6 months. Overall, in this timeframe the risk appears highest in patients aged >65 years and lowest in those aged 15-65 years.

Conclusions: Future analyses will investigate further the role of age in seizure recurrence, considering the difference between acute symptomatic and unprovoked seizures, seizure etiology, and other prognostic factors.

## USE OF PERAMPANEL IN ORAL SOLUTION IN THE TREATMENT FOR SEIZURES RESISTANT TO INTRAVENOUS ANTI-SEIZURES MEDICATIONS

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Introduction: Perampanel (PER) is a non-competitive receptor antagonist of beta-amino-3propionic acid (AMPA), that has been shown to be useful in treating status epilepticus in animal models. For humans, there isn't much information available.

Aims: The aim of the study is to identify how patients with super-refractory status epilepticus (SESR) respond to therapy with PER at various doses.

Methods: Retrospective study of SESR patients treated with PER. The treatment response was based on (1) attenuation of the EEG-graphic ictal pattern within 96 hours of first administration of PER and (2) survival after hospital discharge. In order to compare treatment responses, the population was then split into two groups depending on PER intake (cut-off 24 mg).

Results: A total of 12 patients were included in the study (83.3% F, 16.7% M, average age 60 years ± 18.14, 25% with focal motor epileptic status, 75% with generalized convulsive epilepsy status). PER was given with an average load dose of 17.16 mg ± 8.26, on average 271 ± 362.21 hours after the beginning of SESR and typically as 4.4 ± 1.5 anti-seizures medication. On the total population, 8 patients resulted responders assessing EEG (66.7%), whereas 11 considering the survival after discharge (91,67%). Response rates were (100%) and (100%) in the PER 24 mg group (7), while they were (20%) and (80%) in the PER < 24 mg group (5).

Conclusion: PER, especially at the dose of 24 mg, showed to be a successful treatment for SESR despite the limitations brought on by the limited sample size.

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## FAMILIAL GENERALIZED EPILEPSY WITH BROAD PHENOTYPE, INCLUDING SUNFLOWER SYNDROME

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Aims: Sunflower Syndrome (SS) is a rare form of generalized epilepsy characterized by significant photosensitivity, heliotropism, and potential self-induced seizures associated with repetitive movements of the upper limbs in front of the eyes [1].

Materials: An 18-year-old woman with a positive family history of epilepsy presented to our clinic. Her mother and maternal aunt have juvenile myoclonic epilepsy with photosensitivity, while her maternal great-grandfather, another maternal aunt, and a cousin have epilepsy with eyelid myoclonus. Since the age of 8, she has been experiencing weekly episodes characterized by a compulsion to face the light from a window at home and rapidly move her left hand in front of her eyes. This is followed by a cessation of behavior, occasionally accompanied by bilateral tonic-clonic movements. At the age of 13, after visiting another medical center, she began treatment with valproic acid up to 400 mg/day, carbamazepine 800 mg/day, and clobazam 20 mg/day, but the seizures persisted.

Results: Neurological examination and blood tests were normal. Standard EEG showed diffuse paroxysmal abnormalities and Grade IV Waltz photoparoxysmal response. During video-EEG monitoring, 23 generalized epileptic seizures were induced by approaching the window with a curtain-like movement of the left hand. Mild atrophy of the right hippocampus was observed on the brain MRI. Exome sequencing has been performed on affected family members, but results are not yet available. Gradual tapering of carbamazepine was initiated, and the dosage of valproic acid was increased to 1000 mg/day. Perampanel was introduced and gradually titrated up to 8 mg/day.

Discussion: Although the original description of SS suggested that it is characterized by self-induced photosensitive seizures [2], more recent evidence has raised doubts about this assumption by proposing that hand movements themselves may already be an ictal manifestation [3]. In our case, the repetitive temporal association between stereotyped hand movements and the appearance of electroencephalographic abnormalities supports the reasonable hypothesis of seizure self-inducibility. The diagnostic and therapeutic implications of the mutations detected in the genetic analysis are still to be clarified. They could potentially provide crucial information for a more precise diagnosis, prediction of the clinical course, and selection of targeted therapies.

Conclusions: The present family provides strong evidence that genetic factors may play a major role in the pathogenesis of SS. Further research is needed to understand the role of genetics and its impact on the diagnosis and treatment of SS.

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## DOES EPILEPSY SURGERY REFLECT THE NEEDS AND EXPECTATIONS EXPRESSED BY PATIENTS? EVALUATION THROUGH THE EPILEPSY SURGERY SATISFACTION QUESTIONNAIRE (ESSQ-19)

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Objectives: Approximately 30% of people with epilepsy do not respond to anti-seizure medications. Epilepsy surgery can be proposed as a treatment option in this population. The efficacy and safety of epilepsy surgery are however, still poorly understood, and the only internationally validated tool is the Epilepsy Surgery Satisfaction Questionnaire (ESSQ-19) (Wiebe et al. 2020), which measures satisfaction with epilepsy surgery. The aim of our study was to apply this measurement tool for the first time in Italy.

Methods: We formally translated the English ESSQ-19 into Italian language. Seventy-five patients that entered the epilepsy surgery program at Modena comprehensive epilepsy centre (2018-2022) were invited to participate during their follow-up outpatient visits. Sixty-six of them accepted and completed four questionnaires: IT-ESSQ-19 (Epilepsy Surgery Satisfaction Questionnaire), PCGI (Patient Clinical Global Impression), QOLIE-31 (Quality Of Life In Epilepsy Inventory), and NDDI-E (Neurological Disorders Depression Inventory for Epilepsy). The ESSQ-19 questionnaire consists of 19 items segregated into four domains. Patients were asked to mark the response that best represented their condition, referring to the four weeks prior to completion. Responses were then converted into a score from 0 to 100, where 0 indicated the worst level of satisfaction possible and 100 indicated the best.

Results: The average values of the four domains and total score were: seizure control (83,4; DS 16,7), psychosocial functioning (79,3; DS 17,1), surgical complications (90,8; DS 14,9), recovery from surgery (81,4; DS 16,9), total score (83,7; DS 13,3). The correlation between the QOLIE-31 score and the ESSQ-19 score was positive ($r = 0.6$; $p = 1.54x10\text{-}7$). Most of the interviewed population was not at risk of depression, and the satisfaction level with their pharmacological treatment was positive (4.58 out of 5).

Discussion: The results of our study reveal a high level of satisfaction among individuals who underwent epilepsy surgery. Overall satisfaction is high, considering all the aspects characterizing the treatment process, as well as the respondents' expectations regarding surgical therapy, freedom from seizures, individual functioning within society, complications of the procedure, and post-operative recovery.

Conclusions: The results and the participants' feedback suggest that evaluating the quality of life and satisfaction with a treatment is crucial in clinical practice. Comparing with the original study by Wiebe et al. also revealed some differences between the two samples that should be considered when interpreting the results. These differences may explain the disparity in outcomes but do not diminish the significance of our findings.

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## LACOSAMIDE INDUCED ACNE: A CASE REPORT

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Acne is an inflammatory disease of the pilosebaceous unit, which significantly impacts on patients' quality of life, with a critical psychological burden. Acne presents a complex pathogenesis and a wide number of drugs have been proved to provoke it. Lacosamide (LCS) belongs to a new generation of sodium channel blockers, which has been widely employed in people with epilepsy. In the last ten years, new adverse reactions to this drug have been gradually recognized, among which cardiotoxicity and hyponatremia. Differently from several other antiseizure medications (ASM), LCS has not yet been reported in the literature to cause acne as a side effect. Herein, we describe a case of LCS induced acne. A 21-year-old man, with a family history of epilepsy, affected by drug-refractory focal epilepsy of unknown etiology with onset during childhood, but only diagnosed at the age of 19 years presented a painful papulo-pustular eruption, which appeared two months after the introduction of LCS 150 mg BID. The patient presented multiple focal onset seizures with impaired awareness per day. The patient did not take any new drug in recent times, aside from LCS, prescribed in place of levetiracetam for its ineffectiveness. The patient denied any history of acne vulgaris in his youth. The patient was prescribed

minocycline 100 mg 1 tablet/day, with partial improvement at seven months, but immediate relapse upon discontinuation. Suspecting this acne to be drug-induced, it was decided to discontinue LCS, replacing it with brivaracetam. As LCS was tapered, the acne substantially improved and, at 4 months follow-up, mainly solely scars persists. Various ASMs have been associated to acne eruptions. Cases of acne induced by felbamate (4), lamotrigine, ethosuximide and topiramate have been reported in recent years. The lesions arose from one to three months from the administration of the suspected drugs and rapidly improved as the drugs were discontinued. LCS has been associated to the induction of generally mild skin rashes, dermatomyositis and even toxic epidermal necrolysis. However, to our knowledge, this is the first case of LCS caused acne reported yet in the literature.

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## ICTAL FEAR MISDIAGNOSED AS PANIC ATTACK: A VIDEO-EEG STUDY


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Objectives: To describe the electro-clinical features of a patient with focal epilepsy misdiagnosed for years as panic attacks (PA), highlighting the role of video-EEG monitoring in the differential diagnosis.

Materials: A 25-year-old young patient admitted to our epilepsy centre in early 2023; since the age of eight, she has experienced episodes of visual and olfactory hallucinations accompanied by intense fear. For approximately ten years, she has been under psychiatric follow-up for panic disorder, without deriving significant benefit from treatments.

Methods: The patient was evaluated by a multidisciplinary team and underwent the following: prolonged polygraphic video-EEG monitoring (18 hours) during wakefulness and REM/NREM sleep (using additional bilateral zygomatic electrodes), neuropsychological assessment, brain MRI with targeted study of the temporal lobes and perfusion MRI study.

Results: We recorded 5 focal seizures characterized clinically by intense feeling of fear, epigastric discomfort with nausea/vomiting, visual and auditory hallucinations, oroalimentary and gestural automatisms with the right hand, accompanied by corresponding EEG patterns characterized by paroxysmal activity predominantly in the right temporal and zygomatic derivations. The neuropsychological evaluation revealed a mild visuospatial disorganization, while the brain MRI documented a dysplastic lesion of the right amygdala with concurrent hyperperfusion.

Discussion: The overlapping semiological features between PA in patients with panic disorder and affective epileptic seizures (CA) in patients with focal temporal epilepsy represent a diagnostic challenge. In fact, in approximately 10-15% of patients with temporal epilepsy, sudden sensations of fear can be observed among the ictal symptoms [1]. The epileptogenic focus of "ictal fear" is typically localized in the right temporal lobe [2], particularly in the amygdala and anterior cingulate cortex [3]. Our electroclinical, neuropsychological, and neuroradiological data support a right temporal epileptogenic focus responsible for the symptoms experienced by the young patient for years.

Conclusions: Prolonged video-EEG monitoring allowed us an accurate diagnostic classification of affective ictal manifestations that were mistakenly interpreted for years as PA.

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## A CASE SERIES OF LATE-ONSET EPILEPSY, COGNITIVE DECLINE AND MRI FLAIR TEMPORAL HYPERINTENSITY: WHERE TO GO FROM HERE?


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Introduction: The etiological diagnosis of late-onset epilepsy(LOE) is a challenge for neurologists, especially when it is associated with non-specific clinical and radiological features that can be found across several neurological conditions.

Methods: Between January and April 2023 we evaluated four patients diagnosed with LOE, all presenting with Mild Cognitive Impairment and MRI T2-FLAIR hyperintensity in the mesial temporal lobe. We evaluated EEG findings, results from CSF analysis, neuroradiological and Fluorodeoxyglucose (FDG) whole-body PET imaging features.

Results: The four patients were all women (mean age 63.5±3.1 years) with recent onset of memory deficits and FLAIR hyperintensity at the left temporo-mesial lobe. Patient n°1 presented generalized seizures, FDG hypermetabolism in the left temporal lobe, focal subclinical epileptiform activity on EEG, increase of t-tau (876pg/ml) and LGI1 antibodies positivity at CSF evaluation. Patient n°2 had focal impaired awareness seizures, FDG hypometabolism in the left temporal structures, minimal interictal focal EEG discharges and increased CSF t-tau (535pg/ml). Patient n°3 had generalized seizures, normal FDG PET, subclinical epileptiform activity on EEG. Patient n°4 had focal seizures and nonconvulsive status epilepticus, both FDG PET and CSF were normal. Both patient n°1 and patient n°4 underwent significant amelioration after the administration of empirical therapy with steroids.

Discussion: Despite our efforts, we were able to reach a definite diagnosis only in patient n°1 (anti-LGI1 encephalitis). In fact, hyperintense temporal signal in MRI FLAIR weighted images can underpin different disorders (i.e. herpetic encephalitis, temporal glioma, or autoimmune encephalitis), and,while some radiological features are more common in certain diseases(such as unilateral involvement and loss of differentiation between grey and white matter in tumours), MRI alone cannot discriminate between different aetiologies. Thus, reaching a definite diagnosis can be difficult in the absence of neuropathological confirmation. Brain metabolic patterns at FDG-PET could help investigating MRI findings, but distinct types of lesions can lead to different findings (es. a paradoxical hypometabolism in case of necrotic

tumours) and timing of FDG injection can also influence its results, since FDG hypermetabolism can also be caused by ongoing seizure activity. Moreover, case 4 offers proof that, as supported by literature, the autoimmune aetiology should always be considered, and that empirical immunotherapy could help preventing permanent structural damages and long-term sequelae, even in the absence of CSF antibodies positivity.

Conclusions: The triad formed by LOE, cognitive impairment, and MRI temporal alterations should prompt to carefully consider of all diagnostic possibilities, including lesser-known ones, as they are potentially reversible with pharmacological treatment.

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## SLEEP-RELATED HYPERMOTOR EPILEPSY IN A PATIENT WITH SKANK 2 MUTATION: A CASE REPORT


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Objective: SHANK genes encode for postsynaptic scaffold proteins which are involved in excitatory synapse development, function and plasticity. Mutations of SHANK family genes are typically associated with intellectual disability, speech delay and autism spectrum disorders. Epilepsy is commonly reported in patients with SHANK3 gene mutations, while association with SHANK2 remains unclear. We report a case of a 36-year-old man with sleep-related hypermotor epilepsy (SHE) carrying a de novo SHANK2 pathogenic mutation.

Case report: A 36-year-old left-handed man presented with a history of seizures that began at the age of 15. He was diagnosed with specific language impairment and learning disability at the age of 2. The past medical history was insignificant for febrile seizures, status epilepticus, head injury, central nervous system infections and skin lesions. His family medical history was negative for seizures. Seizures were brief, mostly during sleep, and characterized in sequence by sensation of throat constriction, fear, epigastric aura, grimacing, moaning, rhythmic pelvic thrusting, left hand opening, hyperkinetic movements of the right upper limb ending with him covering his face with his hands. Electroencephalography (EEG) and video-EEG showed ictal and inter-ictal discharges in the frontocentral regions, predominant over the left hemisphere. After being seizure-free for 7 years on carbamazepine monotherapy, he developed drug-resistant seizures. Brain magnetic resonance (3T) was negative for structural abnormalities. Genetic analysis performed with Next Generation Sequencing panel for epilepsy revealed de novo heterozygous pathogenic variant c.1869_1873dup of SHANK2 gene, determining the introduction of a premature stop codon p.Ala625GlyfsTer8.

Discussion and Conclusions: Clinical phenotype of SHANK2 gene mutation is variable and very few data are available about its correlation with epilepsy. Indeed, a single case of a patient with generalized tonic-clonic seizures and de novo pathogenetic mutation of SHANK2 has been reported so far. This report enlarges the phenotypic spectrum of SHANK2 mutations and may expand the possible genetic causes of SHE.

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## ANTI-LGI1 LIMBIC ENCEPHALITIS, A TREATABLE ENTITY WITH POTENTIAL GOOD PROGNOSIS: A CASE-SERIES


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Anti-LGI1 encephalitis is a rapidly progressive Limbic Encephalitis (LE) with LGI1-antibodies in serum and CSF, although their positivity is not necessary for the diagnosis but helpful to predict prognosis. Main clinical features are seizures, including Facio-Brachial Dystonic Seizures (FBDS), short-term memory loss and cognitive impairment. The aim of this case-series is to compare three patients diagnosed for LGI1-LE with regard to clinical presentation, diagnosis and prognosis. We retrospectively analyzed data of three patients diagnosed in the Department of Neurology at Hospital of Novara, Biella and Borgomanero. We compared clinical presentation and data from blood and cerebrospinal fluid (CSF) tests, electroencephalogram (EEG), brain Magnetic Resonance Imaging (MRI) and total-body Positron Emission Tomography with Fluorodeoxyglucose (PET-FDG). All patients were tested for onconeural and anti-surface receptors antibodies on serum and CSF. We compared cognitive outcomes in short-term follow-up. Two of three patients are male, the average age at onset is 65 years. All patients had a subacute onset of confusion and short-term memory loss; moreover, the woman developed seizures, both men developed involuntary stereotyped movements on upper limbs. One case had flu twenty days earlier, another was positive for SARS-Cov2 infection. Only one had hyponatremia at blood tests. EEG in two cases proved positive for abnormalities in temporal lobes; in the third, a video-EEG proved positive for lateralized FBDS without EEG-abnormalities. MRI proved positive for temporal-medial-hippocampal abnormalities in two cases. Total-body PET was negative for occult neoplasia for all. Everyone had negative virological panel and positive anti-LGI1 Antibodies in both serum and CSF. In the suspicion of LE, they were treated with high-dose intravenous methylprednisone followed by intravenous immunoglobulines with benefit. Only one developed a recurrence of FBDS after flu, treated with steroid. At short-term follow-up, they returned at the pre-morbidity status reporting no residual cognitive impairment. All patients were diagnosed for LE without delay, as on the basis of Graus et al. criteria, and confirmed with anti-LGI1 antibodies positivity. Even

if LGI1-LE is known to be a rapidly progressive disease, early treatment in these cases contributed to achieve good short-term prognosis, even if a long-term follow-up is still ongoing. In conclusion, our case-series confirms literature data about the clinical, laboratory and instrumental presentation and helps clinicians to place the right suspicion of the rare entity of LGI1-LE, in order to start promptly immunosuppressive treatments, to achieve better short-term outcomes and reduce irreversible deficits in the long-term.

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## CANNABIDIOL IS ASSOCIATED WITH THE IMPROVEMENT OF NEUROPSYCHIATRIC PROFILE IN PATIENTS WITH LENNOX-GASTAUT SYNDROME


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Introduction: Lennox-Gastaut syndrome (LGS) is a severe, refractory epilepsy syndrome with onset in early childhood. Treatment of LGS is challenging and most of the available anti-seizure medications (ASM) currently available fail to control seizures. LGS is also associated with an increased frequency of psychiatric comorbidities such as depression and anxiety. Cannabidiol (CBD) is a phytocannabinoid with antiseizure properties in absence of psychoactive effects. This study aims to evaluate CBD neuropsychiatric effects in adult patients suffering from LGS.

Methods: Patients with a diagnosis of LGS according to International League against Epilepsy (ILAE) criteria were consecutively enrolled at the Epilepsy Center of "G. d'Annunzio" University of Chieti-Pescara. Neuropsychiatric effects of CDB were monitored using the Beck Inventory Scale (BDI) and Beck Anxiety Inventory (BAI) at the baseline visit and the 6-month follow-up.

Results: Seven patients were enrolled (mean age:25.4±8.2 years). Mean CBD dosage was 7,5 mg/kg/die (IQR:5-10). Median epilepsy duration was 18.2±5.2 years. At the baseline, 3 patients showed mild depression according to BDI score (median:17, IQR:8-18). At a 6-month follow-up visit, BDI evaluation showed a great improvement in depressive symptoms (median: 8; IQR: 5-10). BAI evaluation at baseline highlighted low anxiety in just one patient. The median BAI score was 9 (IQR:5-22). At a 6-month follow-up visit, CBD treatment was associated with a notable improvement in BAI score (median:4; IQR:2-10). A seizure frequency reduction of>50% was observed in the entire cohort.

Conclusion: Treatment with CBD is associated with a decreased frequency and severity of neuropsychiatric symptoms in patients with severe epilepsy.

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## NAA20-RELATED SYNDROME: NOVEL MUTATIONS ASSOCIATED WITH EPILEPSY


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Introduction: NAA20 is the catalytic subunit of NatB, which is responsible for N-terminal acetylation. Pathogenic variants in NAA20 are associated with human disorders characterized by developmental delay, intellectual disability and microcephaly.

Objective: Five patients carrying two different variants in NAA20 have been described with limited clinical information. We report two Italian siblings carrying biallelic novel variant and their clinical data, expanding the phenotype of this neurodevelopmental disorder and of this epileptic syndrome.

Material and Methods: Whole Exome sequencing (WES)with triobased approach was performed in both. Brain Magnetic Resonance Imaging (MRI)and electroencephalogram (EEG)were performed in both.

Results: In Patient I epilepsy started at age 14, with focal motor to bilateral tonic–clonic seizures, occurring in clusters, several times a month. A partial response to oxcarbazepine, lamotrigine and valproate was observed. EEG showed epileptiform discharges over the frontal regions, both synchronous and asynchronous, and a low amplitude background rhythm. Brain MRI revealed microcephaly with a simplified gyral pattern and marked calvarian thickening, corpus callosum dysgenesis, anterior commissure agenesis, frontal periventricular nodular heterotopias, periventricular white matter signal alterations and cerebellar dysplasia associated with focal areas of cortical gliosis. Patient II presented a single short focal motor episode at age 15. Valproate was started with no seizure recurrence. EEG showed generalized epileptiform discharges and a moderately slow background rhythm. Brain MRI revealed superimposable brain malformations to ones of Patient I. The stepwise filtering identified compound heterozygous variants in NAA20(NM_016100.5): c.100C>T(p.Gln34Ter) of maternal origin and c.11T>C(p.Leu4Pro) of paternal origin. These mutations have never been described in the literature in unrelated parents.

Discussion: Siblings developed epilepsy during adolescence suggesting this could be part of syndrome evolution. In these two patients, we found a similar pattern of brain malformations characterized by microcephaly with a simplified gyral pattern, corpus callosum dysgenesis with an aberrant anteroposterior white matter bundle, cerebellar dysplasia and malformations of cortical development. Similar callosal abnormalities were described in one subject with a NAA20 variant, suggesting a possible role in the development of telencephalic commissures. Furthermore, cerebellar dysplasia with foliar abnormalities was noted, suspected of a possible role of NAA20 in the development and cortical organization of the cerebellum.

Conclusion: Our patients have in common with others previously described microcephaly, limited ability to speak and mild to moderate ID, but they present compound heterozygous variants in NAA20 never been described in the literature in unrelated parents. We expanded the phenotypic and mutational spectrum of NAA20-related syndrome, characterized by epilepsy.

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## IDENTIFICATION OF RISK FACTORS FOR DRUG-RESISTANT EPILEPSY

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Purpose: Drug-resistant epilepsy (DRE) is a therapeutic challenge for epileptologists and affects 30% of epilepsy subjects. Early identification of people at risk of drug resistance would help tailor pharmacological and nonpharmacological management. The aim of our study was to identify risk factors for DRE in the population of people with epilepsy afferent to the Epilepsy Center of Cagliari University Hospital.

Methods: Data were extracted from the medical records of subjects treated at our Epilepsy Center. Several conditions related to DRE were analyzed by a combination of univariate analysis and logistic regression to assess the effects of different factors: gender, age at onset, etiology (structural, genetic, immune, etc...), history of status epilepticus, seizure type (focal, generalized or combined), learning disability, comorbidities, duration of illness and family history of epilepsy.

Results: 804 people with epilepsy were examined: 201 of them were DREs (26%). Univariate analysis demonstrated a statistically significant association between DRE and age of onset, structural etiology, presence of status epilepticus, type of seizure, presence of psychiatric and neurological comorbidities, learning disability, and family history of epilepsy. Multiple regression analysis showed a significant association between DRE and age of onset, structural etiology, psychiatric and neurological comorbidities, and learning disability.

Discussion: Our data showed that the presence of a structural etiology, psychiatric and neurological comorbidities, learning disabilities, and an early age of onset were statistically significant risk factors for DRE.

Conclusion: Early identification of these factors could guide clinicians in a personalized management of these subjects and improve tailored therapeutic strategies.

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## SEX STEROID HORMONES AND EPILEPSY: EFFECTS OF HORMONAL REPLACEMENT THERAPY ON THE SEIZURES' FREQUENCY OF POSTMENOPAUSAL WOMEN WITH EPILEPSY – A SYSTEMATIC REVIEW

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Background: Hormonal replacement therapy (HRT) is used for symptomatic treatment of menopause. Some evidence suggests a proconvulsant effect of estrogen and an anti-convulsant role of progesterone. Thus, the use of exogenous sex steroid hormones might influence the course of epilepsy in peri- and postmenopausal women with epilepsy (WWE). We conducted a systematic review on the impact of HRT on the frequency of seizures of WWE.

Materials and Methods: PubMed and Scopus were searched for articles published from inception until August 2022. Abstracts from the last five years from the European Academy of Neurology and European Epilepsy Congresses were also reviewed. Article reference lists were screened, and relevant articles were retrieved for consultation. Interventional and observational studies on WWE and animal models of estrogen deficiency were included. Critical appraisal was performed using the Revised Cochrane risk-of-bias tool for randomized trials and ROBINS-E tools.

Results: Of 497 manuscripts screened, thirteen studies were included, including three human studies. One cross-sectional study showed a decrease in seizures' frequency in WWE using combined HRT, a case-control study showed an increase in comparison with controls and a Randomized Clinical Trial found a dose-dependent increase in seizures' frequency in women with focal epilepsy taking combined HRT. Ten studies addressing the impact of HRT in rat models were also included, which showed conflicting results.

Discussion and Conclusion: There is scarce evidence of the impact of HRT in WWE. Further studies should evaluate the harmful potential and prospective registries are needed for monitoring in this population.

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## DIAGNOSIS AND TREATMENT OF LATE-ONSET MYOCLONIC EPILEPSY IN DOWN SYNDROME (LOMEDS): A SYSTEMATIC REVIEW WITH INDIVIDUAL PATIENTS' DATA ANALYSIS

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Introduction: The late onset myoclonic epilepsy in Down Syndrome (LOMEDS) is a peculiar epilepsy type characterized by cortical myoclonus and generalized tonic-clonic seizures (GTCS), in people undergoing cognitive decline associated with dementia in Down syndrome (DS). In this review, we analyzed available data on the diagnostic and therapeutic management of individuals with LOMEDS.

Methods: We performed a systematic search of the literature to identify the diagnostic and therapeutic management of patients with LOMEDS. The following databases were used: PubMed, Google Scholar, EMBASE, CrossRef. The protocol was registered on PROSPERO (registration code: CRD42023390748).

Results: Data from 46 patients were included. DS was diagnosed according to the patient's clinical and genetic characteristics. Diagnosis of Alzheimer's dementia (AD) preceded the onset of epilepsy in all cases. Both myoclonic seizures (MS) and generalized tonic-clonic seizures (GTCS) were reported, the latter preceding the onset of MS in 28 cases. EEG was performed in 45 patients, showing diffuse theta/delta slowing with superimposed generalized spike-and-wave or polyspike-and-wave. A diffuse cerebral cortical atrophy was detected in 34 patients on neuroimaging. Twenty-seven patients were treated with antiseizure medication (ASM) monotherapy, with reduced seizure frequency in 17 patients. Levetiracetam and valproic acid were the most used ASMs. Up to 41% of patients are unresponsive to first-line treatment and need adjunctive therapy for seizure control.

Conclusions: Brain structural changes induced by AD may play a role in LOMEDS onset, although the mechanism underlying this phenomenon is still unknown. EEG remains the most relevant investigation to be performed. A significant percentage of patients developed a first-line ASM refractory epilepsy. ASMs which modulate the glutamatergic system may represent a good therapeutic option.

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## DYSPHAGIA, DYSARTHRIA AND OCULOMOTOR DISTURBANCES IN A YOUNG MAN WITH HISTORY OF EPILEPSY: COINCIDENT SYMPTOMS OR COMPLEX SYNDROME?

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Objective: We present the case of a 43-year-old man with history of generalized epilepsy who presented slowly progressive dysarthria, dysphagia and oculomotor disturbances, describing the clinical reasoning behind this complex and yet unresolved case.

Case Description: The patient did not have family history of neurological disorders nor neurodevelopmental diseases. Previous cocaine abuse was reported. The patient started to suffer from generalized tonic-clonic seizures at the age of 20 years. The EEG showed diffuse 3 Hz spike-polyspike and wave abnormalities while brain MRI was normal. Epilepsy was diagnosed as idiopathic generalized epilepsy and valproic acid was started. Last seizure occurred at the age of 37 years. Aged 40 years, he started to complain dysarthria and dysphagia, which were evident at the neurological examination together with a limitation in vertical saccadic eye movements, particularly affecting downward saccades; muscle trophism, strength, tone, and reflexes were normal; no muscle fasciculations were observed. These disturbances slowly progressed during the next 6-8 months. Recently, worsening of bulbar symptoms, postural instability, falls and mild right extrapyramidal syndrome became evident.

Neurological Reasoning and Diagnostic Work-up Results: As first diagnostic hypotheses we evaluated: i) CNS stroke/vasculitis possibly related to cocaine abuse, ii) motor neuron disease, iii) junction neuromuscular disease, iv) myopathy due to mitochondrial disease or oculopharyngeal muscular dystrophy. Brain MRI and MR angiography (3T) were unremarkable. Electromyography demonstrated a mild myopathic pattern, which was characterized later as non-specific by muscular biopsy. Anti-acetylcholine receptor and anti-Musk antibodies were negative. None of the previous hypotheses were confirmed. Marked hyperthyroidism due to Graves' disease was then identified. A possible thyroid-associated ophthalmopathy was suspected. However, despite treatment with tapazole, his symptoms persisted even after normalization of the thyroid profile. Thus, further diagnostic hypotheses were considered: v) genetic disease, vi) neurodegenerative disease, vii) autoimmune encephalitis. Cerebrospinal fluid analyses were normal including absence of intrathecal immunoglobulin synthesis; TAU, p-TAU, and β -amyloid were normal. Brain FDG-PET revealed bilateral hypometabolism of the putamen. Genetic tests for Niemann Pick type C, SCAs, DRPLA, Friedreich ataxia, and NGS panel for mitochondrial diseases were negative. First-line analyses exploring the hypothesis of an autoimmune encephalitis were also negative.

Conclusions: Summarizing, our patient presented a Progressive Supranuclear Palsy-like phenotype in association with generalized epilepsy. Diagnosis is still uncertain and second-line investigations both for neurogenetic disorders - including whole-exome sequencing - and autoimmune neurologic disorders are now ongoing.

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## EFFECTIVENESS OF CANNABIDIOL IN DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES BEYOND DRAVET AND LENNOX GASTAUT SYNDROMES: REAL-WORLD EVIDENCE FROM A LEVEL 3 EPILEPSY CENTER

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Purpose: The highly purified CBD oil (Epidiolex) is licensed as adjunctive antiseizure treatment in patients with Dravet (DS) or Lennox Gastaut (LGS) syndromes and Tuberous-Sclerosis-Complex [1]. Nevertheless, evidence about CBD effectiveness in other Developmental and Epileptic Encephalopathies (DEEs) have been provided in few cases [2]. The aim of our study was to assess the effectiveness of CBD as adjunctive treatment in a cohort of patients with DS, LGS and other drug-resistant epileptic syndromes, particularly genetic DEEs.

Materials and Methods: We conducted a 12 months observational prospective clinical trial. We enrolled 13 patients (aged 13-52 years) affected with drug-resistant epilepsy of different etiology. Patients received CBD 5mg/kg/day for two weeks, then titrated up to 20 mg/kg/day. Seizures' frequency, EEG and blood exams were assessed at 3, 6, 9 and 12 months. Further effects were evaluated using QoLIE-10P, QoLCE-16, Pittsburgh and Epworth Scales, BDI-II, PGIC, CGIC. The primary endpoints were median percent change from baseline in weekly seizure frequency and responder rate at 6, 9 and 12 months. Comparison for percent change was over time was done using a Friedman test.

Results: Four patients presented with LGS or LGS-like phenotype, one with DS, four with genetic DEEs (of these one related to MEF2C, one to PCDH19, one to STXBP1 and one to dupXq28), four with cryptogenic DEEs. Whole-Exome-Sequencing is ongoing in 4 patients with no genetic diagnosis to date. Nine patients concluded the 12 months study; two discontinued CBD after one month owing to lack of compliance, the patients with STXBP1 and MEF2C-related DEE discontinued after six and ten months respectively owing to lack of efficacy and minor adverse effects (AEs). We observed a significant reduction in seizure's frequency at 6, 9 and 12 months in all the nine patients who completed the study ($\chi 2$ (3)=17,67, p<0,001), with no significant differences between 6 and 12 months ($\chi 2$ (2)=0,5, p=0,48). At 12 months the median percent change was 66%, the responder rate 66,7% (6/9), the retention rate 70% (9/13). Seizure freedom was achieved in three patients, particularly in the individual with PCDH19-related DEE it correlated with an improvement in quality of life. In one patient with cryptogenic DEE we observed improvement in gross motor skills with reacquisition of autonomous walking. No serious AEs were registered; the most frequent was somnolence.

Discussion and Conclusion: CBD adjunctive antiseizure treatment is effective and well tolerated in DEEs beyond LGS and DS and, particularly in PCDH19-related DEE.

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## GENDER VARIABILITY OF CARDIOVAGAL OUTPUT ACCORDING TO HEART RATE VARIABILITY (HRV) ANALYSIS IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

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Objectives: Heart rate variability (HRV) analysis evaluates cardiac autonomic control and may represent a biomarker for sudden unexpected death in epilepsy (SUDEP). SUDEP is more frequent in males. It is plausible that female sex hormones may influence HRV. These changes may be more pronounced in patients with drug-resistant epilepsy. This study aims to compare changes in HRV in two groups of patients with drug-resistant epilepsy differentiating them according to gender.

Methods: 60 adult patients (mean age 41.9 ± 15.7, 30 M and 30 F) with drug-resistant epilepsy were enrolled. Each patient underwent a 20-min resting state EEG + ECG recording. Patients were divided into two subgroups based on gender: EPI-M and EPI-F. HRV parameters were calculated with a short-lasting ECG analysis. Patients treated with drugs that interfere with the functioning of the autonomic nervous system (ANS), had a history of heart disease, endocrine disorders, metabolic deficits, uremia, or any other known disease that may affect autonomic functions, including sleep-related apnea, were excluded from the study. Time-domain and frequency-domain HRV short-term analysis was performed on EKG records.

Results: When comparing EPI-M and EPI-F groups, no differences were observed according to age, clinical characteristics (comorbidities and concomitant medications), and epilepsy-related features (seizure frequency, ASM type, and treatment response). Compared to the EPI-M group, the EPI-F subjects showed a significant decrease in low-frequency naturalized units (LF n.u.) (p=0.0067), in low-frequency percentage (LF %) (p=0.0174) and LF/HF ratio (p=0.002), In addition, an increase in root mean square of the difference between contiguous RR intervals (RMSSD) (p=0.04), high-frequency naturalized units (HF n.u.) (p=0.068) and high-frequency percentage (HF%) (p=0.0117) were reported, parameters indicative of increasedin cardiac vagal tone.

Conclusions: Compared with EPI-M, EPI-F is associated with an increase in cardiac vagal tone. These results support the biological base of a possible difference incidence of SUDEP between males and females.

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## PERI-ICTAL NEUROIMAGING OF STATUS EPILEPTICUS: PRELIMINARY RESULTS OF A PROSPECTIVE STUDY

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Objectives: Peri-ictal MRI abnormalities (PMAs) following status epilepticus (SE) show variable prevalence (12%-100%) in the literature. These alterations are frequently transitory, but the timing of appearance and disappearance is poorly investigated. We aimed to further characterize the type and timing of the MRI findings associated with SE.

Materials and methods: In this prospective, observational, controlled study we enrolled all consecutive patients with SE, cluster of seizures, or a single seizure referring to our tertiary Epilepsy Centre in Reggio Calabria. All patients underwent video-EEG monitoring (21 channels, International 10-20 system) and they were treated as per standard guidelines. Brain MRI was performed in all patients within 24 hours from seizure termination, acquiring axial T1-weighted, T2-weighted, fluid-attenuated inversion recovery and DWI images; the ADC maps was obtained from the diffusion images. A follow-up MRI with a more extended protocol including GRE and IR sequences was performed in all patients after at least 14 days from seizure termination or later. All patients were clinically followed for at least 1 year after the event. The primary outcome was to evaluate the timing of onset of cortical high DWI signal during or immediately after an epileptic event, when present. For subjects with MRI abnormalities, additional follow-up studies until normalization have been performed.

Results: We recruited 90 patients with a mean age of 63,2 years. Thirty-two (36%) had SE, 21 (23%) had cluster of seizures and 37 (41%) had a single seizure. First MRI was positive in 16 patients (50%) from the SE group, 9 (43%) for the cluster group and 18 (54,3%) for the single seizure group. There was no statistical difference among the three groups for the primary outcome (p value= 0.3672). Thirteen patients completed the follow-up MRI. In seven cases the follow-up was terminated for identification of a specific etiology of the lesion (vascular, neoplastic). In six patients the alterations were no longer present (confirming as PMAs). Seven patients presented persistent anomalies and follow-up is still ongoing.

Discussion and conclusions: Our findings emphasize that PMAs are not specific to SE given the non-significant differences in prevalence between the three groups investigated. These preliminary data warrant further investigation.

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## EFFECTIVENESS OF HIGHLY PURIFIED CANNABIDIOL IN SUPER-REFRACTORY STATUS EPILEPTICUS (SRSE): A CASE-SERIES

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Objectives: Super-refractory status epilepticus (SRSE) is a medical emergency that must be promptly treated to prevent irreversible brain damage and death. [1] Nevertheless, the evidence of effective treatments is scarce, deriving from case series. Among these, highly purified cannabidiol (CBD), approved for the treatment of Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex-related epilepsy demonstrated significant efficacy in reducing seizures. [2] Here we present two cases describing the effective use of CBD in the treatment of SRSE.

Materials and methods: A 51 y.o. woman affected by drug-resistant focal epilepsy secondary to limbic seronegative encephalitis, and treated by brivaracetam 250 mg/die, phenobarbital 200 mg/die, lacosamide 400 mg/die, carbamazepine 400 mg/die and clonazepam 4 mg/die, presented with generalized status epilepticus. Following administration of diazepam in iv bolus, her first neurological examination showed drowsiness, aphasia, and right arm hyposthenia with continuous myoclonus of the homolateral shoulder. Blood testing, head CT scan, and lumbar puncture, with microbiological tests, showed no abnormalities. EEG showed frequent bilateral frontotemporal paroxysmal slow waves. Brain MRI confirmed bilateral temporo-mesial gliotic lesions of previous encephalitis. Despite the optimization of antiseizure treatment (lacosamide 400 mg/die iv, phenobarbital 200 mg/die im, valproic acid 1400 mg iv, levetiracetam 3000 mg/die iv) critical episodes persisted and nasogastric tube was placed and treatment with CBD 8 ml/die was started and 24 hours later increased to 12 ml/die (20 mg/kg/die) with full recovery from the status epilepticus, and change in neurological examination 36 hour later the first administration of CBD (vigilance, coordination, verbal fluency, no motor deficit). A 18 y.o. man affected by Lennox-Gastaut-like epileptic encephalopathy (structural origin), in treatment with valproic acid 1600 mg/die and clonazepam 3 mg/die presented with generalized tonic-clonic seizures refractory to the administration of diazepam 10 mg in iv bolus, requiring intubation and sedation with propofol. Levetiracetam 3000 mg/die iv, valproic acid 3600 mg/die iv and lacosamide 400/die mg iv were prescribed, but EEG showed synchronous ad rhythmic bilateral spikes, polyspikes and waves, indicative of SRSE. Nasogastric tube was placed and CBD was started at 5 mg/kg/die and then titrated up to 20 mg/kg/die in 24 hours. 48 hours later, the patient's conditions markedly improved, allowing the tapering of sedatives and extubation. EEG also improved showing residual bilateral fronto-centro-temporal interictal abnormalities.

Conclusions: According to our experience, CBD may be used in case of SRSE considering the possible beneficial effects of it when used as oral solution administered in nasogastric tube.

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## CLINICAL CHARACTERISTICS AND TREATMENT APPROACH OF ESTABLISHED NEW-ONSET STATUS EPILEPTICUS (ENOSE): A REAL-WORD MULTICENTER EXPERIENCE

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Background: Status Epilepticus (SE) can occur in patients without a previous epilepsy diagnosis, a condition identified as "new-onset status epilepticus" (NOSE). Treatment with benzodiazepine may fail in

NOSE termination, requiring anti-seizure medication (ASM) employment. In this context, the term "established NOSE" (eNOSE) is generally employed. This study aims to describe the main clinical characteristics of a large sample of patients suffering from eNOSE comparing the ASM efficacy and exploring the risk factors associated with ASM treatment unresponsiveness and eNOSE associated mortality.

Methods: Adult patients with diagnosis of eNOSE were retrospectively selected between January 2016 and December 2022. Demographics and clinical data as well as diagnostic work-up and treatment were reviewed. We considered effective the last ASM introduced or increased in dose before the eNOSE termination.

Results: 123 patients were included (age: 67.9 ± 17.3). eNOSE etiology was defined in 109 cases and the acute one was the most frequent. In the total cohort, phenytoin showed the highest response rate. The comparison among all the employed drugs (i.e., phenytoin, valproate, levetiracetam, and lacosamide) showed phenytoin as the most effective ASM (p=0.005). In the pairwise comparisons, valproate was superior to levetiracetam (p=0.02), but not to lacosamide (p=0.65). Phenytoin had a significantly higher resolution rate compared to levetiracetam (p=0.0005) but not to lacosamide (p=0.16). Thirty patients (25%) were refractory to ASM treatment. No predictors of refractoriness were identified. Thirty-nine patients died. Age and GCS were identified as eNOSE related mortality risk factors.

Conclusion: eNOSE frequently shows an acute etiology with several associated semiologies. PHT show the higher effectiveness in eNOSE management, even if LCM and VPA can represent further therapeutic options. eNOSE can eventually become refractory and being associated with a higher burden of SE-related complications. Age and GCS represent the main risk factor of eNOSE associated mortality.

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## ASSOCIATION OF CSF AND PET MARKERS OF NEURODEGENERATION WITH ELECTROCLINICAL PROGRESSION IN LAFORA DISEASE


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Purpose: Although progressive and fatal evolution of Lafora Disease (LD) has been previously reported, full data on long-term electro-clinical follow-up is very rare. We evaluate the electro-clinical features in association with laboratory and instrumental correlates of neurodegeneration to detect the progression of LD.

Methods: We investigated the electro-clinical longitudinal data and CSF Aβ42, p-tau181 and t-tauAg, amyloid and 18F-FDG PET of 5 unrelated LD families.

Results: Three progressive electro-clinical stages were identified. The early phase was characterized by rare generalised tonic-clonic and focal visual seizures, followed by the occurrence of myoclonus after a period ranging from a 2 to 12 months. The intermediate stage, usually occurring after two years from the onset of epilepsy, was characterized by a worsening of epilepsy and myoclonus associated with a progressive dementia and cerebellar signs. Finally, the late stage, evolving after a mean period of 7±1.41 years from the onset of the disease, was characterized by gait ataxia resulting in bedriddenness, severe dementia, daily/pluri-daily myoclonus, drug-resistant epilepsy and clusters of seizures or status epilepticus and medical complications. Amyloid (CSF Aβ42, amyloid PET) and neurodegenerative (CSF p-tau181 and t-tauAg, FDG-PET) biomarkers suggest a pattern of cognitive impairment of non-Alzheimer disease type. Eighty per cent of the LD patients showed a more severe hypometabolism in the second FDG-PET compared to the first scan performed in a lower phase; lateral temporal lobe and thalamus hypometabolism were associated with the presence of phase intermediate or late.

Discussion: An early diagnose of LD is essential because patients will be more likely to benefit from promising new therapeutic strategies. It is therefore important to develop biomarkers that are sensitive to this early stage, but also during the progressive evolution of the disease. We identified four main and progressive symptoms (epilepsy, myoclonus, ataxia, dementia), included in three evolutive electroclinical stages. Dementia presented during the second electro-clinical stage with a non-Alzheimer pattern. The combination of CSF traditional biomarkers and 18F-FDG PET findings biomarkers may improve the diagnostic accuracy of cognitive decline in LD patients, suggesting also the implication of the thalamus in the LD pathogenetic mechanisms.

Conclusions: Three electroclinical and 18F-FDG PET evolutive stages are useful biomarkers for the progression of LD and could help to evaluate the efficacy of new disease-modifying treatments. The combination of CSF traditional biomarkers improves the diagnostic accuracy of cognitive decline in LD patients, suggesting a cognitive impairment of non-Alzheimer disease type.

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## IMPACT OF FIRST-LINE ANTI-SEIZURE MEDICATION (ASM) ON HEART RATE VARIABILITY (HRV) IN PATIENTS WITH NEWLY DIAGNOSED TEMPORAL LOBE EPILEPSY (TLE): A COMPARISON BETWEEN LEVETIRACETAM, LAMOTRIGINE, LACOSAMIDE AND CARBAMAZEPINE


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Objectives: Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy. The temporal lobe plays a central role in regulating the "Central Autonomic Network" and cardiovascular functions. Heart rate variability (HRV) is a non-invasive method to evaluate cardiovagal output, which reduction may represent a risk factor for sudden death. Anti-seizure medications (ASM) can alter HRV. This study aims to evaluate the impact of first-line ASM treatment in patients with newly diagnosed temporal lobe epilepsy (TLE).

Methods: We consecutively enrolled 75 adult patients with a new diagnosis of TLE treated with LEV (LEV-group, 30 patients), Lamotrigine (LMT-group, 15 patients), Carbamazepine (CBZ-group, 15 patients) or Lacosamide (LCS-group, 15 patients) as monotherapy. Each patient underwent a 20-minute EEG + EKG recording in resting state at baseline at most 1 month (mean interval: 15 days) before introducing the ASM therapy (pre-ASM) and a second standard EEG+EKG at six months after starting the specific treatment (post-ASM). Patients treated with drugs that interfere with the functioning of the autonomic nervous system (ANS), had a history of heart disease, endocrine disorders, metabolic deficits, uremia, or any other known disease that may affect autonomic functions, including sleep-related apnea, were excluded from the study. Time-domain and frequency-domain HRV short-term analysis was performed on EKG records. Linear Mixed Models (LMM) were used to analyzed HRV variables according to time (baseline and 6-months follow-up) and groups.

Results: In the four groups, no differences were observed according to demographics (age and sex), clinical characteristics (comorbidities and concomitant medications), and epilepsy-related features (seizure frequency, ASM response, lateralization of epileptic focus). According to HRV comparative analysis, treatment with LEV showed significantly increased LnRMSSD (natural logarithm of the root mean square of the difference between contiguous RR intervals) (p-value=0.05), LnHF ms2 (natural logarithm of high-frequency absolute power) (p-value=0.03), and HF n.u. (high-frequency power expressed in normalized units) (p-value=0.05). In addition, the LEV group exhibited decreased LF n.u. (low-frequency power expressed in normalized units) (p-value=0.04) and LF/HF (low frequency/high frequency) ratio (p-value=0.05).

Conclusions: Treatment with LEV as first-line ASM is associated with an increased vagal tone in patients with newly diagnosed TLE. The result of this study may support the use of LEV to reduce the risk of cardiovagal imbalance in patients with newly diagnosed TLE.

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## DETECTION OF SOMATIC AND GERMLINE PATHOGENIC VARIANTS IN EPILEPTOGENIC LESIONS

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Objective: Epileptogenic lesions, such as focal cortical dysplasia (FCD) and low-grade epilepsy-associated neuroepithelial tumors (LEAT), are two of the main cause of drug-resistant structural epilepsy [1]. Recent studies have disclosed a growing number of pathogenic somatic and germline variants responsible for these lesions especially in genes encoding components of PI3K-AKT-mTOR and RAS-MAPK pathway, respectively [2]. However, the exact prevalence of pathogenic variants and their role in surgical outcome have still to be clarified.

Materials: Consecutive patients who underwent epilepsy surgery at Claudio Munari Epilepsy Surgery Center and at IRCCS Istituto delle Scienze Neurologiche between 2018-2021 were included in the study. For each patient were analyzed the DNA obtained from Fresh Frozen (FF) brain specimen resected during surgery and matched peripheral blood. Retrospective formalin-fixed paraffin-embedded (FFPE) brain tissues obtained from the Clinical Epileptology and Experimental Neurophysiology Unit IRCCS, Neurological Institute "C. Besta" were also analyzed.

Methods: We designed 2 target panels of genes associated to FCD and LEAT using single molecule Molecular Inversion Probes (smMIPs). The FCD panel comprised 14 genes (AKT1, AKT3, CASK, DEPDC5, MTOR, NPRL2, NPRL3, PIK3CA, PTEN, RHEB, SLC35A2, TSC1, TSC2, KRAS) while LEAT panel includes 10 genes (TRX, BRAF, FGFR1, GFAP, IDH1, KRAS, NF1, PDGFRA, RB1, TEK, TP53, PTEN).

Results: A total of 164 pediatric and adults patients were included (72F, mean age 30,6 range 6-65). FF brain specimen was available for 143, FFPE for 21. Based on histopathological analysis patients were classified in 4 group: FCD 60 patients, LEAT 28, Scars 10, other-lesion or not-lesional 66. We performed preliminary genetic analysis on 127 brain and blood specimens (30 FCD, 28 LEAT patients and 10 Scars). We identified 11 pathogenic variants in FCD group (36%): 2 germline in TSC1 and 9 somatic (7 in MTOR with Variant Allele Frequency (VAF) 1-3%, 1 in RHEB (VAF: 2%) and 1 in SLC35A2 (VAF: 2,49%). Ten patients in LEAT group showed pathogenic somatic variant in BRAF (VAF 2-9%) and 1 in IDH1 (VAF 25%). None of patients in scar group had positive results for both panels.

Discussion: We confirm that mTOR and BRAF mutations account for the majority of FCDII and LEAT cases, further contributing to recognize a genetic basis of these epileptogenic lesions. Somatic mutations of SLC35A2 are increasing detecting in FCDI-related epilepsy.

Conclusion: Our study reports the optimal diagnostic accuracy of smMIP in the identification of somatic variants with low VAF both in FCDI, FCDII and LEAT patients underwent epilepsy surgery.

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## OCULOLEPTOMENINGEAL AMYLOIDOSIS PRESENTING WITH PROLONGED POST-ICTAL STATE AND RELAPSING VISUAL LOSS

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Aim: To describe a rare case of possible oculoleptomeningeal amyloidosis presenting with prolonged post-ictal state.

Methods: Oculoleptomeningeal amyloidosis (OLMA) is a rare phenotype of hereditary transthyretin (ATTRv) amyloidosis, which is caused by transthyretin (TTR) mutations that decrease the stability of the TTR tetramer thereby forming amyloid fibrillar aggregates that lead to organ dysfunction. Here, we present the case of a 40-year-old man who presented in the emergency room with altered mental status, right gaze paresis, right hemiplegia, and global aphasia, followed by a gradual recovery over 5 days.

Results: After the post-ictal phase resolution, neurological examination revealed impaired word retrieval for less commonly used nouns, brisk deep tendon reflexes in all four limbs and mildly decreased vibration sense in the distal lower limbs. Moreover, a weak pupillary reflex was present in the left eye, compatible with the severe visual loss after a previous episode of acute angle closure glaucoma, and bilateral decreased visual acuity. On head CT scan two small non-traumatic convexity subarachnoid haemorrhagic foci located along the fronto-parietal cortex were visible. Brain MRI and CT angiography ruled out ischemic lesions and focal arterial stenoses. Interestingly, the patient had a history of recurrent panuveitis and retinitis without a clear etiology and a poor response to immunosuppressive treatments that lead to re-consider infectious and inflammatory CNS processes among the possible causes. CSF analysis showed a xanthochromic fluid, mild pleocytosis (15 cells/μL), and an increased protein level (1350 mg/L). Brain MRI with gadolinium showed diffuse leptomeningeal enhancement. EEG monitoring revealed lateralized delta slowing over the left temporal region that progressively abated, paralleling the clinical improvement. Optical coherence tomography and fluorescein angiography findings were consistent with ocular amyloidosis, corroborated by the disease relapse after vitrectomy. Nerve conduction studies showed bilateral carpal tunnel and sensory-motor axonal distal symmetric polyneuropathy. Systemic screening for amyloid light chain amyloidosis was negative. Given the highly suggestive positive family history, consistent with an autosomal dominant transmitted disease, genetic testing of the TTR gene and genetic counselling were offered.

Discussion: ATTRv classically presents with cardiac and peripheral nervous system involvement but can also be a great mimicker by disproportionately affecting the central nervous system and eyes, as TTR protein is also produced by the choroid plexus and retinal pigment epithelium. Recognition of this syndrome is important to avoid unnecessary treatment and ensure enrolment in clinical trials with recently emerging therapies.

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## ANTI-LGI1 AUTOIMMUNE ENCEPHALITIS PRESENTING AS ADULTHOOD-ONSET TEMPORAL LOBE EPILEPSY

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Aims: We report a case of LGI1-antibody encephalitis started with adulthood-onset temporal seizures as first symptom, associated with mild memory loss.

Materials: A previously healthy 42-year-old woman developed focal seizures characterized by motor arrest, left head version, flexion of the right arm and fixed gaze. These episodes lasted approximately 10 seconds, were followed by confusion and in a single occasion progressed into a bilateral tonic-clonic seizure. The patient also complained of mild short-term memory loss and irritability. She had no family history of epilepsy or febrile seizures.

Methods: Neurological examination revealed mild attention and memory impairment. An extensive work-up, including routine blood tests and cerebrospinal fluid (CSF) analysis was carried out. The patient also underwent neuropsychological assessment with electroencephalography (EEG). Furthermore, a 3-Tesla brain Magnetic Resonance Imaging (3T-MRI) was acquired.

Results: Routine blood tests, including electrolytes, were unremarkable. At admission, neuropsychological assessment documented severe impairment of anterograde memory skills, anxiety, emotional lability and irritability. A previous brain MRI, acquired 4 weeks before admission, showed hyperintense left mesial temporal lobe on T2/Fluid Attenuated Inversion Recovery (FLAIR) weighted. Standard EEG recorded a seizure originating from left temporal lobe, so we started levetiracetam up to 1000 mg/day. Serum and CSF analysis detected LGI1 auto-antibodies, fulfilling diagnosis of anti-LGI1 limbic encephalitis. Thus, she received intravenous immunoglobulin (IVIGs) combined with methylprednisolone 0,4 g/kg/day and 500 mg/day for 5 consecutive days respectively. Immunotherapy led to a significant resolution of cognitive and psychiatric symptoms. At one-week follow-up, neuropsychological assessment documented improved memory performances and brain 3T-MRI reported a T2/FLAIR hyper-intensity combined to T1 atrophy of left hippocampal region, configuring a left hippocampal sclerosis. Standard and prolonged EEG recordings were unremarkable. To rule out the paraneoplastic etiology, the patient performed a total body Computerized Tomography (CT) scan, with no significant findings.

Discussion: Leucine rich glioma inactivated 1 (LGI-1)-IgG encephalitis is a well-shaped immune-mediated disorder often presenting as cognitive impairment, epileptic seizures and behavior disturbances, responding to immunotherapy. Nonetheless, anti-LGI1 encephalitis includes a wide spectrum of cognitive and psychiatric manifestations, until rapidly progressive dementia and mental status changes. [1] This case contributes to understand the wide spectrum of this condition and emphasizes the importance of neuronal antibodies investigation in suspected immune-mediated encephalitis.

Conclusions: An immune pathophysiology should be routinely considered in individuals with adult-onset temporal lobe epilepsy, combined with memory impairment and behavior abnormalities, even mild. Awareness of electroclinical features of anti-LGI1 encephalitis has important implications for diagnosis and treatment. [2,3]

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## THE USE OF CENOBAMATE FOR THE TREATMENT OF DRUG-RESISTANT FOCAL EPILEPSY: A SINGLE CENTRE REAL-LIFE EXPERIENCE

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Pharmacoresistance affects approximately 1/3 of patients with epilepsy and, despite the availability of many antiseizure medications (ASM), the percentage of seizure-freedom in this population is less than 5% after the second pharmacological trial. [1] Cenobamate (CNB) is a new ASM that has demonstrated high efficacy in drug-resistant focal epilepsy in regulatory clinical trials. [2] We report the real-life experience of the Careggi Epilepsy Center in the use of CNB. We evaluated 39 patients with drug-resistant focal epilepsy, most affected by long-term epilepsy, treated with Cenobamate. The seizure frequency was assessed before and at 3-6-9 months after the start of treatment. Associated drugs and side effects were also evaluated. Out of the 39 patients treated, one dropped the treatment before the end of the titration. At the follow-up, among 33 patients evaluated at 3 months, 5 were seizure-free and 8 had a 50% reduction in seizure frequency; among the 23 patients evaluated at 6 months, 3 were seizure-free and 10 had a 50% reduction in seizure frequency; 1 of the 8 patients treated for 9 months was seizure-free and 3 had a 50% reduction in seizures. Of the 27 patients with side effects 16 reported dizziness (14/16 in therapy with sodium channel blockers), 10 drowsiness (7/10 in concurrent therapy with GABAergic ASMs), 5 instability in 3 cases associated with vomiting and in 2 with ataxia (in all 5 patients experienced before reducing concomitant sodium channel blockers), in 5 diplopia/blurred vision, in 3 irritability, in 4 fatigue. All the side effects were mild and the most resolved after reducing the dosage of concomitant sodium channel blockers and GABA-ergics ASMs, without impact on the therapeutic efficacy of CNB. In this case series of patients with a long history of illness and significant drug resistance, Cenobamate confirm to be an effective drug, yielding excellent results in terms of seizure reduction, consistent with data obtained from clinical trials. The data also suggest that tolerability is good and could be improved by reducing the dosage of concomitant ASMs during the titration phase, without affecting the efficacy of CNB but further improving compliance and quality of life.

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## TELENEUROLOGY AND INTERNATIONAL HEALTH COOPERATION: IMPROVING EPILEPSY CARE IN SUB-SAHARAN AFRICA

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Introduction: There are more than 70 million people with epilepsy (PWE) worldwide, 80% in low income countries (LIC) as sub-Saharan Africa (SSA) where more than 75% have no access to treatment. The WHO-Intersectoral Global Action Plan (IGAP) 2022-2031 aims to increase access to epilepsy care particularly in LIC and SSA. In SSA the vast majority of PWE are managed by non-physician clinicians (NPC) with poor education in epilepsy hampering proper diagnosis and treatment to PWE. In the last few years, we conducted an intensive education and training programme on epilepsy to NPC in Malawi and Central African Republic. A teleneurology system was initiated along between Italian neurologists and the SSA NCP. We report the results of this international cooperation on epilepsy.

Method: Disease Relief through Excellent and Advanced Means (DREAM) is a public health program in ten SSA countries. In Malawi and Central African Republic (CAR), DREAM follows 18836 patients, more than 85% are HIV+. In 2020, an epilepsy program was started in Malawi and CAR DREAM centers in partnership with the Italian Society of Neurology, the "Besta Neurologic Institute", the "Mariani Foundation" and the Global Health Telemedicine (GHT). Several remote education sessions and 12 in-person training courses were provided to local NPC. Teleneurology platforms were installed along with two video-EEGs. Italian Volunteers neurologists actively answer from remote to the teleneurology consultation requests sent by SSA NPC; they also analyzes EEGs sent through the telemedicine platform.

Results: The number of teleneurology consultations requests from SSA NCP to Italian neurologists have gradually increased: 141 in 2020, 802 in 2021 and 815 in 2022. And the number of PWE under care is increasing: 1064 in 2022, 5.6% of the DREAM patients in Malawi and CAR; 68,6% of the PWE are under the age of 18 (median age is 19,8 years), 11% are older than 40 years. More than 500 EEGs have been transmitted to the Italian neurologists.

Conclusions: Teleneurology and digital systems coupled with education and training-on-the-job to SSA NPC are a cost-effective tool to bring neurologists where there are no neurologists. Our partnership is contributing to improve access to care to an increasing number of PWE in SSA thus fulfilling IGAP goals. A long term approach is necessary to apply IGAP indications, a shift from projects to programs.

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## EPILEPSIA PARTIALIS CONTINUA FOLLOWING GUNSHOT WOUND

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Aims: Epilepsia partialis continua (EPC) is a rare focal status epilepticus arising from a variety of lesions in the perirolandic area. EPC presents as continuous unilateral or, more rarely, bilateral jerks over hours, days, or even years. [1] Several etiologies have been addressed, including structural, immune-mediated, neoplastic, toxic-metabolic causes. [2-3] Here, we propose a unique case of EPC in a man who developed myoclonic jerking in the upper limbs related to a penetrating gunshot head injury.

Materials: The patient is a 63-year-old man. At the age of 12, he reported a head gunshot wound. Thereafter, he developed isolated repetitive episodes of jerking in the upper limbs. Neurologic examination revealed continuous jerking in the arms bilaterally, without evidence of loss of consciousness. He had no family history of neurological disorders.

Methods: An extensive clinical, neurophysiological assessment, and brain computed tomography (CT), was carried out. The neurophysiological study included video electroencephalography-electromyography (v-EEG-EMG) polygraph and somatosensory evoked potentials (SEPs) with cortical-reflex (c-reflex).

Results: Routine blood analysis, including screening for infectious and toxic-metabolic diseases, was all unremarkable. The v-EEG-EMG polygraph revealed abrupt brief myoclonic jerks time-locked to sub-continuous focal epileptiform discharges over the fronto-centro-parietal regions bilaterally, with a maximum in the right hemisphere. The background activity was normal. He also depicted giant SEPs with no c-reflex. The electroclinical findings fulfilled the criteria of EPC. Interestingly, the brain CT showed retained bullets with metal artifacts in the left fronto-temporo-parietal regions. Intravenous therapy with levetiracetam dramatically resolved EPC.

Discussion: To our knowledge, our patient represents a unique case of EPC in a man without a previous history of epilepsy. EPC includes a wide spectrum of etiologies, but its pathophysiology is not fully established and is largely driven by the underlying cause. [2,3] We identified a unique case of EPC related to a head gunshot wound, further broadening its clinical spectrum. In our case, the evidence of epileptiform discharges at EEG time-locked to the muscle jerks and the giant SEPs confirmed the cortical origin of the myoclonic jerks. The underlying mechanism remains to be elucidated. It is conceivable that the localization of the bullets may lead to cortical disequilibrium, resulting in the oscillatory epileptic activity characterizing EPC.

Conclusion: Overall, the present case is unique as it further enlarges the wide spectrum of etiologies underlying EPC. Intriguingly, it highlights the importance of carefully investigating its potential pathophysiology. Indeed, awareness of this unusual ictal semiology has important implications for diagnosis and treatment.

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## POSTURAL TREMOR IN JUVENILE MYOCLONIC EPILEPSY: A NEUROPHYSIOLOGIC ASSESSMENT

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Objectives: Juvenile myoclonic epilepsy (JME) is a genetic generalized epilepsy in which cortical hyperexcitability plays a major role [1]. Subjects with JME may depict postural tremor, typically considered as side effect of valproic acid (VPA) and underrecognized in clinical practice [2]. However, tremor has been recently related to cortical hyperexcitability in JME [2]. In this study, we aim to explore the neurophysiological features of postural tremor in JME.

Materials: We prospectively recruited 53 consecutive subjects with JME (32 female, mean age 30.22+12.99 years; mean age at onset 12.51+12.99 years) from October 2020 to May 2023.

Methods: All subjects underwent clinical, neurophysiologic assessment, 3T brain MRI. The neurophysiologic assessment included: standard electroencephalography (EEG), median somato-sensory evoked potentials (SEPs) with long-loop reflex (C-reflex), tremor analysis. Student's t test verified the differences among groups for normally distributed data otherwise Mann-Whitney was applied. Pearson's correlation coefficient verified association between variables for normally distributed data, otherwise Spearman's rho was applied. A p-value $<0.05$ was considered significant.

Results: Thirty-one/fifty-three (59%) subjects depict postural tremor with frequency of 8.05+1.56 Hz. Forty-four/fifty-three subjects had normal SEPs: 24 with postural tremor (JME+tremor: 14 female, mean age 32.90+14.33 years; mean age at onset 11.77+4.95 years); 20 without postural tremor (JME: 12 female, mean age 27.30+10.25 years; mean age at onset 13.58+7.63 years). The two groups matched for age at time of observation, epilepsy onset, gender, anti-seizures medications (ASMs) and VPA assumption. In the JME+tremor group, the short (N20, p=0.01; P22, p=0.01) and the long (P25, p=0.002) latencies, the central conduction time (N20-N13: p=0.005) were significantly increased than the JME group, regardless VPA. In the remaining 9/53 subjects (16.98%), we observed giant SEPs. Among these, 7/9 subjects (77.78%) with postural tremor displayed significantly higher N20-P25 amplitudes than those with giant SEPs in absence of tremor (p=0.01).

Discussion: Our findings demonstrated that subjects with JME exhibited postural tremor, regardless VPA assumption. Most important, our study suggests that tremor may underlie two different mechanisms: the association of tremor with giant SEPs led to identify a group of patients with cortical hyperexcitability signs. On the other hand, in the absence of cortical hyperexcitability, the postural tremor may characterize those patients with more altered thalamo-cortical pathways and primary somatosensory cortex.

Conclusions: Overall, our study confirms the theory of JME as a network disorder. A careful and systematic clinical and neurophysiologic assessment of tremor may help to detect phenotypes that are more homogeneous and clarify the pathophysiology underlying JME.
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## ROLE OF AMBULATORY EEG RECORDING IN JUVENILE ABSENCE EPILEPSY (JAE), JUVENILE MYOCLONIC EPILEPSY (JME) AND GENERALIZED EPILEPSY WITH TONIC CLONIC ALONE (GTCA)

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Objectives: In JME, the occurrence of longer epileptiform discharges (EDs) on prolonged ambulatory EEG (paEEG) displays a characteristic relationship with sleep-wake cycle (mainly at the awakening) and possibly predict seizure recurrence [1]. Less is known about JAE and GTCA [2]. The aim of this study is to compare clinical and EEG characteristics between these syndromes 1) describing the occurrence of seizures in long term follow up, 2) describing the EDs distribution over the sleep-wake cycle 3) defining the use of paEEG for predicting seizures.

Materials and Methods: Clinical data, generalized tonic clonic seizure (GTC) occurrences from the time of diagnosis and antiseizure regimen (ASM), were analysed by Kruskal-Wallis ANOVA and multiple comparisons with Bonferroni-correction. PaEEG recordings lasting 24 hours have been reviewed marking and measuring the length of each ED; sleep have been scored according to AASM criteria.

Results and Discussion: We included 34 and 22 JAE, 44 and 17 JME, 23 and 10 GTCA, for the 5 and 15 years follow up, respectively. The total number of GTCs was higher for GTCA compared to JAE and JME in the 5 years follow up period ($p=<0.01$) and to JAE in the 15 follow up period. In JME A higher number of adequate ASM-trials were required for seizure-freedom and drug resistance was more common in the longer follow-up (1% in JAE, 27% in JME, 0% in GTCA, $p<0.01$). Thirty-two, 20 and 23 paEEG with an available clinical outcome were analysed for JME, JAE and GTCA respectively. EDs were longer in wake but more frequent in sleep in all groups. None of the paEEG or clinical variables was able to predict GTC in JAE and GTCA. It was even more difficult to predict absences in JAE considering people often misreport their seizures [3]. Conversely, in JME, we found longest EDs as a marker of seizure risk. The absence of GTC predictors in GTCA and JAE may be due to underpowered testing, indeed, we calculated a sample size of 40 patients for each syndrome to assess the effectiveness of longer EDs in this regard.

Conclusions: JAE carried the more benign prognosis. GTCA could experience more GTCs in the first five years of follow up. JME required the highest number of adequate ASM trials and were more drug resistant. Sleep wake cycle has a similar effect on EDs. A small increase in sample size could help to establish if longest EDs predict seizures in GTCA and JAE, as it does in JME.
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## SOCIAL COGNITION IN THE SPECTRUM OF MESIAL TEMPORAL LOBE EPILEPSY

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Purpose: Increasing evidence suggests that social cognition is impaired in mesial temporal lobe epilepsy (MTLE). Refractory MTLE (rMTLE) has been found to affect (i) Theory of Mind (ToM), which is the ability to recognize and comprehend others' mental states, and (ii) facial emotion recognition. Milder forms of MTLE (mMTLE), characterized by response to antiseizure medications (ASMs) and seizure-freedom, have not been evaluated. The aim of this study was to analyze social cognition in the spectrum of MTLE.

Methods: Forty-five patients with MTLE (25 mMTLE, 25 rMTLE) were compared to 25 healthy controls (HC). ToM was explored using the Faux Pas Test (FP) and Reading the Mind in the Eyes Test (RMET). Facial emotion recognition was studied using the Ekman Faces Test (EFT). Additionally, a specific battery of tests was performed as a screening for cognitive and mood disturbances.

Results: Compared to HC, both mMTLE ($p=0.025$) and rMTLE ($p<0.001$) patients had lower scores on the RMET, with no differences identified between the two subgroups of patients. Moreover, only rMTLE patients had lower performances in FP recognition when compared to HC ($p=0.002$). In EFT, mMTLE patients had lower scores in fear ($p<0.001$) and anger ($p=0.013$) recognition, while rMTLE underperformed in happiness ($p=0.006$), sadness ($p=0.002$), fear ($p<0.001$), anger ($p=0.004$), and disgust ($p=0.005$) recognition. Considering all patients and the main clinical variables (age of onset, duration of disease, number of ASMs used, and seizure frequency), our findings indicate that an earlier age of onset independently predicts poorer performance on the EFT ($p=0.008$).

Conclusions: MTLE affects the circuitries of ToM and emotion recognition even in subjects with mMTLE, albeit to a more limited extent compared to rMTLE. This supports the idea that epilepsy itself, even when seizure control is achieved, could damage key areas involved in the complex neural circuits of social cognition.
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## LONG-TERM EFFECTIVENESS OF PERAMPANEL AS ADD-ON TREATMENT IN SLEEP-RELATED SEIZURES: REAL-WORLD EVIDENCE FROM A SINGLE CENTER

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Objectives: In view of the evidence in the literature about the positive effects of perampanel (PER) on sleep assessed by both objective and subjective parameters [1,2], the aim of the study is to verify effectiveness and discontinuation rate in patients with sleep-related epilepsy (SRE) [3] compared with patients with non-sleep-related epilepsy (nSRE).

Methods: Retrospective analysis of medical records of consecutive patients treated with PER in add-on at the Epilepsy Center of Policlinico Tor Vergata from 2018 to 2022. Only patients who completed diaries concerning the seizures frequency and who underwent periodic follow-up visits were included. Based on seizure onset pattern, patients were divided into SRE and nSRE. Patients were classified as seizure-free, responders (seizure reduction >50% compared to baseline) or non-responders at follow-up. Efficacy of PER and retention rate were compared in SRE vs nSRE patients and subgroups (focal epilepsy, generalized epilepsy, first-add-on, late add-on). Statistical analysis was set at $p > 0.05$.

Results: 94 patients (48M, 46F, 72 with focal epilepsy and 22 with generalized epilepsy) were included. According to epilepsy onset 49 were SRE (26 females, mean age 41.45±17.16 y.o., 38 with focal epilepsy and 11 with generalized epilepsy) and 45 nSRE (23 females, mean age 42.3±15.72 y.o, 34 with focal epilepsy and 11 with generalized epilepsy), who did not differ in age, age at seizure onset, number of previously taken anti-seizure medications (ASMs), monthly seizure frequency at baseline, mean PER daily dose (5.18±1.95 vs 5.2±1.67 mg/day) and follow-up (21.91 ± 19.93 vs 18.09 ± 17.61 months). PER was administered as adjunctive treatment and slowly titrated (2 mg every two weeks). A significant higher responder rate was observed in SRE than nSRE patients (87.76% vs 71.11%, $p<0.05$), with no significant differences in seizure freedom rate (55.1 vs 44.4%) and discontinuation rate (18.3% vs 15.5%). There were no significant differences when comparing subgroups (patients with focal vs generalized epilepsy, first add-on vs late add-on).

Conclusions: Our results demonstrate the effectiveness of PER as adjunctive treatment, especially in patients with SRE, which seems to be independent of the type of epilepsy and timing of PER introduction. The effectiveness maintained over the long term, can be attribute to both the direct and indirect effect of PER, probably mediated by the improvement of nighttime sleep quality.

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## ACUTE TOXIC-METABOLIC ENCEPHALOPATHY OR NONCONVULSIVE STATUS EPILEPTICUS? IFOSFAMIDE-INDUCED NEUROTOXICITY IN A PATIENT WITH TYPE 1 NEUROFIBROMATOSIS

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Introduction: Acute toxic-metabolic encephalopathy and nonconvulsive status epilepticus (NCSE) are two neurological emergencies both characterized by impairment of consciousness and altered electroencephalogram (EEG), whom differential diagnosis could be challenging for clinicians. Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic multisystem disorder characterized primarily by multiple cutaneous and plexiform neurofibromas; also, optic nerve, central nervous system and soft tissues can develop both benign and malignant tumors. Furthermore, compared with the general population, NF1 patients have twice the risk of developing seizures and epilepsy [1].

Case Report: Here we describe the case of a 47-years-old male affected by NF1, on neoadjuvant chemotherapy with ifosfamide and epirubicin for a retroperitoneal sarcoma, who came to our attention after his first tonic-clonic seizure. He had no previous history of epilepsy; he had undergone ifosfamide infusion the previous day. The patient was admitted to our emergency department; his brain computed tomography scan and a routine complete blood test were negative. On neurological examination, he presented an altered mental status with confusion, disorientation and ideomotor slowdown. No other neurological signs were detected. An EEG recording was performed, that showed the presence of diffuse generalized 2 Hz discharges with an atypical triphasic morphology, that promptly responded to diazepam administration. Electrical response was not followed by a fair clinical improvement. Even though Salzburg criteria for SENC were not satisfied [2], a first line antiepileptic therapy with levetiracetam was started (at 2000 mg/daily). The patient was admitted to our neurological department. His Magnetic Resonance Imaging was also negative. In the suspicious of a pharmacological acute neurotoxicity, according to our oncologists, a Methylthioninium chloride (or "methylene blue") infusion was started as antidote. The patient began to improve in the subsequent 24 hours. His EEG record also showed a clear improvement. We concluded for an acute toxic-metabolic encephalopathy caused by ifosfamide infusion.

Conclusion: Acute toxic-metabolic encephalopathy and NCSE could share both clinical and electroencephalographic features, as atypical triphasic waves [3]; an electrical response to benzodiazepine is not univocal suggestive for an epileptic origin. Ifosfamide-related encephalopathy is generally characterized by impaired consciousness, with disorientation, delirium, or lethargy and distinct pattern of generalized periodic discharges on EEG [4]. In our case, patient medical and pharmacological history, a negative brain imaging and a defined response to a specific antidote clarified the etiology.

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## ANTI-SOX1 ENCEPHALITIS AS A PREDICTOR OF OCCULTED CANCER: A CASE REPORT

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Paraneoplastic neurological syndrome (PNS) is a rare immune-mediated consequence of an immune cross response between a tumour and the nervous system. Interestingly, PNS can predates a cancer diagnosis, therefore determining whether anti-SOX1 antibodies (abs) are present could be useful for localizing underlying malignancy. We present a case of a 60-years-old man with an history of cognitive and memory impairments from about a month, hospitalized because of aphasia and confusion, followed by bilateral tonic-clonic epileptic seizures, evolving into a non-convulsive status epilepticus, which required anti-seizure therapy with Levetiracetam 3000 mg/die and Lacosamid 300 mg/die. Brain angio-CT excluded acute vascular events. EEG showed diffuse mild alterations of cerebral electrogenesis with prevalence on the left fronto-temporal region, without any epileptiform discharges. Brain MRI/Intracranial Angio-MRI showed multiple FLAIR-T2 hyperintensity areas in the retro and bilateral supratrigonal regions, mixed with small areas of reduced diffusivity of ischemic nature and a general aspect of chronic vasculopathy and microangiopathy-hypertensive of severe degree. The angiographic study was normal, biopsy of vessels was not performed. Lumbar puncture revealed mild pleocytosis (96 mononuclear cells), hyperproteinorrachia (126 mg/dl), very mild hypoglycorrhachia (43 mg/dl with pre-procedure stick 96 mg /dl), negativity of bacteriological, viral PCR, oligoclonal bands and autoimmunity panel. Laboratory investigations on serum excluded acute infectious and systemic rheumatologic diseases but revealed a positivity of anti-SOX1 abs at Line Blot immunoassays. Chest-abdomen CT-scan was negative for neoplasms but highlighted multiple mediastinal and mesenteric lymph nodes. Body-PET was negative for oncological findings but revealed hypometabolism of the right lateral prefrontal region, bilateral posterior cingulate and left inferior parietal area. Anti-SOX1 paraneoplastic autoimmune encephalitis was supposed, although the hypothesis of a cerebral amyloid angiopathy-related inflammation (CAARI) was not totally excludable. The patient received solumedrol 1g /day IV for 5 days and immunoglobulin IV followed by Rituximab 1000 mg IV, with only partial benefit and persistence of important space-time disorientation, aphasia, and apathetic state. PNS includes neurological syndromes such as paraneoplastic cerebellar degeneration (PCD), Lambert-Eaton myasthenic syndrome (LEMS), encephalomyelitis, sensory neuronopathy and paraneoplastic limbic encephalitis (PLE). The evidence of positivity to anti-SOX1 abs in association with one of these syndromes should lead to the suspicion of an occult neoplasm. High titres of anti-SOX-1 is associated with an improved response to treatment in patient with SCLC. Usually, patients with NSCLC or non-lung cancers have a better outcome. In light of the above, a clinical-radiological surveillance of patients with serum anti-SOX1 abs should be carried out to early detection of an occult tumour.

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## EPILEPSY OCCURRENCE AMONG HIV POSITIVE PATIENTS IN MOZAMBIQUE: A PILOT STUDY


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Introduction: Prevalence of epilepsy in sub-Saharan Africa (SSA) is higher compared to high-income countries due to consequences of bad delivery conditions, brain infections, stroke, road trauma and others. In Mozambique seizure disorders have been estimated between 1,6% and 4,9% among urban and rural population (2% standardized prevalence ratio) [1] in accordance with recent door-to-door prevalence studies in other SSA countries [2]. HIV is highly prevalent (>10%) in Mozambique, and it is a risk factor for epilepsy. Aim of this pilot study was to investigate epilepsy occurrence in a HIV positive population in Mozambique.

Patients and Methods: The study was conducted at the Disease Relief through Excellent and Advanced Means (DREAM) centre in Beira, Mozambique. DREAM is a public health program operating in ten SSA countries treating HIV/AIDS as well as non-communicable diseases as hypertension, diabetes, stroke, cancer and recently also epilepsy. To screen for epilepsy a previously validated questionnaire for SSA patients was employed [3]. The questionnaire contains five questions that were translated into local language. The healthcare personnel received two teaching courses on epilepsy followed by training with the questionnaire. To make the healthcare personnel more familiar with neurologic disorders and the epilepsy questionnaire repeated teaching was dedicated to better distinguish among tremors, involuntary movements, absence, loose of contact, loss of consciousness, syncope and others. Then the questionnaire was administered to 315 consecutive HIV+ patients. The questionnaire was considered "positive" if one or more of the answers to the 5 questions was YES. Positive questionnaires and patients were checked by a neurologist to confirm the diagnosis of epilepsy.

Results: 99,3% (313) of the screened patients were HIV+; 8 (2,53%) were positive at the epilepsy screening questionnaire. The diagnosis of epilepsy was then confirmed. No one of the healthcare providers had previously received a teaching course on epilepsy; less than one quarter of the healthcare providers knew that two thirds of people with epilepsy (PWE) become seizures free if properly treated and that the disease is more common among children and in HIV+ patients. After the teaching courses certain beliefs about the supernatural nature of epilepsy and that it could be contagious were still present among the healthcare providers.

Discussion: This study shows high epilepsy occurrence among HIV+ patients. Further studies are necessary to confirm this preliminary result. Integration of epilepsy and HIV treatment is necessary to accomplish the WHO-Intersectoral Global Action Plan on epilepsy in SSA.

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## QUANTITATIVE ANALYSIS OF EEG IN EPILEPTIC PATIENTS TREATED WITH PERAMPANEL


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Goals: Perampanel is a non-competitive antagonist for ionotropic glutamate receptor AMPA type primarily indicated for the adjunctive treatment of partial onset seizures with or without secondary generalization and for primary generalized seizures [1]. We evaluated the changes in the spectral maps induced by the therapy.
Materials: Ten patients followed by our center affected by focal and generalized epilepsy and who undertook perampanel therapy in ADD ON.

Methods: We recorded two serial EEG performed on day T0 (first prescription of the drug) and on day T1 (after one year). The basic traces were evaluated and the quantitative analysis was performed using "EEGLAB" on MATLAB extrapolating the spectral maps at the frequencies 4Hz, 8Hz, 10Hz and 12Hz for each patient in the two times. Then, a comparison study was carried out between the spectral maps at times T0 and at T1 on the same frequencies and studied in statistical comparison by means of a t-test, with the drug administration time as factor.

Results: There is a variation of the frequencies 4-8-10-12 Hz from T0 to T1 which becomes statistically significant for the faster frequencies in the mid-rear areas. Furthermore, there has been a reduction in crisis assessments at subsequent follow-ups.

Discussion: The chromatic variation of the spectral maps for a single patient on the frequencies 4-8-10-12 Hz, in agreement with the statistical analysis carried out on the same frequencies, shows that the perampanel is able to modify the excitability of the cortex with an increase in the frequencies rapids especially in the mid-rear areas. In general, the slowing of background EEG activity has been interpreted as an indicator of brain dysfunction and related to cognitive impairment. The increase of alpha frequencies on qEEG analysis is in agreement with previous results with consequent improvement of attentional functions and complex cognitive processes [2-3].

Conclusions: Increased alpha frequencies on qEEG analysis can clinically lead to increased attention and complex cognitive processes. Furthermore, the aforementioned modification of the cortical activity is in agreement with the reduction of the number of seizures in the patients analysed, confirming the efficacy of the drug.
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## CANNOT STOP MOVING! EPILEPSIA PARTIALIS CONTINUA AND SUBSEQUENT "BELLY DANCE" SYNDROME IN A PATIENT WITH NON-KETOTIC HYPERGLYCEMIA: A CASE REPORT

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Introduction: Severe hyperglycemia can be associated with a wide spectrum of movement disorders ranging from epilepsia partialis continua (EPC), chorea-ballismus, myoclonus, rubral tremor, dyskinesia, restless leg syndrome, hemifacial spasm to parkinsonism. These neurological manifestations might herald the onset of acute ketotic or non-ketotic complications among previously undiagnosed diabetics. Although hemiballismus-hemichorea has fairly been reported as a direct complication of hyperglycemia, EPC and diaphragmatic myoclonus (DM) are rare.

Case report: A 73-years old woman was admitted to our Emergency Room due to the sudden appearance of continuous unremitting clonic movements involving the left forearm. A concomitant electroencephalogram (EEG) recording showed rhythmic medium amplitude 5 Hz theta bursts evolving in 8 Hz monomorphic sequences with superimposed diphasic sharp waves, over the right central regions. A diagnosis of epilepsia partialis continua (EPC) was made. Blood analysis showed a marked non-ketotic hyperglycemia (827 mg/dL). The brain MRI showed a hypointense cortico-subcortical signal in T2-weighted and FLAIR images over the right central region. The CSF examination was normal. The patient was treated with intravenous (i.v.) boluses of Lorazepam 4 mg and subsequentially with Levetiracetam 3000 mg and Lacosamide 400 mg, with resolution of the symptoms. Two days later, the patient developed left hemi-diaphragmatic myoclonus. A further EEG was performed which was unremarkable. Jerk-locked back-averaging and EMG-EEG coherence analysis showed no correlation between brain activity and myoclonus. Myoclonus progressively improved after introducing Clonazepam at 2 mg/day and adjustment of glycemic values. At 6-month follow-up visit, anticonvulsant therapy was progressively suspended without the occurrence of any relapses.

Conclusion: EPC and DM may represent two neurological symptoms associated with hyperglycemia. Acute treatment of these condition consists of a combined therapy of ASM and adjustment of glycemic values. Long-term seizure prophylaxis is questionable.
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## ELECTRICAL SIGNAL MODULATION IN PATIENTS WITH FOCAL FRONTAL EPILEPSY AND BEHAVIORAL DATA

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Background: Patients with frontal deficits may have automatic and compulsive behaviors (Environmental dependency syndrome with utilization and imitation behaviors [1]). The aim of this study is to analyze whether subjects affected by focal frontal epilepsy present such dysregulations of frontal functions.

Materials: We recruited 9 patients affected by focal frontal epilepsy. We selected only patients treated with less than 3 antiepileptics who did not require the addition of another drug and that did not present more than 5 seizures in the previous twelve months. We also included a group of 9 healthy controls. All patients had a Mini Mental State Examination score $\geq$ 25.

Method: In a preliminary session, we evaluated frontal functions through a neurocognitive test battery (Frontal Assessment Battery, trail making test, the modified Wisconsin Card Sorting Test and the

Stroop interference task). Then, we used a paradigm that involves pointing on luminous targets placed in different positions on the surface of a table. Patients were instructed to touch luminous targets following specific array, that could be interfered or not by other lights. At the same time, we recorded the electroencephalogram; the signal was processed by averaging the periods preceding the execution of the motor task. The EEG signal elaborated was correlated with the data obtained during the motor task and with the scores of neurocognitive tests.

Results: Patients with focal frontal epilepsy have a significant tendency to increase the number of errors in pointing task compared to controls. We have found a large heterogeneity in the results of neurocognitive tests. The number of errors in pointing task was not related with neurocognitive tests score in correlation analysis.

Discussion: Our results support the hypothesis of behavioral frontal dysfunctions in patients with focal frontal epilepsy that causes a tendency to be distracted by spatially irrelevant targets during the execution of motor tasks. However, it is not possible to disentangle whether these results depend on drugs effects or disease per-se. Consequently, a further control study will be necessary in which we will include patients with the same therapy but without focal frontal epilepsy.

Conclusion: This study provides new insights about patients with focal frontal epilepsy and their tendency to have typical frontal lobe disorders (behavioral disorders) during the interictal phases.

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## IS BLOOD-BRAIN BARRIER IMPAIRMENT AN EARLY SIGN OR A RISK FACTOR FOR NEURODEGENERATION IN PATIENTS WITH LATE ONSET EPILEPSY OF UNKNOWN ORIGIN?

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Objectives: The incidence of new-onset epilepsy increases with age, especially over age 50, with 15-20% of late-onset cases with unknown aetiology (LOEU) [1]. Growing attention has been given to LOEU since an association with biomarkers of cerebral amyloidopathy has been demonstrated, as well as the possibility to develop a neurodegenerative disorder [2]. Blood-brain barrier (BBB) is essential for maintaining brain health, and in the early stages of neurodegeneration its dysfunction may concur to the neuropathological processes underlying cognitive impairment and dementia. In the present study, cerebrospinal-fluid (CSF)/serum albumin ratio, as a marker of BBB functionality [3], and biomarkers for Alzheimer's disease (AD) pathology were analysed in patients with LOEU compared to a group of elderly controls.

Materials: This observational retrospective study included patients diagnosed with LOEU who were admitted to the Epilepsy Centre of the University Hospital of Rome "Tor Vergata".

Methods: Patients were classified in accord with the classification of seizures by the International League Against Epilepsy – ILAE. Patients and controls underwent a neurological visit, cognitive evaluation (to exclude cognitive impairment) and a lumbar puncture for CSF biomarker analysis [β-amyloid42 (Aβ42); total-tau (t-tau); phosphorylated tau (p-tau); CSF/serum albumin ratio]. Lumbar puncture was performed at least 3 days following the last seizure.

Results: Thirty LOEU patients (mean age 68.63±7.78) and twenty-five controls (mean age 65.64±8.10) were included. LOEU patients showed lower CSF Aβ42 levels (p=0.036) and higher CSF/serum albumin ratio (p=0.011) than controls. Seven patients (23.33%) showed a pathological value of CSF Aβ42 and 8 patients (26.66%) had a pathological value of CSF/serum albumin ratio. No significant differences were found between LOEU patients and controls on CSF t-tau and p-tau levels. Considering the subanalysis between patients with pathological CSF Aβ42 compared to those with normal levels, no difference in CSF/serum albumin ratio was evident. Moreover, distributing patients on the basis of the t-tau/Aβ42 ratio suspected for AD (>0.52), no differences in the CSF/serum albumin ratio were evident.

Discussion: Patients with LOEU exhibit BBB impairment, with more than one fourth of patients showing pathological values of CSF/serum albumin ratio. This BBB alteration was independent of the pathological reduction of both CSF Aβ42 and CSF t-tau/Aβ42 ratio suspected for AD.

Conclusions: Whether BBB impairment may represent an early marker of neurodegeneration or a seizure-related manifestation inducing neuropathological processes in patients with LOEU remains an unresolved question and further studies also hypothesizing treatments aimed at preserving BBB integrity in patients with LOEU should be planned.

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## A CASE OF FOCAL STATUS EPILEPTICUS AS A PRESENTATION OF SMART SYNDROME

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Introduction: Stroke-like Migraine Attacks after Radiation Therapy (SMART) syndrome is a very rare late complication of radiation therapy in cerebral neoplasms. Approximately 150 cases have been reported in the literature.

Case presentation: We describe the case of a 60-year-old man with a grade 2 WHO oligodendroglioma of the left temporal lobe, presented in 2018 with an aphasic seizure with bilateral tonic-clonic evolution, and treated with neurosurgery, radiotherapy and chemotherapy at progression. After two years of complete seizure freedom with BRV 175 mg/day and stability on clinical-radiological follow-up, in November 2022, he developed a focal motor status epilepticus, associated with confusion, headache, and aphasia. Brain MRI showed extensive vasogenic edema at the site of the previous lesion and focal and meningeal contrast enhancement located in the anterior side of surgical cavity,

suggestive for disease recurrence. After the resolution of status epilepticus with BRV 200 mg, LCS 200 mg, and CNZ 8 mg and the implementation of steroid therapy, aphasia and confusion progressively improved and the aforementioned MRI contrast enhancement disappeared at follow-up.

Discussion and Conclusion: The clinical expression and the radiological pattern and evolution plus the dramatic response to corticosteroid therapy questioned the disease recurrence and supported the diagnosis of SMART syndrome. This entity, though extremely rare, should be considered among the differential diagnoses in the case of neurological deterioration in patients affected by cerebral neoplasms treated with radiotherapy, in order to choose the optimal treatment.
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## HIPPOCAMPAL AND STRIATAL SYNAPTIC DYSFUNCTIONS IN A MOUSE MODEL OF LAFORA DISEASE


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Background and objectives: Lafora disease (LD) is a rare, fatal and recessive form of progressive myoclonic epilepsy caused by mutations in the EPM2A or EPM2B genes [1,2], which code for laforin and malin respectively. Dysfunctions in either laforin or malin result in the formation, in the brain and other tissues, of aberrant polyglucosane aggregates, known as Lafora bodies, which constitute the histopatological hallmark of the disease and are considered the main cause of its progression [3]. The physiopathological mechanisms underlying LD are still poorly understood. We performed an electrophysiological study on a mouse model of LD in order to identify, in a temporal and region-specific manner, the molecular mechanisms underlying LD and driving its course.

Materials and methods: We performed ex vivo patch-clamp and extracellular recordings to investigate possible alterations of the intrinsic membrane properties, neuronal excitability and synaptic transmission and plasticity, in two different brain areas particularly involved in the mechanisms of epileptogenesis and synaptic plasticity (cognitive and procedural): the hippocampus (dentate gyrus -DG- and CA1) and the nucleus striatum.

Results: Our electrophysiological data demonstrated enhanced excitability and lower epileptic threshold, along with pathological LTP, only in the DG of LD mice, whereas basal membrane properties and synaptic plasticity in CA1 were not impaired. In the nucleus striatum, we found alterations of the cortico-striatal transmission and LTP impairment.

Discussion: Our electrophysiological data demonstrated a region-specific impairment of the hippocampus, in which the hyperexcitability of the granule cells is at the basis of the hyperplasticity observed, which is related to cognitive deficits. In the nucleus striatum we demonstrated age-dependent alterations of synaptic transmission and plasticity possibly related to cortico- and nigro-striatal network dysfunctions. Conclusions: Our electrophysiological study lead to the identification of region-specific and time-dependent alterations in a mouse model of LD. The identification of the mechanisms underlying hyperexcitability and neurodegeneration in these animal models is fundamental not only to define possible therapeutic targets, but also to delineate a "time window" in which a therapeutic approach may be most effective.
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## A CASE OF BRAIN ABSCESS CAUSED BY NOCARDIA ABSCESSUS


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Introduction: Nocardia are aerobic gram-positive bacteria that can infect humans, mostly immunocompromised individuals, through inhalation or inoculation into the skin. Its epidemiology is not well established, even if most of the cases were signaled in United States, India and Mexico. An immunocompromising state, due for example to immunosuppressive medications, HIV infection or primary immune deficiencies, is the principal predisposing condition to nocardial infection. Dissemination occurs in 20-50% of cases. The brain abscess is the most common form of dissemination disease involving the 20-58% of the infected by Nocardia, even if it constitutes only the 1-2% of all brain abscess. The cerebral lesions may manifest with focal neurologic deficits, altered mental status, headache, seizures and ataxia. Brain MRI typically shows ring-enhancing lesions which can be surrounded by edema in the 40-50% of cases.

Case report: We present the case of a 69-year-old man, affected by a B-cell Non-Hodgkin Lymphoma treated with chemotherapy (CHOP-Rituximab) in 2003, arrived to our emergency department for confusion and bradipsychia. When he was hospitalized in Neurological Clinical, he presented focal seizures at left arm and leg associated with head version and impaired awareness. A first cerebral CT scan showed lesions compatible with metastasis. The radiological exam was repeated using contrast and multiple ring-enhancing lesions were revealed. Furthermore, an enhancing pseudo nodular lesion was found in the right lung at chest-abdomen CT scan with contrast. Laboratory examinations showed non alterations in oncological markers but low value of CD 4+ lymphocytes indicating an immune reconstitution post chemotherapy. Hence, cerebral lesions were better characterized through brain MRI which displayed perilesional edema, central hyperintensity on diffusion-weighted images and ring enhancement. This aspect was suggestive both for metastasis and for brain abscess. Culture of bronchoscopy was decisive for the diagnosis. It demonstrated the presence of a Nocardia abscesses on lung. Antibiotic therapy, based on Imipenem, was began. The patients presented a clinical improvement

and was discharged after two weeks. Actually, he was in radiological follow-up.

Discussion: Thanks to radiological exams and cultural examination, we could remove the suspect of cerebral metastasis and make diagnosis of Nocardia brain abscess in an immunocompromised patient with an oncological history.

Conclusions: Nocardia brain abscess is a rare but possible cause of cerebral expansive process. Clinicians have to consider this hypothesis, especially in immunocompromised subjects, in order to start as soon as possible a correct antibiotic therapy.

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## BENIGN ADULT FAMILIAL MYOCLONUS EPILEPSY (BAFME) PRESENTING AS FAMILIAR TREMOR AND PHOTOMYOCLONIC RESPONSE


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Objectives: Benign adult familial myoclonus epilepsy (BAFME) is an autosomal dominant condition characterized by onset in the second-third decade of life, tonic-clonic seizures, and spontaneous or stimulus-sensitive cortical myoclonus at a variable frequency [1]. Mood disorders, predominantly anxiety and depression, are commonly observed. The clinical course is overall benign with a normal life expectancy. However, the severity of cortical tremor and myoclonus usually increases with aging [2]. We describe a family with a clinical pattern resembling benign adult familial myoclonus epilepsy phenotype with hand tremor as prominent feature.

Materials: a 44-year-old woman presented to our Epilepsy Center with a 4-year history of involuntary jerks involving the upper limbs. She referred a positive family history for hand tremor and epilepsy, being the mother, maternal aunt, uncle, and grandmother affected. At the age of 43 years, she developed hand tremor and dizziness. Concomitantly, the arm jerks worsened over time and an electroencephalographic recording (EEG) revealed diffuse spike-waves. In the following months, she experienced clinical worsening, having a more severe hand tremor with superimposed myoclonic jerks involving all limbs and face.

Methods: We performed a comprehensive clinical and laboratory work-up, including EEG and polygraphic video-EEG recording, somatosensory evoked potentials (SEPs), cortical reflex (C reflex), and 3-T brain magnetic resonance imaging (MRI). Genetic investigations were also performed on other family members. Informed consent was obtained according to the protocols approved by the local ethics committee.

Results: At admission, neurological examination revealed severe postural and action hand tremor, as well as myoclonus of the upper limbs during action. EEG showed diffuse spike-waves and photomyoclonic response at low-medium stimulation frequencies. The polygraphic EEG recordings demonstrated hand tremor with myoclonic jerks of upper limbs related to spike-waves. SEPs study showed giant potentials. The 3T-brain MRI was unremarkable. Therefore, an antiseizure therapy with levetiracetam at 2000 mg/day and clonazepam 0,5 mg/day was started.

Discussion: BAFME is rare form of epilepsy syndrome, with infrequent generalized tonic-clonic seizures, myoclonus and cortical tremor. The cortical tremor often resembles the clinical characteristics of essential tremor, leading to misdiagnosis. Our study illustrates the heterogenous phenotypes in BAFME, ranging from milder phenotypes to more severe clinical phenotypes.

Conclusions: Our findings confirm the cortical origins of hand tremor, besides of myoclonic jerks. Furthermore, considering the positive family history with hand tremor and epilepsy, we interpreted our family case as clinically indicative of BAFME, a rare form of epilepsy syndrome, often misdiagnosed.

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## SLEEP DISORDERS IN PEOPLE WITH EPILEPSY. AN OBSERVATIONAL STUDY IN A TERTIARY SLEEP AND EPILEPSY CENTER


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Objectives. To describe the prevalence and associations of sleep disorders in people with epilepsy (PWE) in a tertiary Sleep and Epilepsy center.

Materials: All patients admitted to the Sleep and Epilepsy outpatient clinic of the IRCCS Ospedale Policlinico San Martino from January to April 2023 were asked to fill three self-administered sleep questionnaires, namely the Pittsburgh Sleep Quality Index (PSQI) along with its subitems (total score, duration of sleep, sleep disturbances, sleep latency, day disfunction, sleep efficiency, sleep quality, need of sleep-medication), the Epworth Sleepiness Scale (ESS), and the Insomnia Severity Index (ISI). The following clinical characteristics of PWE were systematically collected: seizure freedom (yes/no), mono/polytherapy, need for changes in anti-seizures medication (ASM; yes/no), new versus old generation ASM, number of ASM, and changes in ASM in the last visit (yes/no).

Methods: First, the prevalence of abnormal questionnaires' scores in PWE was assessed. Then, the associations between sleep and epilepsy features were evaluated.

Results: Among the 191 patients assessed, 85 (52 females, 56±21yo) had a diagnosis of epilepsy, of whom 4.71% had abnormal ISI, 18.82% abnormal ESS%, and 62.35% abnormal PSQI. Concerning PSQI sub-items, 25.88% had abnormal sleep duration, 84.71% sleep disturbances, 45.88% abnormal sleep latency, 18.82% daytime disturbances, 84.71% abnormal sleep efficacy, 12.94% reported abnormal sleep quality, and 17.64% reported the need for sleep-inducing medications. Sleep quality abnormalities were more frequent in patients without (21.7%) compared with patients with (2.6%) seizure freedom ($p=0.010$), and in patients with (24.1%) compared with those without (7.1%) the need of a change in ASM ($p=0.040$). Patients with the need of ASM changing also reported a higher frequency of sleep

disturbances (96.6%, p=0.030) and daytime disturbances (31.0%, p=0.046). At multivariate analysis, seizure freedom inversely correlated with sleep quality abnormality and the use of old generation ASM, and directly with monotherapy ($p<0.05$).

Discussion. Sleep disorders can be both a consequence and a cause of epilepsy [1]. In agreement with current literature [2], we found a high prevalence of sleep disorders in persons with epilepsy. Interestingly, while PSQI and ESS were frequently found abnormal, ISI was normal in the vast majority of patients. Epilepsy features were variably associated with sleep disorders, but as expected, seizure freedom was associated with a better sleep quality.

Conclusion: A systematic and standardized evaluation of sleep quality in patients with epilepsy is needed, especially in patients without seizure freedom.

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## PROGNOSTIC PATTERNS AND LONG-TERM SEIZURE OUTCOME OF NON-SURGICALLY TREATED PATIENTS WITH CORTICAL DYSPLASIA

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Objectives: Malformations of cortical development represent a common cause of surgically remediable focal epilepsy [1]. However, little is known regarding the long-term prognosis of non-surgically treated patients. The objective of the study was the identification of prognostic patterns and long-term seizure outcome in a cohort of patients with neuroimaging features suggestive of cortical dysplasia who did not undergo surgery.

Materials: Data from patients with focal epilepsy followed from 1975 to 2022 were retrospectively reviewed. We included patients with MRI-documented cortical dysplasia who did not undergo surgical treatment due to their choice or clinical reasons, followed up for more than 5 years from epilepsy diagnosis.

Methods: After revision of their electroclinical data, we defined the following prognostic patterns: early remission (no seizures within 2 years from diagnosis), late remission (after 2 years), relapsing-remitting (2 periods free of seizures for more than 2 years), non-remitting. Univariate analysis was conducted to identify electroclinical variables associated with remission.

Results: 38 patients were included (18 females and 20 males). The median age at diagnosis was 10 years, with a median age at the last evaluation of 49.5 years and a median follow-up of 11.5 years. The most common prognostic pattern observed was non-remitting (52.6%), followed by relapsing-remitting and late remission patterns (18.4% each), and by early remission (10.5%). 16% of patients presented seizures with daily frequency. Remission was associated with the parietal localization of the dysplasia, whereas no remission course was associated with the presence of focal seizures with impaired awareness and epileptiform abnormalities on baseline EEG ($p < 0.05$).

Discussion: While surgery represents the gold-standard treatment for cortical dysplasias [2], our findings indicate that up to 30% of patients can achieve remission with anti-seizure medications. This is consistent with previous studies examining prognostic patterns in focal epilepsy [3]. The presence of focal seizures with impaired awareness and epileptiform abnormalities on baseline EEG may be associated with the non-remitting pattern because of a wider epileptogenic network involved in this subgroup of patients.

Conclusions: Our study highlights the heterogeneity of prognostic patterns of patients with non-surgically treated cortical dysplasia and shows that remission can be achieved in up to 30% of patients.

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## HOME ULTRA-LONG-TERM EEG MONITORING IN RARE EPILEPSIES: AN OPEN-LABEL PROSPECTIVE STUDY USING MINIMALLY INVASIVE WEARABLE EEG DEVICE. THE EMIRE TRIAL

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Objectives: A fundamental aspect that limits the clinical management of patients with difficult to treat epilepsy is the phenomenon of the undersampling of seizures. It is in fact known that ascertaining the frequency of seizures from the patient's subjective report diaries detects about 50% of the seizures that actually occur, with great variability (i.e. seizures in sleep are not reported in 80% of cases). To overcome these limits, a long-lasting recording of EEG activity is expected to greatly improve our clinical management of the patient.

Methods: This project aims to develop a personalized medicine approach to improve the management of rare epilepsies and developmental and epileptic encephalopathies (DEE) by means of ultra-long-term EEG monitoring. We will use a minimally invasive subcutaneous implanted EEG device (sqEEG) to record the EEG activity for 3 to 6 months, while the patient is at home.

Results: We expect and test the following hypothesis: (1) subscalp EEG is be able to correctly detect more than 80% of the seizures of the enrolled patients compared with the gold-standard represented by traditional video-EEG monitoring. (2) that ultra-long-term home monitoring will be able to detect more ictal events than the patient's clinical diary. (3) that the information obtained from the subscalp EEG can be translated into useful information in the patient's clinical management that are not gained by the standard of care. Specifically, in assessing the response to drug treatments, and in being able to identify patterns for predicting seizure risk on an individual basis. (4) we expect the device to be well tolerated and more than 80% of subjects to be able to terminate home monitoring for 3-6 months.

Discussion: The development of subscalp EEG devices is motivated by an unmet clinical need that neither scalp nor intracranial EEG addresses. This may have many advantages for personalized epilepsy care. These goals are of particular relevance in patients with rare epilepsies and DEE. If the expected goals are confirmed, clinical trials using this technology can be developed to objectify the effects of pharmacological interventions from a precision medicine perspective in these patient populations.

Conclusions: A majority of patients and caregivers want some form of seizure monitoring, either at night only or 24/7, to feel safer and less stigmatized. This is where subscalp EEG is most likely to improve the everyday life of a person with epilepsy and DEE in particular.

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## A CASE OF SERONEGATIVE AUTOIMMUNE LIMBIC ENCEPHALITIS WITH SUPERIMPOSED HYPERKINETIC SYNDROME DUE TO PHENYTOIN TOXICITY

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Background: Autoimmune limbic encephalitis (ALE) is an increasingly recognized cause of refractory status epilepticus. Seronegative forms without any identifiable antibody constitute a major subtype of ALE and encompass a heterogenous group of disorders. Treatment requires antiepileptic drugs and immunotherapy. Antiepileptic combination therapy is burdened by many adverse effects, including neurological ones, which can smear the clinical picture and sometimes be hardly distinguished from those due to the underlying neurological disorder.

Case report: We report the case of a previously healthy 39 y/o woman who was hospitalized in Belgium for cluster seizures, impaired consciousness and repetitive facio-brachial dystonic episodes, a few days after developing fever and skin rash with a positive Influenza B swab. Seizures hastily evolved into a refractory status epilepticus requiring various combinations of sedative and antiepileptic drugs. MRI, EEG, clinical and laboratory findings led to a diagnosis of definite ALE according to Graus criteria, with bilateral involvement of mesial temporal lobes and basal ganglia. The patient tested negative for infectious and immuno-rheumatological diseases and for antibodies against CNS intracellular or cell-surface antigens in blood and CSF. After a failed high-dose steroid treatment, she was successfully weaned from deep sedation following five sessions of plasma exchange. Final seizure control was achieved with four antiepileptic medications, including phenytoin, at its maximum allowed dosage (600 mg/day). Then the patient was transferred to our Unit for additional treatment and care. She presented executive, language and memory deficits, and hyperkinetic syndrome with sporadic dystonic-like limb postures. Antiepileptic drug monitoring found toxic phenytoin blood levels (40.5 mg/L, therapeutic range 10.0-20.0); therefore this drug was gradually discontinued with complete resolution of hyperkinesia. Given the persistent pleocytosis in CSF and residual increase in hippocampal FDG-uptake at PET scan, further immunotherapy was started, firstly with IV immunoglobulins (2 g/kg in 5 days), then with Rituximab (375 mg/m2 once a week for 4 weeks), with gradual improvement of cognitive impairment. The patient was finally discharged with a combination of only two antiepileptic medications, lacosamide and sodium valproate, without seizure recurrence in the subsequent month.

Conclusions: This case provides a useful insight into management pitfalls in ALE, in terms of efficacy and tolerability of both immunotherapy and antiepileptic drugs, burdened by many insidious neurological side effects. Wise medication and clinical choices are thus essential to discern drug adverse reactions from manifestations of the underlying disease.

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## DRUG-RESISTANT TEMPORAL LOBE EPILEPSY DUE TO HIPPOCAMPAL SCLEROSIS AND SEIZURE OUTCOME AFTER SURGERY: PREDICTIVE VALUE OF ICTAL EEG PATTERNS

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Background and aims: To assess the predictive value of ictal EEG pattern on seizure outcome in a group of consecutive subjects with drug-resistant temporal lobe epilepsy associated to hippocampal sclerosis (TLE-HS) who underwent presurgical evaluation and subsequent resective surgery (anterior temporal lobectomy).

Methods: We retrospectively included all consecutive adult subjects with refractory TLE-HS who underwent presurgical assessment, subsequent resective surgery and met the following inclusion criteria: 1) at least one seizure recorded during presurgical video-EEG study and available for revision; 2) histological confirmation of hippocampal sclerosis 3) at least 12 months post-operative follow-up. Based on literature data, the following different EEG patterns were considered for case classification: Type 1: antero–temporal 5–9 Hz discharge, with a minimum duration of 10 seconds, associated with a highly probable onset in the mesial temporal structures; Type 2: temporal 2–4 Hz discharge, with a minimum duration of 10 seconds, associated with a highly probable onset in the lateral temporal structures; Type 3: combination of type 1 and type 2 EEG patterns, indicating an early involvement of both mesial and neocortical structures. Demographic, clinical data and seizure outcome were systematically collected; subjects who were in Engel Class Ia at the last visit were classified as having a favorable outcome.

Results and Conclusions: A total of 111 TLE-HS cases surgically treated were included in this study: 59 males (65.5%) and 52 females (34.5%). Mean number of recorded seizures: 2.8 (range 1-10). In 69/111 subjects classified with Type 1 pattern, 57 (82.7%) were seizure free, 12 (17.3%) experienced post-operative seizures (in 3/12 cases only aura were reported). By contrast, 42 subjects were classified having Type 2 and 3 patterns. A favorable outcome were reported in 12 (28.6%) cases, seizure persistence in 30 (71.4%). The mesial pattern is associated with a better surgical prognosis compared to other ictal EEG patterns. This study provided preliminary data on the role of EEG seizure pattern as a possible predictor of post-operative outcome in drug resistant TLE-HS. In particular, this data could suggest a more "discrete" epileptogenic zone in the Type 1 group, limited to the hippocampal structures. By contrast, the Type 2 and 3 patterns may suggest, in selected cases, the opportunity to perform further presurgical

investigations, such as brain PET or exploration by using intracranial electrodes.

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## CLUSTER TONIC-CLONIC SEIZURES IN AN LGI1 ENCEPHALITIS: A CASE REPORT

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Objectives: LGI1 encephalitis represents the second most frequent subtype of autoimmune encephalitis. Clinical features usually include memory impairment and faciobrachial dystonic seizures, but tonic-clonic or focal aware seizures are frequently described [1].

Materials: We presented the case of a 66 years old woman admitted to our ER because of a first episode of tonic-clonic seizure at home, followed by two more episodes during the delivery to hospital. A month before she complained of influenza-like symptoms, followed by confusion, disorientation and visual hallucinations.

Methods: Electronic medical records, neuroimaging, neurophysiological reports and laboratory results were reviewed.

Results: After a first line ASM with midazolam the patient remained in a status of impairment of consciousness. She was intubated and taken to the Intensive Care Unit. She started ASM with levetiracetam with a complete regression of seizures. The EEG shown a diffuse cerebral dysfunction, without epileptic abnormalities. The plasma sodium level upon admission was 136 mmol/L. The patient was extubated the next day and she was subjected to a lumbar puncture. The preliminary analysis of the liquor did not show pathologic results or evidences of infections. At the brain MRI there was evidence of T2/FLAIR hyperintensity in the left temporo-mesial cortical-subcortical region, suspected for auto-immune encephalitis. The patient was admitted to the Neurology Department in good conditions: she was confused, disoriented in time with a short term memory impairment. She was subjected to immunotherapy with methylprednisolone 1g/day for a week, follow by 3 cycles of plasmapheresis. The brain FGD-PET shown an hypermetabolism in the left mesial temporal and parahippocampal regions. A paraneoplastic syndrome was excluded by negative results of total body imaging, such as CT and FDG-PET. After a few days it was confirmed the presence of LGI1 auto-antibodies in liquor and serum.

Discussion: The patient was discharged after 30 days of hospital stay with an high dose of oral dexamethasone. After 6 months there remained a significant short term memory deficit. The subsequent EEGs showed a bitemporal slowing activity. During the follow up, the dosage of levetiracetam and dexamethasone was gradually reduced until the medication was discontinued.

Conclusion: Cluster tonic-clonic seizures could be the clinical presentation of anti-LGI1 encephalitis. Specific imaging and neurological tests, included the lumbar puncture, must be performed to obtain the diagnosis. Immunotherapy with steroids is usually necessary to achieve clinical improvement. Long-term memory impairment is a common finding in these patients [2].

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## EPILEPSY POWER: SURVEYS FROM A MULTICENTRIC EUROPEAN STUDY ABOUT EPILEPSY AND EMPLOYMENT

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Objectives: Epilepsy affects all aspects of individual life, including employment. Despite good seizure control, unemployment and underemployment are more common among people with epilepsy (pwE), for several reasons including stigma and misconceptions. The Epilepsy-POWER is a European project, financed by the programme Erasmus+, involving five Countries (Italy, Bulgaria, France, Ireland, Germany), aimed to improve the workplace inclusion of PwE in Europe. We created surveys to explore employment conditions among European pwE and conceptions of Higher Educational Institutions (HEI).

Methods: We developed two anonymous surveys for each target group: pwE and HEI. Questions focused on demographic and clinical features, employment, stigma and disclosure in workplace for pwE, general knowledge and attitudes about epilepsy for HEI. We translated surveys from English in each partner language (Italian, French, Deutsch, and Bulgarian) and shared them throughout e-mails and official websites.

Results: We collected 567 answers from PwE (183 from Italy, 38 from Ireland, 123 from France, 25 from Germany and 198 from Bulgaria) and 291 from HEI (100 from Italy, 14 from Ireland, 67 from France, 10 from Germany and 100 from Bulgaria). For pwE unemployment rates were 7,9% in Italy, 6,7% in Ireland, 8,5% in France, 15% in Germany, 9% in Bulgaria; while people employed full time were 42,9% in Italy, 53% in Ireland, 31,7% in France, 40% in Germany, 47,9% in Bulgaria. As for disclosure, in Italy 24,2% of pwE did not disclose their condition at work; in Ireland 17,9%; in France 21%; in Germany 15% and in Bulgaria 48,5%. About the 70% of pwE in all countries thought that stigma impair finding and keeping a job. As regards HEI, most of respondents defined epilepsy as a neurological disorder, treatable in most cases, in all countries. They also thought that unemployment is more common among pwE. Although most respondents have seen a seizure in person, in some countries (Germany and Bulgaria), they did not know how to give medical aid to a person experiencing a seizure.

Discussion: In this study we illustrated unemployment rates in five European countries, and we proved that stigmatization and disclosure still stand as issues for pwE in workplaces. Complete knowledge of epilepsy and its consequences remains challenging for HEI.

Conclusion: Exploring pwE work conditions and HEI perspectives could help to spread a good culture of inclusion and fight marginalization of pwE in workplaces, allowing them to get the right job position and better quality of life.

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## MANAGEMENT OF NON CONVULSIVE STATUS EPILEPTICUS: DATA FROM THE STATUS EPILEPTICUS PROJECT IN EMILIA-ROMAGNA (STEPPER)

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Objective: To evaluate the incidence, clinical features and outcomes of Non Convulsive Status Epilepticus (NCSE) in Emilia-Romagna.

Materials: Prospective multicentric observational study of adults patients with NCSE. Data collection occurred from October 2019 to October 2021 in 17 Italian neurology units.

Methods: The diagnosis and classification of NCSE were performed according to the 2015 ILAE proposal. The information collected for every NCSE included: demographic variables, site and date of SE observation and onset, etiological and semeiological classification of SE, duration of SE before treatment, ASMs and any other therapies used to treat SE, SE resolution and type of treatment response, functional outcome and mortality either at hospital discharge and at 30 days from SE onset. Categorial variables were analysed with X2 test, whereas parametric or non-parametric tests were used to analyse continuous variables, as appropriate.

Results: 285 NCSE episodes were included (64% female; mean age: 71.6 ± 14.9 y/o), 157 of whom occurred outside the hospital setting. Cerebrovascular diseases (80/285; 28%), brain tumors (25/285; 9%) and anoxic brain injury (21/285; 7%) were the most frequent causes of NCSE. Median times from NCSE onset to EEG execution and treatment initiation were 11.1 and 10.3 hours, respectively. Comparing NCSE with in-hospital and out-of-hospital onset, both times were significantly more delayed in the latter group (9.2 vs 11.8 hours [$p = 0.009$] and 9.1 vs 11 hours [$p = 0.041$]). Even if 47% of cases were refractory to first- and second-line agents, SE finally resolved in all but 15 cases. On the other hand, 30-day mortality rate was 24% and it significantly increased in case of in-hospital onset ($p=0.0001$), severe consciousness impairment ($p<0.0001$), acute symptomatic aetiologies ($p=0.01$) and SE refractoriness ($p=0.009$).

Discussion: Status Epilepticus (SE) is a neurologic emergency with high mortality and morbidity rates. As concerns epidemiology, clinical and demographic features of NCSE in Emilia-Romagna patients are consistent with the results of previous studies [1-2]. Diagnosis and treatment of NCSE frequently required several hours, leading to a delay in treatment initiation especially in case of out-of-hospital onset. However, NCSE aetiology and clinical features, were the main predictors of short-term outcome.

Conclusion: Our prospective multicentric study confirmed that the diagnosis and treatment of NCSE are challeging with extremely prolonged time-to-evaluation and treatments times. NCSE aetiology and clinical features, as well as treatment refractoriness, are confirmed to be strong predictors of short-term outcome.

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## EFFICACY AND TOLERABILITY OF PERAMPANEL IN ADULT PATIENTS WITH DRUG-RESISTANT EPILEPSY AND SEVERE INTELLECTUAL DISABILITY

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Rationale and Objectives: To evaluate the efficacy and safety of Perampanel (PER) in add-on in adult patients with drug-resistant epilepsy and severe intellectual disability. Irritability and other psychiatrics symptoms are counted among the common adverse effects of this drug, and patients with intellectual disabilities are at higher risk of developing such behavioural disorders.

Methods: Retrospective analysis of patients with severe intellectual disability treated with PER at the Epilepsy Center of Policlinico Tor Vergata in Rome from 2018 to 2022.

Results: 14 patients (9 males and 5 females, with a mean age of 28.64 years (range 19-58) and mean age at epilepsy onset of 7±5.9 years), including 5 with severe autism, 2 with genetic mutations, and 5 with a history of perinatal distress. All patients with drug-resistant epilepsy (4 generalized, 3 focal with structural etiology, 6 focal with unknown etiology) with mean number of drugs previously taken 2.8±1.42. PER in add-on, at mean dosage of 4.85±2.32 mg/day, induced a significant reduction in monthly seizure frequency (from 7.46±15.45 vs. 0.8±2, $p< 0.05$) with 92.8 % responders and 78 % seizure free patients. Mean follow-up of 23.14±19 months with only one case of discontinuation. The caregiver was administered the CGIC (Clinical Global Improvement or Change) (2), showing global clinical improvement after therapy with PER in 12 out of 14 patients. Behavioral disturbances evident at baseline in 5 of 14 patients, remained unchanged or improved in 4 of 5 cases. The occurrence of irritability and/or aggressiveness was not observed in the remaining 9 patients.

Conclusions: PER, even at low doses, shows long-term efficacy and safety in a particular and fragile population at high risk for psychiatric comorbidities.

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## THE ROLE OF MACHINE LEARNING IN PREDICTING SEIZURE RECURRENCE AFTER A DE NOVO STATUS EPILEPTICUS

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Objectives: The incidence of seizure recurrence after Status Epilepticus (SE) in patients without a history of epilepsy (de novo SE) is unknown to date, so tools to predict it and guide clinicians' decisions are lacking [1]. Machine Learning (ML) is the artificial intelligence application providing systems the capability to learn from experience without being explicitly programmed. In this study, we explored the ability of ML models to predict seizure recurrence after a de novo SE.

Materials and Method: Consecutive SE patients aged ≥16 years without previous history of seizures admitted to Vall d'Hebron University Hospital (Barcelona, Spain) from 2011 to 2021 were reviewed. Different Machine Learning techniques (k-NN, Naïve Bayes, Artificial Neural Networks, Support Vector Machines, Decision Trees, Random Forests) and the classic Logistic Regression (LR) model were applied to develop one- and two-year predictive models of seizure recurrence. 70% of the total sample was randomly selected to train the models; the remaining 30% was used for validation. The area under receiver operating curves (AUROC) with 95% confidence interval (95%CI) were performed to assess their predictive capability.

Results: 268 patients were included, of which 73 (27.2%) and 88 (32.8%) had seizure recurrence within one and two years, respectively. Factors significantly associated with two-year seizure recurrence were progressive symptomatic SE etiology ($p<0.001$) and time from diagnosis to SE treatment >1.5 hours ($p=0.001$). Among ML techniques, all were superior to the LR model in predicting two-year seizure recurrence (overall accuracy >70%, compared to 67.2% in the LR model). K-NN (AUROC 0.801, 95%CI = 0.687–0.915), Support Vector Machines (AUROC 0.803, 95%CI = 0.693–0.914), Random Forests (AUROC 0.822 (95%CI = 0.709–0.935) algorithms proved the best predictive ability in the validation dataset, showing a better performance than the LR model (AUROC 0.738, 95%CI = 0.618–0.858). No ML technique was superior to LR in predicting one-year seizure recurrence.

Discussion and Conclusions: In our study, ML techniques were superior to the LR model in predicting two-year seizure recurrence after SE in adults without previous history of seizures.

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## PERAMPANEL AS ONLY ADD-ON EPILEPSY TREATMENT IN ELDERLY PATIENTS: REAL-WORLD DATA FROM RETROSPECTIVE, MULTICENTER, OBSERVATIONAL STUDY

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Background and aims: Epilepsy represents the third most common neurological diagnosis in elderly patients after dementia and stroke. Management of epilepsy in elderly individuals represents a likely common situation in daily practice, due to the rapidly growing of this segment of population [1]. Perampanel (PER) is a third generation ASM, highly selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist. The aim of this study was to assess 12-month effectiveness and tolerability of adjunctive Perampanel (PER) in elderly patients (≥65 years of age) with focal or generalized epilepsies treated in a real-world setting.

Materials: This study was a subgroup analysis of elderly patients involved in a previous 12-months multicenter, retrospective, longitudinal study, including adult patients receiving PER as only add-on treatment (PEROC study) [2].

Methods: We evaluated seizure response (≥50% reduction of frequency), seizure-freedom, retention rate, incidence of adverse events (AEs) and rate of treatment discontinuation at 3, 6 and 12 months after PER introduction.

Results: The sample included 64 subjects (34 female, 53.1%; median age: 74.6 years), with focal (87.5%), generalized (10.9%) and undetermined (1.6%) epilepsy. Median daily doses of PER at 3, 6, and 12 months were 4, 6, and 8 mg, respectively. Only 27 patients reached the 12th month follow-up visit. At 12 months 18/27 (66.7%) patients had at least 50% reduction of seizure frequency, with a seizure freedom rate of 9/27 (33.3%). Retention rate was 80%, 84%, and 86% after 3, 6, and 12 months, respectively. The reasons of treatment withdrawal were insufficient efficacy in 3 (4.7%) patients and poor tolerability in 7 (10.9%) patients. AEs were reported by 27 (42.2%) patients, the most common being dizziness and irritability. One patient only had a serious AEs (suicidal ideation).

Discussion: All efficacy measures confirmed the usefulness of PER as single add-on treatment. The high retention rates and the low rate of serious AEs proved that the treatment with PER was effective and well tolerated in elderly patients.

Conclusions: In elderly patients with epilepsy, adjunctive PER may represent a suitable therapeutic option.

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## DESCRIPTION AND PHENOTYPIC CHARACTERIZATION OF A CASE OF DRUG-RESISTANT EPILEPSY ASSOCIATED WITH A DE NOVO MUTATION OF THE MED13L GENE

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Introduction: MED13L haploinsufficiency syndrome is a rare condition caused by mutations in the MED13L gene, characterized by intellectual disability, language impairment, muscle hypotonia, facial dysmorphisms, and more rarely associated with heart defects and epilepsy. Epilepsy has been described in association with de novo missense variants and characterized by febrile seizures, late-onset infantile spasms, and Lennox-Gastaut syndrome.

Case presentation: We report the case of a 40-year-old patient followed for epilepsy and severe psychomotor delay. The epilepsy, started at the age of 3, is characterized by tonic, atonic, spasms, absences, and multi-daily generalized tonic-clonic seizures despite a complex polytherapy with Carbamazepine, Valproic Acid, Brivaracetam, Perampanel, and Clonazepam with numerous previous therapeutic failures. The EEG shows a disorganized background activity with superimposed and frequent polymorphic and multifocal epileptiform discharges and rapid and diffuse paroxysmal activity during sleep. Brain MRI has revealed a picture of mild atrophy. In addition to epilepsy, the patient presents dysmorphisms, psychomotor delay with severe intellectual disability and autistic traits, absence of language acquisition, muscle hypotonia and ligamentous laxity and dysphagia. Genetic analysis with WES has only recently revealed the presence of the 3482C>T variant in heterozygosity of the MED13L gene. The mediator complex subunit 13-like gene MED13L encodes for a subunit of a mediator that functions as a transcriptional coactivator for almost all RNA polymerase II-dependent genes. This is a mutation that has not yet been described and is not present in international databases, likely responsible for the patient's clinical picture.

Discussion and conclusion: The case underlines the importance of genetic investigation in epilepsy of unknown etiology, especially in patients affected by developmental encephalopathy. It also confirms the phenotypic variability in relation to the type of mutation of the MED13L gene and, in particular, that severe epilepsy is a manifestation related to missense mutations.

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## LONG TERM EFFICACY OF VAGAL NERVE STIMULATION IN DRUG-RESISTANT EPILEPSY

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Introduction: Vagal nerve stimulation (VNS) represents a palliative surgical treatment for drug-resistant epilepsy (DRE), able to reduce frequency and severity of seizures, overall improving patients' quality of life. Aim of this study is to assess efficacy, safety, and tolerability of VNS on medium-long term follow-up in a cohort of patients affected by DRE.

Methods: Retrospective study on 74 patients underwent VNS surgery for DRE, recruited from four Epilepsy Centres in Nord-Est Italy, with a follow-up period up to 10 years. Data concerning epilepsy syndrome and etiology were collected from 59 patients, considering seizures frequency at baseline and during the follow up period for every patient. Furthermore, data concerning neurological and psychiatric comorbidities, settings of stimulation, side effects, and antiseizure medications at the moment of follow-up.

Results: This study shows the reduction of seizures frequency of 38.53 at 18 months, up to 62.56% at 120 months. Non-significant side effects were reported; in only 1 case, VNS was turned off due to continuous and severe side effects. Our study reports an equal efficacy of VNS in both focal and generalized onset seizure (67.3% vs 61.66% at 120 months). In our cohort, the median number of ASMs used remained constant during all through the follow-up period.

Conclusions: Our study demonstrates efficacy, safety and tolerability of VNS in a medium-long term follow-up, with a reduction of frequency above 50% of focal and generalized onset seizure at 10 years in patients affected by drug-resistant epilepsy.

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## EPILEPSY IN 6P TRISOMY SYNDROME: A CASE REPORT AND REVIEW OF LITERATURE

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Objective: Pure partial trisomy 6p is considered a clinically distinct syndrome and can be caused by tandem duplications, inverted duplications, a supernumerary marker chromosome, interchromosomal insertions, and unbalanced chromosome rearrangements. [1] The phenotype is heterogeneous depending on the gene contents of the duplicated region, mainly dosage sensitive genes can be involved. [2] Epilepsy or seizures have only been reported in a few cases of 6p trisomy [2]. We described epilepsy in a case of duplication of the proximal part of chromosome 6p and reviewed all cases of epilepsy in 6p duplication syndrome.

Materials and Methods: The patient is a 21-year-old female born by spontaneous vaginal delivery at the 40th week of unremarkable pregnancy. She is the second child of non-consanguineous parents. Clinical examination showed growth retardation, microcephaly and various anatomical dysmorphisms already described in other patients with the same genetic syndrome. She also had anal atresia and aortic valvular stenosis, pigmentary dystrophy of the retina. The patient developed epilepsy at the age of 14, seizures were characterized by version of the head to the right with impaired of awareness and a duration of a few minutes. Ictal EEG showed spikes and polispikes waves in left fronto-temporal region, interictal EEGs showed theta activity in the same region. MRI was normal. Now seizures occur once a month and she is treated with lacosamide, levetiracetam and clobazam.

Results: Conventional cytogenetic analysis (SNP-array) showed a duplication of the 6p region in the patient. The rearrangement was confirmed by FISH (Fluorescent in situ hybridization) showing a gain of 27.5 Mb from 6p12.1 to 6p22.1.

Discussion and Conclusions: Presence of epilepsy, although rare in patients with 6p duplication, may be linked to genes involved in brain function and synaptic transmission (GABBR1, BRD2 and GRM4) [3]. Evidence has been obtained for loci predisposing to juvenile myoclonic epilepsy on chromosomes 6p and linkage studies provided evidence for juvenile myoclonic epilepsy (JME)/idiopathic generalized epilepsy (IGE) susceptibility loci at 6p11-p12 and linkage to the HLA complex on chromosome 6p21.3 [3]. The fact that epilepsy is rare in patients with 6p trisomy could be to low life expectancy of some of the patients, who may have died before developing epilepsy. Identification of 6p duplication in a child should aware the physicians to the possibility of the patient to develop epilepsy.

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## CHARACTERISATION OF ANTIEPILEPTIC DRUG EFFECTS ON THE EEG NEUROYNAMICS BY FRACTAL DIMENSION

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Objectives: Many linear indices are used to improve the diagnosis and monitoring in epileptic patients, such as spectral power and individual alpha frequency peak. On the other hand, more needs to be explored in electroencephalography (EEG) neurodynamics by using nonlinear approaches [1]. Therefore, this work aims to monitor drug-responder epileptic patients using a nonlinear Fractal Dimension (FD) method [2,3]. We show that FD is more sensitive than linear based on spectral power methods.

Materials: Twenty-five drug-responder Temporal Lobe Epilepsy (TLE) were studied before (T1, named FR1) and after (T2, from 4 to 8 months, named FR2) the introduction of the anti-seizure medications (ASMs). FR1 and FR2 EEG results were compared against 25 age-matched healthy controls (HC).

Methods: EEG data were investigated from two different angles: (1) Frequency domain - spectral properties were investigated in δ, θ, α, β, and γ bands and the individual alpha frequency (IAF) peak, and (2) time-domain - fractal dimension (FD) was used as a signature of neurodynamics underlying nonlinear brain functions. Those features were compared between T1 and T2 among the three groups (FR1 vs Fr2 vs HC). Rm-ANOVA was performed to investigate the interaction effect GROUP (FR1, FR2 and HC) × BAND (δ, θ, α, β, γ). ANOVA was also applied to investigate the GROUP effect on HFD and IAF. Finally, Bayesian analysis was used to test sensitivity across the significant features extracted between FR1 and FR2.

Results: Post-hoc tests revealed that the δ band was different between FR1 and HC ($p<0.001$) and between FR2 and HC ($p<0.001$). θ band was different between FR1 and FR2 ($p=0.015$) and between FR1 and HC ($p=0.01$). IAF value was lower for the FR1 ($9.712 \pm 0.184$, $p < 0.048$) compared to the FR2 ($10.173 \pm 0.157$) and HC group ($10.188 \pm 0.107$). HFD value was lower for the FR1($1.639 \pm 0.013$, $p < 0.0158$) compared to the FR2 ($1.687 \pm 0.013$) and HC group ($1.685 \pm 0.008$). Bayes Factor (BF) among the three significant features discriminating between FR1 and FR2 showed values as follows FD-BF: 973.069, IAF-BF: 4.220 and θ-BF: 4.994.

Discussion: A comparison of BF showed that differences between FR1 and FR2 were 231 times more likely to be detected by FD than the IAF and 195 times by the θ band.

Conclusion: Our work suggests that FD could be used as a sensitive marker to discriminate between drug responder epileptic patients and help decrease misdiagnosis in clinical practice.

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## AETIOLOGICAL LANDSCAPE AND LONG-TERM ELECTRO-CLINICAL FOLLOW-UP IN ADULT PATIENTS WITH LENNOX-GASTAUT SYNDROME

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Aim: Lennox-Gastaut Syndrome (LGS) is a severe Developmental and Epileptic Encephalopathy (DEE) invariably leading to drug-resistant seizures and intellectual disability. It is caused by an heterogenous group of aetiologies, encompassing structural, genetic, and metabolic disorders3. Here we analyse the aetiological landscape and the age at aetiological diagnoses, and the electro-clinical features of a cohort of LGS adult patients, in order to optimise the clinical management.

Materials and methods: We recruited patients satisfying the diagnostic criteria for LGS3 afferring to our Adult Epilepsy Center in San Giovanni Rotondo. We collected electro-clinical, genetic, and neuroradiological data.

Results: We included twenty-two patients (F/M: 12/10), with a mean age of 25 years [range 15 – 50]. Six (27%) were diagnosed with genetic and/or genetic-structural disorders, in form of monogenic disorders (TSC1 variants), chromosomopathies (Trisomy 21, partial tetrasomy of 15q), and Xq28 microduplication. A primary structural abnormalities, was detected in 7 patients (32%). Aetiology is still undetermined in 9 of them. No metabolic aetiologies were identified. Genetic diagnosis was assessed after 16 years of age in 5 of them. Main electro-clinical features were frequent epileptiform abnormalieties with activation during NREM-sleep. Multiple seizure types were recorded (epileptic spasms, tonic, focal and tonic-clonic seizures).

Discussion: LGS is a DDE with high impact on Quality of Life of patients and caregivers. Management is often frustrating because of intractable seizures, cognitive impairment, and behavioral disorders. An eatiological definition is recommended, and the diagnostic work-up is usually performed in childhood, when the symptoms arise2,3. However, in a group of our patients, the aetiological diagnosis was achieved in adulthood despite the previous extensive diagnostic work-up. The recent advantages in neuroradiologic and genetic tests, along with their cost reduction, allow to expand the diagnostic possibilities with remarkable clinical impact.

Conclusions: Reinvestigation of adult patients with LGS could be useful in order to achieve a specific aetiologyical diagnosis. Although a precision therapeutical approach is only available for a few causes1, the identification of a specific aetiology allows a focused follow-up strategy, a complete diagnosis communication to the caregiver, and the possibility of a genetic/surgical consultation. Last but not least, the aetiological definition in adulthood could expand DEE natural history knowledge.

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## NILOTINIB-RELATED POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

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Introduction: Posterior reversible encephalopathy syndrome (PRES) is a clinical entity characterized by acute neurological symptoms including headache, seizures, and visual disturbance, and by typical reversible lesions on brain magnetic resonance images (MRI). Tyrosine-kinase inhibitors (TKI) family includes sunitinib, sorafenib, erlotinib, gefitinib, lapatinib, dasatinib, and nilotinib. Nilotinib is a second-generation TKI that selectively inhibits autophosphorylation of BCR-ABL, thus inhibiting cellular proliferation of imatinib-sensitive and -resistant chronic myeloid leukemia (CML) cell lines. [1] It is used for the first-line treatment of newly diagnosed CML patients and the second-line treatment of most CML patients who are resistant or intolerant to prior therapy (included imatinib). Nilotinib common adverse reactions include headache, rash, fever, nausea, vomiting, increased levels of liver enzymes and bilirubin, upper respiratory infections, QTc prolongation. Long-term use of nilotinib shows some cardiovascular toxicity. We present a case of PRES in a patient with LCM treated with nilotinib.

Clinical case: We report a 67-year-old woman with CML. She had no previous history of systemic hypertension, renal dysfunction, or autoimmune disease. She was treated with nilotinib. She presented to the emergency department for acute confusional state, visual disturbances with blurred vision and epileptic seizures with focal onset and bilateral evolution. Her blood pressure was 125/80 mmHg on admission. Blood tests, including complete blood count, blood chemistry, and coagulation showed no abnormal findings, in particular renal function was in the normal range and urine analysis showed no proteinuria. Brain MRI revealed hyperintense signals in the bilateral parieto-occipital lobes on FLAIR. Under a diagnosis of PRES, she was treated with anti-seizure medication (levetiracetam 2500 mg/day) and low-dose anti-hypertensive drug (ramipril 5 mg/day for one week), with clinical benefit. Levetiracetam was gradually withdrawn and brain MRI and electroencephalogram controls showed no pathological findings, with resolution of prevoius documented abnormalities.

Conclusion: PRES may be caused by hypertension alone, but may also occur due to toxicity of immunosuppressive and chemotherapeutic drugs. The most common drugs are tacrolimus and cyclosporine. However, PRES has also been associated with sirlimus, methotrexate, interferon, rituximab, bevacizumab, sorafenib, sunitinib, fingolimod, and IVIG, and with chemotherapy drugs such as cisplatin, cyclophosphamide, cytarabine, doxorubicin, gemcitabine, and vincristine. [2,3] To our knowledge this is the first report of a case of nilotinib-related PRES, thus widening the drug-related causes of PRES, a clinical entity

due to different possible causes determining vasogenic edema in the subcortical white matter and cortex, predominantly in the bilateral parieto-occipital lobes.

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## PERAMPANEL FOR THE TREATMENT OF PEOPLE WITH IDIOPATHIC GENERALIZED EPILEPSY IN CLINICAL PRACTICE

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Objective: The PERaMpanel pooled analysIs of effecTiveness and tolerability (PERMIT) study included approximately 5200 people with focal and generalized epilepsy who were treated with Perampanel (PER) in clinical practice. [1] The purpose of this study was to assess the real-world effectiveness and safety/tolerability of PER when used to treat people with idiopathic generalized epilepsy (IGE) included in PERMIT.

Methods: The multinational, retrospective, pooled analysis PERMIT explored the use of PER in people with focal and generalized epilepsy treated in clinical practice across 17 countries. This subgroup analysis included PERMIT participants with IGE. Timepoints for retention and effectiveness measurements were 3, 6, and 12 months (last observation carried forward, defined as 'last visit', was also applied to effectiveness). Effectiveness was evaluated by seizure type (total seizures, generalized tonic-clonic seizures [GTCS], myoclonic seizures, absence seizures) and included ≥50% responder rate and seizure freedom rate (no seizures since at least the previous visit). Safety/tolerability was evaluated by documenting the incidence of adverse events (AEs), including psychiatric AEs and those leading to treatment discontinuation.

Results: The Full Analysis Set included 544 people with IGE (51.9% women; mean age 33.3 years). At 3, 6 and 12 months, 92.4%, 85.5% and 77.3% of participants were retained on PER treatment, respectively. At the last visit, responder and seizure-freedom rates were, respectively, 74.2% and 54.6% (total seizures), 81.2% and 61.5% (GTCS), 85.7% and 66.0% (myoclonic seizures), and 90.5% and 81.0% (absence seizures). AEs occurred in 42.9% of patients and included irritability (9.6%), dizziness/vertigo (9.2%) and somnolence (6.3%). Treatment discontinuation due to AEs was 12.4% over 12 months.

Conclusion: This subgroup analysis of the PERMIT study demonstrated that PER was effective and generally well tolerated when used to treat people with IGE under real-world clinical practice conditions. Treatment with PER resulted in statistically significant reductions from baseline in the monthly frequencies of total seizures, GTCS, myoclonic seizures, days with myoclonic seizures, and absence seizures. At the last visit, rates of seizure freedom ranged from 54.6% for total seizures to 81.0% for absence seizures, and responder rates ranged from 74.2% for total seizures to 90.5% for absence seizures. PER effectiveness was also similar in the subgroups of different IGE syndromes. The most frequent AEs and AEs leading to discontinuation were consistent with PER's known safety profile. [2] These findings support data from clinical trials, providing further evidence of the potential use of PER as a broad-spectrum anti-seizure medication for the treatment of IGE.

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## SUPER-REFRACTORY STATUS EPILEPTICUS IN A PATIENT WITH LAFORA DISEASE

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Rationale and Objectives: Lafora disease (LD) is a rare autosomal recessive glycogen metabolism disorder, characterized by the inclusion bodies (Lafora bodies), within the cytoplasm of the cells in heart, liver, muscle, and skin. It presents as a neurodegenerative disorder that causes impairment in the development of cerebral cortical neurons, progressive myoclonus epilepsy (PME), and progressive cognitive and motor impairment. We describe a case of LD that presented for super-refractory status epilepticus (SE), resolved with Perampanel (PER), a non-competitive antagonist of AMPA-receptors.

Methods: A 28-year-old woman, affected by LD treated with valproic acid (VPA) 1000 mg daily, levetiracetam (LEV) 1000 mg daily and Clonazepam 2 mg daily, presented to the Emergency Department for multiple tonic-clonic seizures occurring without recovery of consciousness between them, consisting with convulsive SE.

Results: The patient was treated with diazepam 10 mg, repeated after 10 minutes; due to SE persistence, a load of LEV 30 mg/kg i.v. was administered, without clinical benefit. Fifteen hours after SE onset, midazolam (MDZ) 0.3 mg/kg i.v. load, followed by infusion at 0.3 mg/kg/h, was administered as third line therapy. As SE persisted, 16 hours after the onset, patient was transferred to Intensive Care Unit (ICU) for sedation. A load of Propofol (PPF) 2 mg/kg, followed by infusion at 2 mg/kg/h, was administered. On discontinuation of PPF, after 48 hours, the incoming epileptic seizures reappeared. Patient was diagnosed with super-refractory SE and sedation with MDZ and PPF was continued. Subsequent attempts to suspend MDZ and PPF resulted in SE reappearance. Fifteen days after SE onset, with patient in coma induced with MDZ/PPF, 12 mg of PER oral suspension was loaded with progressive reduction of MDZ and PPF, in the absence of SE reappearance. After a month from the recovery in ICU the patient returned to the sub-intensive Neurology ward. She was discharged with

PER 8 mg, Clonazepam 3 mg, VPA 2400 mg, Brivaracetam 200 mg, Phenobarbital 100 mg daily. Seizure control was satisfactory until the last follow-up one year later.

Conclusions: Status epilepticus may have serious long-term consequences and is potentially fatal. Super-refractory SE is a SE that has continued or recurred despite 24-hours of general anesthesia and has a mortality rate of 30%-50%. Perampanel is not currently licensed for treatment of SE, but many evidence support that it might be a therapeutic option for established SE, refractory and super-refractory SE. Our case adds more evidence even in SE associated with PME.

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## EEG CONNECTIVITY AS A THERAPEUTIC BIOMARKER IN DRUG-RESISTANT EPILEPSY: CORRELATION WITH CLINICAL OUTCOME AND CENOBAMATE THERAPY


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Objective: Epilepsy is a neural network disorder, and the use of quantitative EEG offers measures of cortical connectivity to study its dynamics. EEG connectivity demonstrated high sensitivity to the clinical outcome after a first anti-seizure medication and after surgery in people with epilepsy, suggesting its potential as a response biomarker [1-2]. The clinical usefulness of such a marker needs to be confirmed also in people with epilepsy who are already on treatment. Clinical trials on cenobamate (CNB) have reported excellent efficacy in drug-resistant people with epilepsy (DRE), offering an ideal molecule to test the role of EEG connectivity as a therapeutic biomarker in people with DRE.

Materials: We enrolled 18 DRE (8 females, 47±16-year-old) and twenty-five matched healthy controls (HC). Two DRE participants dropped out, leaving sixteen participants who underwent 19-channel EEG before (T0) and after 6 months (T1) of CNB therapy.

Methods: Power spectral density (PSD) and phase locking value (PLV) connectivity for delta, theta, alpha, beta and gamma frequency bands were calculated. Cognitive performance was evaluated by the Epitrack® test, and seizure frequency was collected.

Results: After CNB therapy, 11 out of 16 (69%) DRE participants were responders (>50% reduction in seizure frequency). PLV EEG connectivity modulation accurately predicted DRE responders (Accuracy 87%, AUC 94%, Sensitivity 91%, Specificity 80%). Reduction of PLV significantly correlated with seizure reduction in all frequency bands, except for alpha (p=0.39-0.004). None of the participants with epilepsy showed cognitive worsening after CNB therapy.

Discussion: EEG connectivity reduction induced by CNB accurately predicted the clinical outcome in DRE participants and corroborated its role as a response biomarker in people with epilepsy. Wider and urgent studies are needed to clinically validate EEG connectivity as a response biomarker in epilepsy.

Conclusion: Our study provides evidence supporting the use of EEG connectivity as a response biomarker in people with epilepsy, particularly in those with drug-resistant seizures. Cenobamate is an efficacious drug choice for DRE patients without impacting their cognitive performance.

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## A CASE OF STROKE LIKE MIGRAINE ATTACKS AFTER RADIATION THERAPY SYNDROME (SMART)


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Introduction: Stroke like migraine attacks after radiation therapy (SMART) syndrome is one of delayed complications of brain radiation therapy. This is a rare condition that can occur till 35 years from radiotherapy. This is a diagnosis of exclusion, according to the criteria proposed by Black et al. SMART can manifest with a series of reversible signs and symptoms like confusion, seizures, headache, motor and sensory deficits, aphasia, visual-spatial deficits, migraine with or without aura not-responsive to therapies. Radiological additional criteria include the presence of transient gadolinium enhancement of the cerebral gyri in the gray matter in a previously radiated field. Some patients who experimented SMART were successfully treated with steroid therapy, but treatment recommendations actually are not well established.

Case report: We present the case of a 70 year-old man with migraine not-responsive to FANS from several days, that arrived to our emergency department with a left hemiparesis. The patient presented a right frontal lobe glioma in the 1986, treated with radical resection and then with of radiotherapy along two months. He assumed prophylactic therapy with levetiracetam. He declined hospitalization and began intravenous steroid therapy (dexamethasone 4 mg/die) at home. After four days he manifested first a focal seizure at the left arm, then bilateral seizures, for which he returned to the emergency department and was admitted to Neurological Clinic. Brain MRI revealed presence of gadolinium enhancement of the right fronto-parietal cortex, suggestive for blood-brain damage. We continued intravenous steroid therapy for another week and increased anti-seizures therapy with levetiracetam(3000 mg/die) and valproic acid(1500 mg/die). The patient showed complete resolution of the symptoms. A brain MRI repeated after three months showed resolution of the enhancement in the fronto-parietal region.

Discussion: According to clinical symptoms and radiological signs, we made a diagnosis of SMART syndrome in a patient with a history of brain irradiation. In this case he showed hemiparesis resolution, probably due to the steroid therapy, but in literature there are patients recovered without any therapy.

Conclusions: SMART is a rare but relevant complication of radiotherapy. It is important to know and recognize this syndrome, in order to understand the better treatment to reverse severe neurological symptoms.

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## CANNABIDIOL IN THE DEVELOPMENTAL EPILEPTIC ENCEPHALOPATHIES: A POSSIBLE THERAPEUTIC STRATEGY FOR EPILEPSY AND COGNITIVE, BEHAVIORAL AND MOTOR SYMPTOMS. A CASE REPORT

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Objective: Cannabidiol (CBD) in its 100% purified form, is approved for the treatment of epilepsy in Lennox-Gastaut and Dravet syndromes associated to Clobazam, and in Tuberous Sclerosis. Some recent evidence suggests Cannabidiol may be used in the treatment of seizures in other Developmental Epileptic Encephalopathies (DEEs). However, we still lack sufficient data about the use of CBD in the treatment of other clinical features of DEEs, and particularly in cognitive, behavioral and motor symptoms. In this case report, we are presenting a patient with DEE treated with CBD, and the global clinical benefit he experienced.

Case discussion: Our case is of a 14 yo boy, affected by a DEE tbd (Whole Exome Sequencing is undergoing). His clinical history started at two years six months old when he experienced a hemisomic clonic seizure. After, he started to manifest more-than-daily focal with secondary generalization drug-resistant seizures. Moreover, he had a regression in developmental psychomotor: he lost speech at the start of the epileptic features, and autonomous deambulation by age six. He was also diagnosed with Autism Spectrum Disorder, and also suffered from a severe sialorrhea resistant to botulinum toxin. He performed multiple MRIs by his third year of life, with signs of progressive left brain hemisphere atrophy. By the age of thirteen his seizures had a frequency of 7-18 per day, with EEG features of subcontinous diffuse epileptiform activity. We decided to add to his therapeutic regimen Cannabidiol, titrating up to 15 mg/kg/day, monitoring on his clinical response (frequency of seizures and their severity, quality of life) and performing EEG controls at two, six, nine and twelve months.

Results: Since the introduction of Cannabidiol, his epilepsy improved: daytime seizures gradually stopped, and his nighttime seizures became less severe and frequent (between 2 and 7 a day, lasting only few seconds). His EEG improved concordantly, with less continuous epileptiform activity restricting itself in right centro-temporal areas. His global functioning ameliorated too: He regained his ability to deambulate autonomously, and his social skills improved (more visual contact interactions, and more gesture and vocal communication). Finally, his botulinum-resistant sialorrhea disappeared.

Conclusion: The response of his epilepsy is in line with medical literature with a 60% reduction of his seizures. We though highlight the global significant benefit our patient had in his cognition and behavior, on sialorrhea disappearance and on deambulation recovery. Further studies will be needed to investigate effectiveness of CBD on these symptoms.

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## USE OF FUNCTIONAL CONNECTIVITY DYNAMICS TO DIFFERENZIATE DRUG-RESISTANT AND NOT DRUG-RESISTENT PEOPLE WITH EPILEPSY

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Background: Recent studies evidenced that electroencephalogram (EEG) functional connectivity (FC) could become a promising tool for a better comprehension of neurophysiological changes induced by epilepsy. [1-2] The aim of this study was to explore temporal dynamics of FC in people with epilepsy (PwE) to identify possible measures able to identify drug-resistant epilepsy (DRE) condition.

Materials and Methods: We retrospectively collected resting-state 19-channel EEGs of 29 PwE affected by DRE and 31 without DRE (nDRE) who underwent two anti-seizure medications trials at the time of recording. EEGs were preprocessed, 180s were selected and Laplacian surface was applied to minimize volume conduction. Inter-site phase clustering (ISPC) was computed for each 200 ms epoch to visualize global connectivity changes in time domain. ISPC was calculated for delta (0-4 Hz), theta (5-7 Hz), alpha (8-12 Hz) and beta (13-30 Hz) frequency bands. Avalance analysis on waiting time (WT, time below threshold, i.e. median connectivity values) and life-time (LT, time above threshold) were computed to characterize the obtained connectivity series. Distribution of avalanches followed a power-low shape; thus, slopes and intercepts of best-fitting lines were compared between PwE with DRE and nDRE via permutation testing (iterations=10000). Significant results (after Bonferroni-Holmes correction) were imputed in a support vector machine (SVM) classification algorithm (radial basis function kernel) to test machine learning accuracy in predicting DRE/nDRE conditions. Accuracy was validated with leave-one-out cross-validation.

Results: LT slopes were lower in PwE with DRE compared to those with nDRE in all frequency bands, with a statistically significant difference in delta band (p-value=.008). LT intercepts in PwE with DRE were always lower compared to PwE with nDRE. WT slopes and intercept of delta band revealed to behave in a completely opposite way (p-value=0.02). SVM algorithm trained with LT and WT slopes was able to discriminate PwE with DRE from those with nDRE with an accuracy of 0.89.

Discussion: Avalance analysis condensate in a single relationship (the slope) the amount of time spent above threshold and the probability

linked to this occurrence. Thanks to this analysis, we demonstrated that PwE with DRE are more likely to exhibit high consecutive FC values during resting state, especially in low-frequency bands (well-known to be associated with epilepsy). [5] Moreover, these features were able to identify DRE condition with great accuracy when implemented in machine-learning algorithm.

Conclusions: We hypnotize that FC could become a promising diagnostic biomarker of DRE, even though further studies are required.

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## SUBACUTE ENCEPHALOPATHY WITH SEIZURES IN ALCOHOLICS (SESA) SYNDROME: A CASE REPORT

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Objectives: Alcohol abuse predisposes to alcohol-withdrawal seizures. Moreover, unusual cases of encephalopathy with generalized, focal motor seizures or non-convulsive status epilepticus have been designated as subacute encephalopathy with seizures in alcoholics (SESA) [1,2]. Here we present a case of SESA, describing clinical, neuroimaging and neurophysiological findings.

Case report: A 65-year old man with a history of alcohol abuse was found at home stuporous, dehydrated and in poor hygienic conditions; last time seen in health was 3 days earlier. In the ED, blood tests revealed undetectable ethanol levels and hypernatremia (163 mmol/L), gradually corrected with mild responsiveness improvement, although he remained confused, producing unintelligible speech. Brain CT scan was negative. During hospitalization, the patient developed fever, respiratory distress and progressive decline of vigilance and empirical ceftriaxone, ampicillin and acyclovir were started along with thiamine. Therefore, he was sedated, intubated and transferred to the ICU three days after the admission. Standard and microbiological CSF analyses were negative. The EEGs showed generalized slowing of the tracing (5-6Hz), with frequent isolated diffuse frontal-predominant sharp waves. One week later, the patient started presenting pseudo-rhythmic jerks of the upper limbs. The EEG showed an ictal-interictal continuum pattern with diffuse left-predominant sharp and slow waves. Levetiracetam 750mg x2/day and valproate 400 mg x3/day were started, with conversion of the EEG (day 10) to an anterior-predominant generalized periodic discharge pattern of 1-Hz triphasic slow waves, interrupted by diffuse theta activity after external stimulations. Valproate was then gradually suspended. On day 11, brain MRI showed confluent chronic vasculopathy (Fazekas 3) and three-minute acute cortical lesions in the right cingulate, left parietal and occipital cortex, with restricted diffusion. Sedation was thus interrupted, leaving the patient under low-dose remifentanil, yet he remained in a coma state until one month after the admission. He eventually became responsive to verbal stimuli and able to inconstantly perform simple tasks. The EEG at day 35 showed reappearance of 8-Hz dominant rhythm, with superimposed frequent bursts of polymorphic bilateral theta-delta central-temporal slow waves. Given the personal history of alcohol abuse, the initial lateralization of EEG abnormalities, the chronic and acute brain lesions at the MRI, in the absence of other plausible causes, we diagnosed a probable SESA.

Conclusions: SESA should be included in the differential diagnosis of encephalopathies with seizures in patients with alcohol abuse history. It is not always related to alcohol withdrawal and prosecution of antiseizure medications is necessary to avoid relapses.

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## AMYLOID ANGIOPATHY RELATED INFLAMMATION AND PAROXISMAL EVENTS REFRACTORY TO ANTI-SEIZURE THERAPY: AMYLOID SPELLS OR SEIZURES?

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Introduction: The accumulation of amyloid within the walls of intracerebral vessels can cause recurring and stereotyped transient focal neurological episodes (TFNE) with positive or negative symptoms, once defined as "amyloid spells". Although the etiopathogenesis is not yet clearly defined [1], TNFE are a differential diagnosis of epileptic seizures. We report the case of a 72 year-old patient who presented late-onset paroxysmal neurological episodes refractory to anti-seizure medications (ASMs), resulting in complex management and difficult interpretation.

Case Presentation: A 72-year-old woman was admitted for an episode of transient mental confusion and aphasia. In anamnesis, some similar transient episodes were present in the previous 2 years, associated with hemiparesis and left hemianopsia or visual hallucinations. For the suspected cerebrovascular origin, ASA was introduced, then associated with Clopidogrel. After following recurrences, an epileptic nature was hypothesized and Levetiracetam was started. In the subacute phase, EEGs demonstrated slow wave abnormalities, which were attributed to post-ictal dysfunction. Hematochemical and cerebro-spinal fluid examinations were negative for inflammatory (including markers of autoimmunity) and infective signs and contrast-enhanced brain MRI shows cortical-subcortical signal alterations in the FLAIR sequences, located in the parieto-occipital region, prevalent on the right where was associated with edema, and right temporo-basal area, in the presence of leukoaraiosis and rare cortical microbleeds. The EEG and neuroradiological findings improved only after high-dose ev corticosteroid therapy and worsened during the recurring episodes. Cognitive functions also temporarily improved, but showed a progressive decline over the two years observation (MoCa test from 25/30 to 21/30). Given the neuroradiological findings and the response to steroids, a "Cerebral amyloid angiopathy-related inflammation" (CAARI) [2] was hypothesized. The cerebral amy-Pet confirms the presence of a widespread accumulation of beta-amyloid [3]. A low-dose corticosteroid therapy was begun and the patient is currently free from paroxysmal episodes for about a year.

Conclusions: The differential diagnosis of transient neurological events like that one reported is challenging, including TIA, amyloid spells, or epileptic seizures in the course of CAARI. This case underlines the importance of considering the presence of amyloid angiopathy

when suspecting late-onset epileptic seizures, resistant to ASMs, especially if in conjunction with cognitive deterioration, in order to establish the most appropriate therapy.

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## SLEEP QUALITY AND COGNITIVE IMPAIRMENT IN IDIOPATHIC GENERALIZED EPILEPSY

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Introduction: The link between sleep and epilepsy is complex and influenced by different factors. A recent meta-analysis about sleep quality in patients with Idiopathic Generalized Epilepsy (IGE) has shown a reduction in quality of sleep efficiency (SE), total sleep time (TST), proportion of N2 stage and prolonged REM onset latency. Moreover, different studies have demonstrated that patients with IGE present impairment in multiple cognitive domains. The objective of our study was to assess the presence of a possible association between quality of sleep and cognitive performances in patients with IGE.

Materials and methods: We enrolled patients with IGE at the Epilepsy center of the Neurology clinic of Policlinico G. Rodolico in Catania. All patients underwent an overnight polysomnography. Patients with a complain of sleep disorders have been excluded. Sleep macrostructure has been evaluated. In particular, TST, sleep latency (SL), SE, wake after sleep onset (WASO) and percentages of N1, N2, N3 and Rapid Eye Movements (REM) sleep have been calculated. Moreover, patients underwent a neuropsycological assessment including global functioning (Mini Mental State Evaluation - MMSE), memory (Rey Auditory Verbal Learning test), attention (Stroop test), executive functions (F-A-S, Frontal Assessment Battery) and praxis (clock drawing test).

Results: Twenty-five IGE patients (mean age 28.8±13.5 years, 64% women) have been entrolled in the study. Mean age of disease onset was 13.7 years. Mean disease duration was 13.6 years. The majority of patients presented juvenile myoclonic epilepsy (n=10, 40%) or IGE with generalized tonic-clonic seizures only (n=10, 40%). Other diagnoses were epilepsy with eyelid myoclonia (n=4, 16%) and juvenile absence epilepsy (n=1, 4%). Four patients (16%) had a positive family history for epilepsy. At the time of the evaluation, about a half of patients (n=12, 48%) were drug naïve. A significant association has been found between lower scores in F-A-S and a higher WASO (p= 0.024).

Conclusions: The result of our study highlights that a worse quality of sleep is associated to a longer WASO in patients with IGE. An appropriate management of sleep issues could lead to better cognitive outcomes in this population.

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## RESILIENCE AND PSYCHOSOCIAL FACTORS IN ADULTS WITH EPILEPSY: A LONGITUDINAL STUDY

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Objectives: Resilience is defined as 'a dynamic process that includes a positive adaptation in the context of significant adversity'. The aim of our study was to measure the resilience, through a dedicated scale, in a group of people with epilepsy (PWE) and to prospectively evaluate its impact on psychosocial factors, in particular the presence of feelings of stigmatization.

Material and Methods: We consecutively enrolled 78 adult PWE (52 F; mean age 42,61 ± 16,11 y). 46 were seizure free (SF, 59%) and 32 were not-seizure free (NSF, 41%). All subjects completed at baseline (T0) the Resilience Scale (RS-14) [1] and questionnaires for the assessment of depressive symptoms, anxiety and quality of life: respectively, Beck Depression Inventory-II (BD-II), Generalized Anxiety Disorder-7 (GAD-7) and QOLIE-31 (Q31). The patients were prospectively followed up and re-evaluated after 6-12 months (T1); at follow up they also completed the Stigma Scale of Epilepsy (SSE) for assessment of stigma associated with epilepsy. Therefore, we correlated RS-14 values with all psychosocial aspects at both times, in particular feelings of stigmatization.

Results: The results showed for the RS-14 a significant direct correlation with the Q31 ($p < 0.001$) at baseline (T0) and inverse with the depressive and anxiety symptoms, as evaluated with BDI-II ($p < 0.001$) and GAD-7 ($p < 0.001$) at both times (T0 and T1). Finally, for the first time, a significant inverse correlation was evidenced between RS-14 at baseline and the levels of stigmatization, assessed with SSE at follow up (p=.005). No correlation was observed between resilience/stigma and seizure frequency at both times (T0 and T1) as well as changes of seizure rate or clinical outcome. Finally, against a significant reduction in the total number of seizures (p=.035) at follow up (T1), we didn't observe significant changes in depressive and anxious symptoms.

Conclusions: Our study showed that in PWE depressive symptoms, anxiety and quality of life were significantly associated with resilience, which was found to be able to prospectively influence the perception of stigma related to epilepsy more than seizures. Finally, the longitudinal evaluation showed that depressive and anxious symptoms were also not affected by seizure frequency, although it improved at follow-up.

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## A CASE REPORT EXTENDING THE PHENOTYPIC SPECTRUM OF VARS2-RELATED MITOCHONDRIAL ENCEPHALOPATHY

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VARS2 gene encodes the mitochondrial valyl-tRNA synthetase, a mitochondrial aminoacyl-tRNA synthetase (mtARSs), key enzyme in the synthesis of mitochondrial respiratory chain proteins. Rare, pathogenetic variants of this gene have been associated with various forms of mitochondrial encephalopathies [1]. Specifically, VARS2 homozygous c.1100C > T (p.Thr367Ile) mutation has been so far described in eight patients, with variable clinical phenotype, mostly characterized by severe psychomotor development delay, hypotonia, microcephaly and seizures. [2] We describe two brothers, born from nonconsanguineous parents, affected by this rare mutation, with atypical clinical features, known to our unit for drug-resistant epilepsy in follow-up. Patient 1. Male, 38 years old. During childhood he was diagnosed with speech delay. At four years old an extrapyramidal syndrome with bradykinesia and rigidity was evident. Later emergence of cerebellar ataxia (6 years old), myoclonus and upward gaze deficit (8 years old). At 10 years seizures began, during sleep, characterized by head version to the left followed by generalized tonic-clonic seizures. In the following years he was often hospitalized for status epilepticus. The current clinical picture is characterized by bradikynesia, limbs rigidity (mainly of the lower limbs) and cognitive impairment with a partial control of seizures. Patient 2. Male, 45 years old. Development delay and ataxic gait were evident since childhood. At 9 years old emergence of tonic-clonic seizures. At 11 years old, evidence of parkinsonism, with dystonia of the upper limbs and myoclonus. In the next years his conditions aggravated progressively, and clinical presentation is now characterized by quadriplegia and spasticity with severe cognitive impairment and no control of seizures. Patient 1 underwent genetic analysis for inherited cerebellar ataxias and genes associated with dystonia which resulted negative. Both patients carry VARS2 homozygous c.1100C>T (p.Thr367Ile) mutation. In conclusion, since very few clinical data are available regarding this rare condition, with our report we might contribute to extend the phenotypic spectrum of this disorder including infantile-onset parkinsonism, which interestingly, has been related also to another mtARS, mitochondrial tryptophanyl-tRNA synthetase (WARS2) [3]. Moreover, it is noteworthy that out of ten patients with this mutation described so far worldwide, five are from North Sardinia.

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## AUTOIMMUNE ENCEPHALITIS (AIE) WITH ANTI-AMPA-GLUR3 ANTIBODIES IN A PATIENT WITH OPSOCLONUS-MYOCLONUS SYNDROME (OPS): A CASE REPORT

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Case presentation: The patient was a 67 years-old woman, suffering from hypertension, chronic cardiomyopathy with PMK implant and surgically treated thyroid cancer. The patient complained of asthenia and migraine, unresponsive to medications. Brain MRI showed mild chronic microvascular disease involving the basal ganglia bilaterally. After two weeks, she developed gait and cognitive impairment with episodic and fluctuating confusional state. As two months passed, the patient showed altered state of consciousness, frequent epileptic crisis, opsoclonus and myoclonus of the upper limbs, so she needed hospitalization.

Methods and results: On admission, clinical evaluation demonstrated axial rigidity, opsoclonus and bilateral myoclonus prevalently involving the upper limbs. After few days she was scarcely responsive to stimulation and showed severe psychomotor agitation. During hospitalization, routine blood tests were mostly normal, only showing slightly elevated liver enzymes. A CT scan of the brain showed no pathological signs; EEG showed frequent slow and paroxysmal intercritical anomalies on the bilateral frontal-central-temporal regions; CSF analysis showed mildly elevated proteins and 16 lymphocyes; virologic and intracellular autoimmune screening were negative. Due to the oncologic history of the patient, oncomarkers were tested on blood sample, resulting in a mild positivity for CA125 antigen. Prion protein and neurodegenerative markers were also negative. Suspecting an autoimmune encephalitis (AIE), screening for extracellular antigen autoantibodies was carried out, demonstrating positivity for anti-AMPA-GluR3 antibodies in both serum and CSF. The patient was treated with high dose corticosteroids and multiple antiepileptic drugs, with poor clinical response. A week later, she suffered from bilateral pneumonia and septic shock, leading her to death.

Discussion and conclusion: OPS in adults is a rare disorder with the clinical features of opsoclonus, myoclonus, ataxia, and behavioral and sleep disturbances. The pathophysiology is thought to be immunological and rarely it may occur in a setting of AIE. Antibodies directed against glutamate receptors are frequently correlated with AIE but, according to current literature, only few cases are reported associated with anti-AMPA-GluR3B antibodies [1-2]. Anti-AMPA-GluR3B antibodies are present in 25–30 % of patients with different types of epilepsy, but in vitro and in animal models they may cause neuroexcitotoxicity and cause brain damage, aggravate chemoconvulsant-induced seizures, and also induce behavioral/motor impairments [3]. In the present case, the clinical manifestations of opsoclonus-myoclonus in AIE, with high serum and CSF GluR3 antibodies suggest a possible pathogenetic correlation, in the absence of other diagnostic cues.

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## HEADACHES

## ONE MONTH OF A VERY LOW-CALORIE KETOGENIC DIET CAN ALTER THE PROPAGATION OF IMPULSES ALONG THE SOMATOSENSORY PATHWAY IN MIGRAINEURS

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Introduction: A very low-calorie ketogenic diet (VLCKD), which stimulates fat metabolism and ketone production by severely limiting lipid and carbohydrate intake, is helpful as a migraine preventive

strategy in obese subjects. Uncertainty surrounds the primary processes causing the clinical response. In this study, we assessed the levels of thalamocortical and cortical activity in a sample of episodic migraine sufferers before and during VLCKD therapy.

Methods: After stimulating the median nerve at the wrist, we recorded somatosensory evoked cortical potentials (SSEPs) in a group of 18 MO patients between attacks. In order to analyze the two bursts of high frequency oscillations (HFOs) reflecting the thalamocortical (early HFO) and cortical (late HFO) activity of the somatosensory system before and after one month of VLCKD treatment, we applied a band-pass filter between 450 and 750 Hz to the SSEP signal. We determined the latency and amplitude of the negative oscillatory maximum and duration, frequency, and number of oscillations for each of the two bursts from the signal acquired.

Results: We saw an increase in the latency of the highest peak of both the early burst and the late burst of HFOs after 1 month of VLCKD ($p = 0.017$ and $p = 0.005$, respectively). No changes were seen in the other HFOs parameters.

Discussion: The results of this study demonstrate that a single month of VLCKD treatment can change how high-frequency impulses propagate along the thalamus-somatosensory cortex loop. It is unclear if ketogenesis has a direct impact on each hub of the somatosensory pathway or only has a cortical effect that may indirectly affect thalamocortical afferents.

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## ERENUMAB TREATMENT IN A PATIENT WITH RAYNAUD PHENOMENON: A CASE REPORT OF AN UNEXPECTED AORTIC DISSECTION AFTER TWO YEARS OF TREATMENT

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Backgroud: Anti-CGRP monoclonal antibodies (mAbs) represent a new promising, effective and safe weapon in the treatment of patients with migraine resistant to conventional prophylactic therapies. CGRP, a potent vasodilator, plays a key role in migraine pathogenesis. CGRP deficiency is involved in Raynaud's phenomenon (RP), consisting of abnormal vasoconstriction of the fingers, and the use of anti-CGRP mAbs in these patients is now not recommended [1,2]. Recent concerns have been raised following postmarketing case reports of elevated blood pressure (BP) associated with the use of anti-CGRP mAbs and there are data supporting an increase in BP in patients receiving this treatment, thus being able to increase the risk of hypertensive crises, dissection phenomena and arteriosclerosis [3].

Case presentation: We present the case of a 59-year-old woman with chronic migraine, treated with several prophylactic therapies (amitriptyline, topiramate, flunarizine, propranol, botulinum toxin) and occipital analgesic blocks without efficacy. The patient was also affected by an anxiety-depressive disorder, systemic hypertension with good pressure control and Raynaud's phenomenon (in the absence of systemic autoimmune diseases). In February 2021, in relation to the presence of pharmacological overuse and high MIDAS values (110), prophylactic therapy with erenumab was introduced, with clear clinical benefit (from 15 attacks/month to 3 attacks/month) and no reported side effects. The patient continued this therapy for two years (with a three-month suspension in between). After 23 total doses of erenumab 140 mg s.c., the patient was urgently hospitalized for abdominal pain and a syncopal episode with evidence on CT angiography of acute Stanford A - De Bakey II aortic dissection, extended to the right common carotid and subclavian arteries. The patient underwent surgery to replace the ascending aorta with a regular post-operative course and in the absence of residual focal neurological deficits. Four months later, the patient made a follow-up visit at our Headache Center; we suggested a brain MRI wich showed hypertensive encephalopathy and multiple ischemic lesions in the right emisphere. The treatment with anti CGRP mAbs was therefore discontinued.

Conclusion: This case report suggests that there may be a potential correlation between RP, the use of anti-CGRP mAbs and acute vascular events such as arterial dissection. Future clinical studies in an adequate sample of patients with RP and an history of hypertension may confirm this relationship suggesting a great caution when prescribing CGRP antagonists to these patients.

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## CSF-HYPOTENSION RELATED HEADACHE: AN ATYPICAL PRESENTATION

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Objective: To describe an atypical case of CSF hypotension headache.

Methods: A 46-year-old patient with a history of hypercholesterolemia currently not on therapy, dysmenorrhea treated with estroprogestogens for 2 months; no history of headache. In March 2023 acute onset, during the night, of intense headache at the top, thunderclap-type, which woke her up from sleep; nausea and vomiting, phono and photophobia were associated. For this reason, she had hospitalization and practiced CT + angioCT, which were negative; the neurological examination at the time of access showed no signs of ongoing neurological pathology. Discharged with indication to perform brain MRI with angio sequences, practiced 7 days after onset and negative.

Results: The patient came to our observation for diplopia due to VI cranial nerve palsy that began 15 days after the onset of headache. She performed in emergency CT and angio-CT, negative, and was admitted to the Neurology department. The MRI carried out at our department highlighted an apparently somewhat stretched aspect of the ventricles with subdural bihemispheric subdural seroematic effusion predominantly parieto-occipital, interhemispheric and tentorial, diffuse thin smooth dural thickening with enhancement after contrast; interpeduncular angle of about 37°, pontomesencephalic angle of about 43°, perioptic liquor film was not clearly demonstrable; all these findings oriented, at least in the first instance for phenomena related to CSF hypotension. She underwent a blood patch procedure, completed without complications. The clinical control at 30 days showed complete regression of the cephalalgic symptoms type thunderclap, diplopia in

the lateral gaze over 45 degrees laterally for VI deficiency; MRI control brain showed no signs of residual intracranial hypotension.

Discussion: The clinical presentation of the patient did not suggest, given the lack of anamnestic elements (trauma, intense physical exertion), the onset of a CSF hypotension headache. Other causes (e.g. cerebral venous thrombosis associated with estroprogestogen use) were more likely, with focal neurological deficits coexisting.

Conclusions: The symptoms of SIH resemble intracranial hypotension from other causes such as postdural puncture, postsurgical and post-traumatic CSF leaks, but in SIH the leak occurs spontaneously in the spine at a site which is unknown at the time of presentation. Our case presents clinical particularities related to onset and neurological symptoms not associated with evidence of risk factors for CSF hypotension.

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## IMPACT OF ATOGEPANT ON MIGRAINE DAY REDUCTION, RESPONDER RATE, AND PATIENT-REPORTED OUTCOMES IN PARTICIPANTS WITH CHRONIC MIGRAINE AND MODERATE TO SEVERE SYMPTOMS OF DEPRESSION AS MEASURED BY PATIENT HEALTH QUESTIONNAIRE-9

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Objectives: Atogepant is an oral CGRP receptor antagonist approved in US for preventive treatment of adult episodic migraine, with demonstrated efficacy also for chronic migraine (CM). Depression is common in people with migraine and predicts increases in headache-related disability and poor health-related quality of life. Using data from the PROGRESS CM trial, this analysis evaluated atogepant effect in CM participants with baseline moderate to severe depressive symptoms.

Materials: In a phase 3, 12-week, double-blind controlled trial, CM participants were randomized to atogepant 30 mg twice daily (BID), 60 mg once daily (QD) or placebo.

Method: Post-hoc analysis evaluated the impact of atogepant on change in monthly migraine days (MMDs), ≥50% and ≥75% responder rates, change in MSQ v2.1 domain scores, and PGIC in CM participants with moderate to severe depression symptomatology (PHQ-9 cut-off score of ≥10). For endpoint change from baseline in MMDs and each MSQ v2.1 domain score, comparison between treatment groups were analyzed using a restricted maximum likelihood-based mixed model for repeated measures. Logistic regression models were used to analyze PGIC responder at week 12 and ≥ 50% or 75% responder rates across 12-week double-blind treatment period. ANCOVA model was used to analyze change from baseline in PHQ-9 score at week 12.

Results: 109 (42.6%) in the atogepant 60 mg QD arm and 89 (36.2%) in the placebo arm were CM participants with moderate to severe depression symptoms at baseline. A greater proportion of CM participants with moderate to severe depression on atogepant 60 mg QD, compared to placebo: had greater reduction in migraine days over the 12-week treatment period, least squares mean differences (LSMDs): −3.04 (95% CI: −4.78, −1.29; p=0·0007); achieved ≥50% (OR = 3.7 [95% CI: 1.86, 7.37; p=0.0002]) and ≥75% reductions (OR = 13.64 [95% CI: 1.75, 106.2; p=0.01]) in MMDs; had greater improvement in the MSQ v2.1 domain scores at week 4 and the effect was maintained through week 12; reported much better or very much better on the PGIC at week 12; had greater reduction in PHQ-9 scores at week 12.

Discussion: In CM participants with moderate to severe symptoms of depression, atogepant 60 mg QD demonstrated a greater treatment benefit over placebo in MMD reduction, ≥50% or ≥75% responder rates, MSQ v2.1 domain scores, and PGIC.

Conclusions: In CM participants with moderate to severe symptoms of depression, atogepant demonstrated a greater treatment benefit compared to placebo.

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## A MULTICENTER, PROSPECTIVE, REAL-LIFE STUDY ON ULTRA-LATE RESPONDER (>24 WEEKS) TO ANTICGRP MABS IN MIGRAINE

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Objective: Responders (>50% response rate at 12 weeks) to monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) in migraine are roughly 60%. Notably, half of non-responders at 12 weeks do indeed respond 24 weeks, being considered late-responders. We assessed frequency and characteristics of migraine patients responding to anti-CGRP mAbs only >24 weeks (ultra-late responders).

Materials and Methods: In this multicenter (n=16), prospective, cohort, real-life study, we enrolled all consecutive patients affected by high-frequency episodic migraine (HFEM: >8 days/month) or chronic migraine (CM) with >3 therapeutic failures, treated with any anti-CGRP mAbs for >48 weeks. Patients were interviewed face-to-face using a semi-structured, shared, web-based questionnaire exploring sociodemographic and clinical characteristics. We defined ultra-late responders those patients achieving a >50% response only >24 weeks. Patients detailed monthly migraine days (MMD) during a 28-day run-in period and throughout the entire study period using a paper-pencil headache diary.

Results: 572 migraine patients (M/F=140/432; age=48.2±10.6; HFEM/CM=154/418;) completed >48 weeks of treatment with anti-CGRP mAbs (erenumab 527 pts; fremanezumab 40 pts; galcanezumab 5 pts). Responders were 60.5% (346/572), late responders 15% (86/572) and ultra-late responders 15.7% (90/572). Among ultra-late responders, 46.7% (42/90) responded at all time intervals following week 24 (weeks 28, 32, 36, 40, 44, 48), whereas 53.3% (48/90) only at some of them (fluctuating ultra-late responders). Only 8.7% patients (50/572) did not respond at any time interval <48 weeks. Differences between ultra-late responders and responders included higher BMI (23.8±4.2 vs 23.0±3.1; p=0.033), less common unilateral pain (46.7% vs 62.3%; p=0.010), longer medication overuse duration (78.4±110.7 vs 35.9±81.7 months; p<0.001), dopaminergic symptoms (78.9% vs 61.3%; p=0.003), psychiatric comorbidities (44.4% vs 30.1%; p=0.014), Numeric Rating Scale (7.3±1.3 vs 7.7±1.3; p=0.017) and HIT-6 scores (63.7±11.6 vs 66.9±7.7; p=0.002).

Discussion and Conclusions: One-sixth (15.7%) of migraine patients treated with antiCGPR mAbs are ultra-late responders (>50% response >24 weeks). Patients refractory to long-term treatment with antiCGRP mAbs are exceedingly rare (8.7%).

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## RIPETITIVE TREATMENTS WITH ANTI-CGRP MONOCLONAL ANTIBODIES COULD MODIFY MIGRAINE COURSE: A MULTICENTER, PROSPECTIVE, OBSERVATIONAL STUDY

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Objective: A single 12-month treatment with anti CGRP monoclonal antibodies (anti CGRP mAbs) is not disease modyifing because migraine frequency increases soon after treatment discontinuation. We evaluated the effect of a second 12-month treatment cycle with anti-CGRP mAbs on the course of high-frequency episodic migraine (HFEM: >8 days/month) or chronic migraine (CM).

Materials and Methods: In this multicenter (n=5), prospective, real-life study we considered consecutive patients affected by HFEM or CM with >3 previous preventive medication failures, treated with two consecutive 12-month treatment cycles with anti-CGRP mAbs. Duration of treatment discontinuation was reduced from 3 to 1 month by the Italian Medicines Agency. Thus, we compared migraine changes at D2 (weeks 1-4 of the second treatment discontinuation) with D1 (weeks 1-4 of the first treatment cessation). Primary endpoint was the change in monthly migraine days (MMD) at D2 compared to D1. Secondary endpoints were variation in monthly headache days (MHD), monthly analgesic medications, Numerical Rating Scale (NRS) and HIT-6 scores at the same time intervals.

Results: Sixty-seven migraine patients (M/F: 19/48; mean age: 47.3±11.6; HFEM/CM: 11/56) completed two 12-month treatment cycles with anti-CGRP mAbs (erenumab: 58 pts; fremanezumab: 7 pts; galcanezumab: 2 pts;). Anti-CGRP mAbs treatment significantly reduced (p<0.001) MMD, MHD, monthly analgesic intake, NRS and HIT-6 score at 12 months (weeks 45-48: 5.6±2.2, 5.7±2.4, 5.7±4.2, 4.3±0.8, 52.6±8.8), D1(weeks 1-4: 12.6±4.1, 12.6±4.1, 12.0±4.1, 6.6±1.2, 60.8±6.7) and D2 (weeks 1-4: 10.1±3.9, 10.2±4.0, 9.7±4.2, 6.0±1.7, 57.6±7.6) compared to baseline (19.4±6.1, 20.3±6.3, 20.5±9.5, 7.9±0.9, 68.2±5.5). At D2, patients showed a significant greater reduction (p<0.001) in MMD (10.1± 3.9 vs 12.6±4.1), MHD (10.2±4.0 vs 12.6±4.1), monthly analgesic intake (9.7±4.2 vs 12.0±4.1), NRS score (6.0±1.7 vs 6.6±1.2) and HIT-6 score (57.6±7.6 vs 60.8±6.7) compared to D1.

Discussion: The second anti-CGRP mAbs 12-month treatment cycle significantly reduces MMD, MHD, monthly analgesic intake, NRS and HIT-6 score compared to the first 12-month treatment cycle, at least comparing the first months of treatment discontinuation. Anti-CGRP treatment effects are reduced during the posttreatment periods, but do not return to baseline.

Conclusions: Prolonged or repetitive treatments with anti-CGRP mAbs could modify migraine course.

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## CEREBRAL VASOREACTIVITY CHANGES IN MIGRAINE PATIENTS AFTER THERAPY WITH ANTI-CGRP MABS

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Aim of the study: The present study was aimed to assess variations in cerebral blood flow and vasoreactivity in migraine patients before and during anti-CGRP monoclonal antibodies (mAbs) treatment.

Materials and methods: In the January 2022 -January 2023 period, 44 chronic or high-frequency episodic migraine patients (37 females, 7 males), eligible for anti-CGRP mAbs treatment, were recruited. They underwent transcranial Doppler (TD) examination before starting (T0), and at one month (T1), three months (T2), six months (T3) and twelve months (T4) of treatment. Scores of migraine related disability and headache impact scales (MIDAS, HIT-6) were assessed at each visit.

Results: The basal mean attack frequency/month was 17.8±7 days. The mean MIDAS and HIT-6 scores were 124.6±42 and 66.9±6.75, respectively. All patients completed the T2 treatment period, 7 ended one year of treatment. A significative reduction in headache frequency and MIDAS scores was detected in 95,4% of patients after three months of treatment. An increase in vasoreactivity index (VRI) of the middle cerebral artery (MCA) was found compared to baseline, with significant differences already at T2 (p=0.046).

Discussion: The VRI expresses the ability of cerebral blood vessels to dilate or constrict in response to metabolic stimuli and is considered an indirect indicator of endothelial dysfunction. The few studies on the effects of anti-GCRP ligand or receptor mAbs on cerebral hemodynamics reported that responders had increased mean velocity values in large intracranial arteries compared to baseline, unlike nonresponders [1]. Our study showed an increase in the MCA VRI during anti-CGRP-mAbs treatment, bringing the values of migraine patients more in line with those of non-migraine population. It is conceivable that intracranial vessel endothelium in migraineurs is in a condition of reduced vascular tone and potentially of maintained vasodilation due to the excessive stimulus exerted by CGRP. CGRP receptor or ligand blockade would counteract this effect on intracranial vascular tone, thus inducing an increase in the values of MCA VRI. If confirmed on a larger number of patients, this finding would suggest that the lower availability of CGRP can potentially limit its protective action against hypoxic and ischemic conditions [2,3].

Conclusions: Anti-CGRP-mAbs therapy may induce modifications in cerebral vasoreactivity consistently with the clinical benefit for the patients. TD is a rapid and non-invasive tool to verify these modifications before and during anti-CGRP-mAbs treatment. Based on our results a pivotal attention should be paid to migraine patients with cardiovascular risk factors or the elderly population.

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## POST HOC ANALYSIS OF PROGRESS: EVALUATING THE SAFETY OF ATOGEPANT IN PARTICIPANTS WITH CHRONIC MIGRAINE AND CARDIOVASCULAR RISK FACTORS

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Objectives: Previous studies have shown an association between migraine, cardiovascular disease, and cardiovascular risk factors; however, there is no evidence on the safety of oral calcitonin gene–related peptide receptor antagonists in the preventive treatment of chronic migraine in those with cardiovascular risk factors. The objective of this study is to evaluate the safety of atogepant in PROGRESS trial participants with chronic migraine (CM) and cardiovascular risk factors (CV-RFs).

Materials: A 12-week, international, randomized, double-blind, placebo-controlled phase 3 trial (PROGRESS; NCT03855137) enrolled participants (18-80 years) with ≥1-year CM (≥15 monthly headache days [MHDs] for 3 months before screening; ≥15 headache days [≥8 migraine days] during the 4-week screening period).

Method: Participants treated with atogepant 30mg twice-daily, 60mg daily, or placebo were stratified by 0, 1, or ≥2 baseline CV-RFs. CV-RFs included age (men: ≥45; women: ≥55), smoking, body mass index (BMI) ≥25kg/m2, hypertension, diabetes, dyslipidemia, sleep apnea, concomitant CVD or diabetes medicines, and history of stroke, myocardial infarction, transient ischemic attack, or peripheral arterial disease. CV treatment-emergent adverse events (TEAEs) were assessed.

Results: Of 773 participants, 518 (1 missing data) comprised the pooled atogepant group (0 CV-RFs: 110[21.2%]; 1 CV-RF: 146[28.2%]; ≥2 CV-RFs: 261[50.4%]) and 255 comprised the placebo group (0 CV-RFs: 47[18.4%]; 1 CV-RF: 92[36.1%]; ≥2 CV-RFs: 116[45.5%]). Among all participants, the majority had ≥2 CV-RFs compared to 0 or 1 CV-RFs. At baseline, participants with ≥2 CV-RFs had higher mean age, BMI, and MHDs versus those with 0 or 1 CV-RFs. Most common CV-RFs were dyslipidemia (47.6%), BMI ≥25kg/m2(43.1%), and hypertension (40.9%). CV-TEAEs occurred at low frequencies among participants with ≥2 CV-RFs (placebo: 3/116[2.6%]; pooled atogepant: 9/261[3.4%]), and none were serious. Treatment-related CV-TEAEs included palpitations (n=2) and increased blood pressure (n=1) in the pooled atogepant group (all 30mg twice-daily) and flushing (n=1) in the placebo group. Palpitations led to 1 discontinuation (assessed as not treatment-related) in the pooled atogepant group.

Discussion: This post hoc analysis demonstrates that CV-TEAEs occurred at low frequencies among atogepant-treated participants with CM and CV-RFs. All CV-TEAEs were nonserious, most were not treatment-related, and only 1 led to discontinuation.

Conclusion: This study provides evidence of the safety of an oral calcitonin gene–related peptide receptor antagonist among a cohort of participants with chronic migraine and cardiovascular risk factors.

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## THE ROLE OF ANTI-INFLAMMATORY AGENTS AS SYMPTOMATIC THERAPY FOR PRIMARY HEADACHES: AN ANALYSIS OF UTILIZATION AND THERAPEUTIC EFFICACY

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Purpose: This study aimed to gather data on the utilization of anti-inflammatory drugs as acute therapy for primary headaches: migraine with or without aura, and tension-type headache [1], at the Headache Center of the Fondazione Policlinico Campus Bio-Medico. The aim was to identify factors influencing drugs efficacy, the most commonly utilized molecules, and potential interactions with other migraine's treatments [2][3].

Methods: This is a retrospective study involved the medical records of 76 patients followed by Headache Center for one year

(2022) diagnosed with migraine and/or tension-type headache. The initial medical visit in the year 2022 (t0) and the subsequent visit after 3-6 months (t1) were evaluated. Collected data included headache frequency, MIDAS, anti-inflammatory drugs type and effectiveness (assessed on a scale of 0 to 2: ineffective, pain relief, pain free), frequency of use, use of triptans and prophylactic therapies.

Results: Population mean age was 43 years (± 13.4 years), predominantly females (90.7%). Chronic migraine was present in 52.6% of patients, and 7.8% experienced aura. Only 2 patients exhibited tension-type headache characteristics. The most frequently employed anti-inflammatory drugs were ketoprofen (40.8%) and ibuprofen (30.3%), followed by indomethacin-proclorperazine-caffein (21.1%), nimesulide (11.8%), paracetamol (10.5%), naproxen (9.2%), indomethacin (9.2%), diclofenac (6.6%), metamizole (6.6%). Prophylactic therapy was used by 18.4% of patients at t0 and by 71.1% at t1. Amitriptyline was the most frequently prescribed drug at both t0 (11.8%) and t1 (26.3%), while topiramate was the most commonly added therapy (t0=1.3%, t1=21.1%). Four patients received monoclonal antibody therapy (Erenumab, Galcanezumab, Fremanezumab) at t0, whereas 13 patients (17.3%) were under this therapy at t1. Statistical analysis indicated an overall reduction in the frequency of migraine attacks (t0=14.7 ± 8.5, t1=6.9 ± 5.8) and a decrease in anti-inflammatory drugs use (t0=13.2 ± 10.4, t1=5.1 ± 3.9). An increase in the efficacy of anti-inflammatory drugs and a reduction in their utilization were observed among patients in whom prophylactic therapy was added or modified between t0 and t1 ($\chi$2=7.706, p=0.006, 95% CI=1.5-21.9). The addition of amitriptyline to prophylactic therapy was significantly associated with increased drug efficacy ($\chi$2=6.792, 95% CI=1.3-12.2, p=0.018).

Conclusions: These preliminary findings suggest that the inclusion of prophylactic therapy, particularly amitriptyline, may enhance the efficacy of anti-inflammatory drugs in the treatment of primary headaches. These results are still preliminary, and the study is ongoing. Future investigations will further explore the effects of initiating monoclonal antibody therapy (infrequently utilized in this population) and factors influencing the efficacy of anti-inflammatory drugs in primary headaches.

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## ANTI-CALCITONIN GENE-RELATED PEPTIDE MONOCLONAL ANTIBODIES FOR THE TREATMENT OF MIGRAINE WITH AURA: A PROSPECTIVE OBSERVATIONAL COHORT STUDY

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Objectives: About 15% of migraineurs experience aura symptoms. Aura is a reversible focal neurological phenomenon involving visual, sensory, speech and motor symptoms that usually precede migraine pain [1]. Monoclonal antibodies against calcitonin-related peptide (anti-CGRP mAbs) are effective in preventing chronic and episodic migraine, but little is known about their effectiveness on specifically preventing migraine with aura. This study aims at evaluating the effectiveness of anti-CGRP mAbs on migraine with aura, and aura symptoms.

Methods and Materials: This is a prospective observational cohort study, aiming at evaluating the efficacy of Erenumab, Fremanezumab or Galcanezumab for the treatment of migraine with aura. We enrolled 14 patients at the Headache Centre of University Federico II of Naples, with a history of multiple failed treatments with validated migraine preventatives. Duration of follow-up was 12 months. We assessed mean monthly days with aura symptoms, with or without subsequent headache, as well as mean monthly days with headache and mean monthly MIDAS score, by reviewing standardized paper patient headache diaries every three months.

Results: We observed a mean reduction of mean monthly days with aura symptoms of - 8.17 (- 5.76, - 10.57; CI 95%) and a mean reduction of mean monthly days with headache of - 15.92 (- 11.09, - 20.75; CI 95%) after 12-month treatment with anti-CGRP mAbs. No significant differences were found between Erenumab, Fremanezumab or Galcanezumab in terms of effectiveness.

Discussion: CGRP has been implicated in the activation of cortical spreading depression (CSD), a wave of neuronal hyperactivity followed by a period of depression that is associated with migraine aura [2]. CSD is thought to be a key mechanism underlying the development of aura. CGRP can increase neuronal excitability and promote the release of other neurotransmitters that may contribute to the initiation of CSD. Furthermore, CGRP has been found to enhance the susceptibility of brain tissue to CSD, possibly making it more likely to occur and propagate [3]. In this study we observed a significant reduction of mean monthly days with aura symptoms, further strengthening this hypothesis.

Conclusions: Our findings show that anti-CGRP mAbs are highly effective in migraine with aura, both in reducing mean monthly headache days and mean monthly days with aura symptoms.

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## ASSESSING BARRIERS TO CARE IN EPISODIC AND CHRONIC MIGRAINE: RESULTS FROM THE CHRONIC MIGRAINE EPIDEMIOLOGY AND OUTCOMES (CAMEO) STUDY

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Objectives: Barriers to good outcomes in migraine include lack of appropriate medical consultation, failure to receive an accurate diagnosis, not being offered a regimen with acute and preventive pharmacologic treatments, and not avoiding acute medication overuse. This study aims to assess rates of traversing fundamental barriers to good medical outcomes in individuals with episodic (EM) and chronic migraine (CM) and evaluate the potential impact of sociodemographic barriers.

Materials: Respondents to the US Internet-based Chronic Migraine Epidemiology and Outcomes (CaMEO) Study who met modified International Classification of Headache Disorders, 3rd edition, criteria for migraine, had a Migraine Disability Assessment score of grade ≥2, and provided health insurance status were included.

Methods: Proportions of EM and CM respondents who successfully traversed each barrier were calculated and the effects of sociodemographic characteristics were examined.

Results: Among 16,789 respondents with migraine, 9184 (EM: 7930; CM: 1254) met eligibility criteria. Current headache consultation was reported by 27.6% (2187/7930) of EM and 40.8% (512/1254) of CM respondents. Among consulters, 75.7% (1655/2187) of the EM sample and 32.8% (168/512) of the CM sample were accurately diagnosed. Among diagnosed consulters, 59.9% (992/1655) of the EM group and 54.2% (91/168) of the CM group reported minimally appropriate acute and preventive pharmacologic treatment. Among diagnosed and treated consulters, 31.8% (315/992) of persons with EM and 74.7% (68/91) of those with CM met acute medication overuse criteria. Only 8.5% (677/7930) of EM and 1.8% (23/1254) of CM respondents traversed all 4 barriers. Higher income was associated with increased rates of traversing each barrier ($P<0.05$).

Discussion: These results show that less than 8% of people with migraine traverse all 4 treatment barriers, and sociodemographic factors were significantly associated with the likelihood of traversing these barriers.

Conclusions: Previous research evaluated barriers to care in either episodic migraine or chronic migraine. These data are the first to evaluate barriers to care in both types of migraine within the same study population and to assess the effects of sociodemographic characteristics. Efforts to improve care should focus on increasing consultation and diagnosis rates, improving delivery of guideline-based acute and preventive treatment, and avoidance of medication overuse.

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## HEADACHE, BRAIN ABSCESS AND A RARE CAUSE OF WEAKENED IMMUNE SYSTEM: A CASE REPORT

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Background: Brain abscess is a frequent infectious disease of the central nervous system. Headache, fever, and fatigue are the most common initial manifestations. A weakened immune system is the main predisposing factor for brain abscess development.

Material and methods: A 37-year-old male with no prior history of headaches referred to hospital for the onset of severe right-sided headaches behind the eye. He had a two-week history of fatigue and slight fever but neurological examination was unremarkable.

Results: Routine blood analysis showed leukocytosis and an increase of C-reactive protein. Brain Magnetic Resonance Imaging (MRI) revealed the presence of a right frontal lobe circular space-occupying lesion with a ring wall contrast enhancement and large patches of edema. Brain frontal mass was drained completely under general anesthesia and microbiology testing of the specimen revealed Nocardia Farcinica. Treatment with trimethoprim-sulfamethoxazole and imipinem was started. HIV 1 and 2 antibody tests were negative and other common predisposing conditions causing brain abscess were ruled out [1]. However, patient past medical history included pulmonary alveolar proteinosis (PAP), a rare autoimmune syndrome caused by anti- GM-CSF (granulocyte–macrophage colony-stimulating factor) antibodies [2].

Discussion: Clinicians should always consider a diagnosis of brain abscess when dealing with a new onset headache associated with fever and fatigue. The great clinical challenge for the physician is recognizing the predisposing factors associated with brain abscess development.

Conclusion: PAP is a rare autoimmune syndrome characterized by high concentrations of anti-GM-CSF antibodies, decreasing its level and biological activity. The brain is highly susceptible from bacterial invasion during GM-CSF depletion. Regarding brain abscess predisposing factors, immunodeficiency secondary to anticytokine autoantibodies should always be reminded especially considering that patients with anti GM-CSF antibodies may have CNS involvement as their first clinical manifestation [3].

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## "DIM LIGHT MELATONIN ONSET" AND CHRONOTYPE PROFILING IN PATIENTS WITH EPISODIC AND CHRONIC MIGRAINE

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Objectives: Chronic migraine with medication overuse headache (CM-MOH) represents one of the most disabling phenotypes across the migraine spectrum. Patients with CM-MOH suffer several comorbidities, including sleep disorders. The aim of this study is to better define the chronotype of migraine patients by means of subjective clinical scales and salivatory melatonin measurements.

Materials: We enrolled 40 CM-MOH patients, 18 episodic migraine (EM) patients and 32 healthy controls (HCs).

Methods: All subjects completed the Morningness–Eveningness Questionnaire (MEQ), the Pittsburgh Sleep Quality Index (PSQI) and a prospective sleep diary. They also underwent 5 saliva melatonin samplings (at hourly intervals with the first sample collected 3 hours before the subject's regular bedtime). We calculated the "Dim Light Melatonin Onset" (DLMO), namely the time of the day at which salivatory melatonin reaches 3 pg/ml, a well-known biological marker of circadian phase in humans.

Results: EM patients were younger when compared to CM-MOH patients and HCs. MEQ score was higher (suggesting a morning-oriented chronotype) in CM-MOH (59.6±7.7) when compared to EM (53.3±11.9, p=0.045) and HCs (51.0±10.1, p=0.001). According to MEQ, a subjective morningness profile was more prevalent in CM-MOH (56.8%) when compared to EM (33.3%) and HCs (17.2%) (p=0.001). Noteworthy, DLMO occurred earlier in CM-MOH (20:31±52 minutes) and in EM (20:28±0:49 minutes) when compared to HCs (21:17±63 minutes; p=0.05 and p=0.014, respectively). This was confirmed in a multinominal regression corrected for age and sex. DLMO did not differ between CM-MOH and EM groups (p=1.000).

According to DLMO, a biological morningness profile was more prevalent in CM-MOH (32.4%) and in EM (33.3%) when compared to HCs (7.4%) (p=0.019). Finally, according to the PSQI, sleep quality was more impaired in CM-MOH when compared to EM.

Discussion: Migraine patients showed a morning-oriented subjective and objective chronotype when compared to HCs. The chronotype based on DLMO revealed no discernible differences between CM-MOH and EM groups, although CM-MOH patients described themselves as more morning oriented.

Conclusions: Our results suggest that chronotype in migraine patients is primarily influenced by an inherited biology rather than disease severity. CM-MOH patients are more inclined towards morningness, indicating that behavioral and environmental factors still play a significant role.

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## THE CRYPT OF NANA'

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Background: Cryptococcus neoformans is a leading cause of fungal meningitis in immunocompromised patients and it often occurs when the CD4+ T cell count is less than 100 cells/microL. Cryptococcosis, the infection caused by C. neoformans, is usually contracted through the inhalation of fungal spores, but the pulmonary infection could remain sub-clinical. Instead, its first manifestation among those with advanced immunosuppression is the meningitis (CM), or often the meningoencephalitis.

Case Report: Nana', a 43-year-old Georgian woman, came to our emergency department for worsening headache, ideomotor slowdown, seizures and visual reduction. In anamnesis, nothing noteworthy, despite some difficulties with the language barrier; vital parameters were altered with evidence of arterial hypertension, bradycardia and tachypnea with a saturation in room air equal to 92%. The objective examination revealed hindrance to neck movements without a real neck stiffness and an oropharyngeal candidiasis. At the ABG, there were no electrolyte alterations or increased lactates; blood tests revealed a neutrophilic leukocytosis with lymphopenia and a slightly increased CRP; the instrumental examinations, skull CT and chest x-ray, were negative. However, during the clinical observation, there was a worsening of her state of consciousness with new episodes of blood hypertension associated with a visual reduction and an absence episode. EEG and brain MRI with contrast agent were performed, for the suspect of a Posterior Reversible Encephalopathy Syndrome, but both were negative. After a new clinical evaluation, the doubt of an intracranial hypertension arose and an ultrasound exam of optic nerve was executed, highlighting its dilatation and confirming the suspect. Therefore, lumbar puncture was performed and tested the cerebrospinal fluid (CSF). The CSF pressure was elevated, with a clear look and evidence of hypoglycorrhachia. Blood culture and HIV test were required considering the presence of oropharyngeal candidiasis and lymphopenia. The tests were positive for Cryptococcal meningitis and HIV infection. She started the specific therapy, and a lumbar CSF drainage was placed. The patient was hospitalized at the infectious department, where a concomitant pneumocystosis and cytomegalovirus infection were observed, and discharged after three months.

Conclusion: CM has the strongest association with patients with HIV infection, but other immunocompromised patients including those with cancer, iatrogenic immunosuppression, autoimmune disease, chronic kidney disease and diabetes are at high risk. Therefore, we must pay attention on this disease considering that developed countries have observed an increase in non-HIV associated cases of CM compared to other immunosuppressed patients by virtue of access to antiretroviral therapy.

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## SOMATOSENSORY EVOKED POTENTIALS IN TENSION-TYPE HEADACHE

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Methods: A prospective cohort of 19 TTH patients (9 with episodic and 10 with chronic presentation) along with 20 healthy controls were recruited for this study. All participants underwent somatosensory evoked potential (SSEP) recordings, enabling the calculation of N20-P25 amplitude and its habituation across three sets of 100 responses. Additionally, by applying a band-pass filter (450-750 Hz) to the SSEP signal, we extracted two distinct bursts of high-frequency oscillations (early and late HFOs), reflecting thalamo-cortical and primary cortical activity, respectively.

Results: The latency and amplitude values of SSEPs, as well as the habituation patterns assessed between the initial two and three sets of 100 responses, demonstrated normal findings in TTH patients, including both the episodic and chronic subgroups. However, TTH patients, regardless of the episodic or chronic nature, exhibited a notable increase in cortical HFO amplitude burst ($p<0.001$) while maintaining normal thalamo-cortical activity.

Discussions: Considering that TTH is a painful pathological condition capable of eliciting sensory neurons to the extent of sensitizing them, it is unsurprising to observe that it indeed does so, as indicated by the findings of increased amplitude of cortical high-frequency oscillations (HFO). However, it is also noteworthy to highlight the presence of thalamocortical activity comparable to that observed in the control group, in contrast to what is typically observed in migraine [1]. Further investigations are warranted to establish the potential association between these observed manifestations and pericranial muscle tension, encompassing the activation or sensitization of nociceptive nerve endings through the release of chemical mediators.

Conclusions: Our findings indicate that TTH patients exhibit electrophysiological evidence of central sensitization and show no differences in their habituation pattern compared to controls.

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## DISABILITY IN MIGRAINE: MULTICOUNTRY RESULTS FROM THE CAMEO-INTERNATIONAL STUDY

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Objectives: Although individual studies evaluating headache burden are available from many countries, few studies have been conducted across multiple countries using the same methodology. This cross-sectional, multicountry analysis, aims to describe disability among individuals with migraine.

Materials: Chronic Migraine Epidemiology and Outcomes-International (CaMEO-I) was a cross-sectional, web-based survey conducted in 2021-2022 in Canada, France, Germany, Japan, the United Kingdom, and the United States. The American Migraine Study/American Migraine Prevalence and Prevention Study diagnostic questionnaire identified respondents with migraine based on modified International Classification of Headache Disorders, 3rdedition, criteria.

Methods: This analysis evaluated migraine burden using the Migraine-Specific Quality of Life Questionnaire (MSQ) and the Work Productivity and Activity Impairment Questionnaire (WPAI). The MSQ is a 14-item questionnaire that measures the effect of migraine on daily functioning across 3 domains, with higher scores corresponding to better quality of life. The WPAI evaluates the impact of migraine on work productivity and regular activities.

Results: This analysis included 14,492 respondents with migraine (~2400 from each country). Mean (SD) MSQ scores ranged from 57.7 (23.4) in Canada to 63.3 (21.1) in France for the role function restrictive domain, 67.6 (22.9) in Germany to 77.3 (22.7) in Japan for the role function preventive domain, and 63.9 (29.1) in the US to 69.2 (24.8) in France for the emotional function domain. Based on the WPAI, the mean (SD) percentage of work missed (absenteeism) ranged from 4.3% (16.2) in France to 9.0% (21.7) in Germany, percentage of work impaired (presenteeism) ranged from 31.2% (28.0) in France to 47.8% (28.6) in Japan, percentage of overall work impaired ranged from 33.5% (30.3) in France to 49.4% (29.4) in Japan, and percentage of activity impaired ranged from 39.3% (30.2) in France to 50.7% (28.4) in Japan.

Discussion: For every country surveyed, migraine is associated with substantial burden, including poor quality of life and work/activity impairment.

Conclusions: This international study demonstrated that migraine is associated with substantial disability, including poor quality of life, work/activity impairment, and losses in productivity across multiple countries. Further research is warranted to explore reasons for potential differences between countries in the prevalence of specific headache disability.

Reference:

– Adams AM, Serrano D, Buse DC, Reed ML, Marske V, Fanning KM, Lipton RB. The impact of chronic migraine: The Chronic Migraine Epidemiology and Outcomes (CaMEO) Study methods and baseline results. Cephalalgia (2015);35(7):563-78

## SWITCHING FROM ONABOTULINUMTOXIN-A TO ANTI-CGRP MONOCLONAL ANTIBODIES IN CHRONIC MIGRAINE PREVENTION

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Objectives: Aim of the present study was to evaluate clinical outcome in patients currently in treatment with anti CGRP monoclonal antibodies (mAbs), previously treated with onabotulinumtoxin-A.

Materials and Methods: This retrospective study was performed at the ASST Spedali Civili of Brescia, between November 2014 and May 2023. All patients had a diagnosis of chronic migraine according to the International Classification of Headache Disorders III (ICHD-III) [1] and currently in prophylactic treatment with anti-CGRP mAbs. The primary endpoint was to evaluate the reduction of monthly headache days (MHDs), monthly migraine days (MMDs) and clinical disability according to MIDAS score in patients previously treated with onabotulinumtoxin-A. The secondary endpoints were to evaluate: (1) whether clinical response to anti-CGRP mAbs was affected by the number of previous onabotulinumtoxin-A administrations; (2) clinical outcome in patients currently in treatment with anti-CGRP mAbs previously treated with onabotulinumtoxin-A compared to those who failed only oral preventive treatments.

Results: One-hundred and thirty-nine patients were enrolled, of which 62 previously treated with onabotulinumtoxin-A. Regarding this latter group, baseline (introduction of anti-CGRP mAbs) mean MHDs was 22.0 (6.5), mean MMDs was 11.1 (8.7) and mean MIDAS score was 92.9 (77.6). Following three months (T3) of anti-CGRP treatment, 66% of patients obtained a reduction of MHDs >=50%. A significant reduction in MHDs (10.3±7.4; p<0.0001), MMDs (3.2±3.6; p<0.0001) and MIDAS score (22.5±20.1 p<0.0001) was found from baseline to T3. Mean onabotulinumtoxin-A cycles received before switching to anti-CGRP mAbs was 5, ranging between 1-11. Patients who discontinued before 3 cycles (minimum number to detect a significant clinical response) did so due to personal choice or scarce tolerance to the injections. At T3, patients who received ≤ 3 onabotulinumtoxin-A cycles documented a higher reduction of MIDAS scores, compared to those who received ≥ 4 treatment cycles (-89.7 versus -68.7, p=0.049). Compared to onabotulinumtoxin-A naïve patients, patients who previously received onabutlinumtoxin-A, documented less MMDs (3.3±3.7 versus 5.2±5.0; p=0.017) and a lower MIDAS score (respectively 23.2±20.9 versus 37.4±39.6; p=0.013).

Discussion: Anti CGRP mAbs are effective in chronic migraine patients' prophylaxis. According to our data, previous treatment with onabotulinumtoxin-A might improve subsequent response to anti CGRP mAbs preventive treatment.

Conclusion: In chronic migraine patients prophylactic treatment with onabotulinumtoxin-A represents a valid option to be considered also in those patients eligible for anti CGRP mAbs prophylaxis, as it might improve their clinical response.

Reference:

1. Jes Olesen et al. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia (2018);38:1-211

## RESISTANCE AND REFRACTORINESS EXTEND FROM PREVENTIVE TO ACUTE MIGRAINE THERAPIES: DATA OF AN INTERNATIONAL REAL-LIFE STUDY ON RESISTANT AND REFRACTORY MIGRAINE (REFINE)

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Backgrounds: The terms "resistant" and "refractory" identify patients who do not respond to preventive medication. However, it is common experience in headache centers that patients may have multiple failures of acute medication. We evaluated the response to acute migraine medication, their frequency of use, and treatment satisfaction in patients with resistant migraine (Res), refractory migraine (Ref), and non-resistant, non-refractory migraine (Nres/Nref) in an international study.

Methods: We reported the baseline data of the prospective multicenter observational REFINE study, which included consecutive patients with Res, Ref and Nres/Nref. Patients with Nres/Nref were matched by age with those with Res and Ref. We assessed demographics, medical history, and history of medication overuse in each patient. We assessed the number of symptomatic drugs taken in the last three months, both overall and by class, and patient satisfaction with acute treatment based on questions 1-5-6 of the Headache Under-Response to Treatment (HURT).

Results: We included 671 patients (82,4% women) with a median age of 46 years (interquartile range – IQR, 37-54) and a median age at migraine onset of 17 (IQR 13-23) years. Two-hundred and fifty-three (37.7%) had Res, 73 had Ref (10.9%) and 345 (51.4%) Nres/Nref. Patients with Res and Ref had a higher prevalence of medication overuse than those with Nres/Nref (47.4% vs 45.2% vs 20.0%; $p<0.001$). Patients with Res, Ref, and Nres/Nref had a median intake of 14 (IQR 10-24), 17.5 (IQR 10-21.5), and 10 (IQR 5-18) monthly doses of analgesics ($p<0.001$). At the HURT questionnaire, in the last month Res, Ref and Nres/Nref patients with headache days ≥6 were respectively (95.6% vs 98.6% vs 58.5%; $p<0.001$). In Res and Ref patients, a single dose of medication was often not sufficient to relieve headache, unlike those with Nres/Nref (73.5% vs 93.1% vs 47.4%, $p<0.001$), and they also reported less feeling control over their headaches (85.1% vs 94.9% vs 61%; $p<0.001$).

Discussion: According to our results, patients with Res or Ref have more headache days and use more acute medications than those with Nres/Nref and have achieved less success and satisfaction with these therapies.

Conclusion: Res and Ref patients should be recognized quickly to find better management to prevent them from having poor headache control. In headache centers, they should be given appropriate and immediate treatment opportunities.

Reference:

– Sacco S., Braschinsky M., Ducros A., Lampl C., Little P., Van den Brink A.M. et al. European headache federation consensus on the the definition of resistant and refractory migraine: Developed with the endorsement of the European Migraine & Headache Alliance (EMHA). Journal of Headache and Pain (2020);21:1

## MIGRAINE WITH AURA AS EARLY MANIFESTATION OF CEREBRAL AMYLOID ANGIOPATHY: A CASE REPORT

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Objectives: Migraine has been described in different cerebrovascular syndromes as an early hallmark or even isolated symptom, supporting the presence of a link between migraine and microvascular changes in early stages of angiopathies. To our knowledge very few studies investigated the correlation between migraine and cerebral amyloid angiopathy (CAA) and to date little is known about prevalence, clinical features and pathophysiology of this association. Here we describe a case of a 55-year-old man affected by migraine with aura and diagnosed with probable CAA (according to the Boston criteria version 2.0).

Material and Methods: We present the case of a 55 years-old man suffering from migraine with visual aura since he was 7 years old. When he was 38 years old, the patient performed an MRI that was unremarkable. After the age of 50, migraine attacks became more frequent, disabling and less responsive to medical treatments.

Results: For these reasons, the patient underwent a brain MRI that revealed small diffuse haemosiderin deposits (microbleeds) in the lobar portion of cerebral hemispheres, especially in the occipital lobes, and in the left cerebellar lobe on gradient echo sequences, suggesting the diagnosis of CAA. For the progressive worsening of symptoms, the patient was admitted to our Department at the age of 55. During hospitalization, the patient underwent EEG and thrombophilia screening, which were unremarkable, and brain MRI, which showed an increased number of the previously described haemosiderin deposits.

Discussion: Migraine is an early manifestation in many cerebrovascular syndromes such as subcortical infarcts and leukoencephalopathy or retinal vasculopathy with cerebral leukoencephalopathy. To our knowledge, the association between CAA and this primary headache syndrome has been only rarely reported in the literature [1,2]. A recent study confirmed that migraine has a relatively high prevalence and is often a prodromal symptom in patients with hereditary Dutch-type CAA, a genetic variant of CAA [1]. It may be hypothesized that migraine in cerebrovascular disease can be caused by vascular changes associated with damage to the intracerebral small vessels leading to

impaired vasoreactivity and increased susceptibility to cortical spreading depression. However, to date, the underlying pathophysiological basis is still not fully understood and further studies are required.

Conclusion: In this context, our report supports the existence of a link between these two conditions and suggests that migraine with aura can be regarded as an early marker of CAA that precedes the occurrence of intracerebral hemorrhages by several years.

References:
1. Koemans EA, Voigt S, Rasing I et al. Migraine with Aura as Early Disease Marker in Hereditary Dutch - Type Cerebral Amyloid Angiopathy. Stroke (2020);51(4):1094-99
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## PAIN PROCESSING AND MODULATION IN EPISODIC MIGRAINE AND MEDICATION OVERUSE HEADACHE. A THERMAL QUANTITATIVE SENSORY TESTING STUDY

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Background and aim: The offset analgesia (OA) phenomenon refers to the disproportionately large decrease in the perceived pain following a slight decrease in intensity of a noxious warm stimulus. This is considered as expression of activation of the endogenous pain-modulation system, whose dysfunction is supposed to be involved in the pathophysiology of migraine and chronic cephalalgias such as medication overuse headache (MOH). Aim of this study was to investigate pain processing mechanisms in patients with episodic migraine (assessed during the different phases of the migraine cycle) and MOH by using the OA paradigm.

Methods: Forty patients with episodic migraine (20 assessed in the interictal period, 10 in the pre-ictal period, and 10 in the ictal period), 10 patients with MOH, and 15 healthy control subjects were enrolled. All subjects underwent an experimental paradigm consisting of 3 stimulus offset trials and 3 constant temperature trials based on the individual heat pain threshold. Both the trigeminal area (supraorbital region) and an extratrigeminal site (ipsilateral hand) were tested in a single session.

Results: The magnitude of OA phenomenon was calculated by subtracting pain ratings from the constant trial from those of the offset trial. OA phenomenon was not observed in patients with MOH when the trigeminal area was tested. No significant differences in the OA phenomenon were observed between patients with episodic migraine evaluated during the different phases of the migraine cycle. Between group comparisons made to assess pain ratings changes during the constant trial showed a significant difference between episodic migraine patients evaluated in the interictal vs peri-ictal phase, i.e. a marked adaptation to the stimulus was observed only in patients in the ictal and pre-ictal phase.

Discussion and conclusions: These data show that a dysfunction in the endogenous pain-modulation system could play a pathophysiological role in patients with medication overuse headache. Changes in adaptation and sensitization phenomena in response to thermal stimuli were also observed throughout the migraine cycle, suggesting a complex interplay between different aspects of painful sensations processing and modulation in migraine.

Reference:
– Szikszay TM, Adamczyk WM, Carvalho GF, May A, Luedtke K. Offset analgesia: somatotopic endogenous pain modulation in migraine. Pain (2020);161:557

## PREVALENCE OF PRIMARY STABBING HEADACHE IN CHRONIC MIGRAINE, CLINICAL FEATURES AND ITS ASSOCIATION WITH VENOUS SINUS STENOSIS

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Objective: Primary stabbing headache is a condition whose prevalence is not well defined, as well as its pathophysiology. The aim of this study is to calculate the prevalence of idiopathic stabbing headache and assess the clinical features of the stabs. The study also evaluated the association between stabbing headache and the presence of dural sinus stenosis, a highly sensitive and specific radiological marker of idiopathic intracranial hypertension. Lastly, it analyzes whether the side of the stenosis corresponds to the site of the stabbing pain.

Material and methods: Data from 579patients referred to the Headache Centre of the AOU Federico II in Naples from 2017to 2021were retrospectively analyzed. The study enrolled patients who showed an MRI with venographic sequences at the follow-up visit. Magnetic resonance was examined for each patient and the venous sinus stenosis of the dura mater were graded according to the "combined conduit score". The characteristics of stabbing headache attacks were assessed in terms of monthly frequency, daily frequency, duration and location. Statistical analyses were carried out with the aid of Microsoft Excel.

Results: 37.6%of patients presented with idiopathic stabbing headache. The monthly frequency is 7, and the daily frequency varies from 1attack per day to more than 10attacks per day. Pain sites among the various patients are distributed throughout the head. The majority of patients presented with stabbing headache in comorbidity with other headaches, mainly chronic migraine. Patients with stabbing headache had significantly more venous stenosis than patients without stabbing headache. In addition, a correlation was observed between the site of stenosis and the site of stabbing pain.

Discussion: There are several hypotheses about the pathophysiological mechanism underlying stabbing headache, including irritation or spontaneous discharge of trigeminal nerve neurons. Some cases in the literature identify the stabbing headache as a presenting symptom of intracranial hypertension, a condition associated with stenosis of the dural venous sinuses. These results support the hypothesis that stabbing headache may underlie a state of intracranial hypertension.

Conclusions: The results suggest that primary stabbing headache is common in patients with migraine and is associated with stenosis of the dural sinuses, which could represent a pathophysiological link with a condition of intracranial hypertension and this could open the way to new therapeutic scenarios. The correspondence between the site of the stenosis and the fit is a new finding, which certainly needs further investigation to be confirmed. Further studies are needed to deepen the understanding of this kind of headache.

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## EFFECTIVENESS OF TRANSCRANIAL DIRECT CURRENT STIMULATION AND MONOCLONAL ANTIBODIES ACTING ON THE CGRP AS A COMBINED TREATMENT FOR MIGRAINE (TACTIC) – PRELIMINARY RESULTS

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Background and aims: Transcranial direct current stimulation (tDCS) is a promising non-invasive neuromodulation technique for migraine prevention. tDCS exerts its effects trough modulation of brain cortex, while monoclonal antibodies acting on the calcitonin gene-related peptide pathway (CGRP-MAbs) are an established migraine treatment acting on peripheral targets. Thus, it is reasonable to hypothesize a synergistic effect of tDCS and CGPR-MAbs. We aimed to assess whether tDCS, as an add-on treatment to CGRP-MAbs, improves migraine prevention. We also measured electroencephalographic (EEG) power changes to estimate the biological effects of this combined therapeutic approach.

Materials and Methods: TACTIC (NCT05161871) 1 is an ongoing randomized, double-blind, multicenter, sham-controlled trial including patients with migraine treated with CGRP-MAbs for ≥90 days and still reporting ≥8 monthly migraine days. We performed a 5-day tDCS protocol with bilateral cathodal electrodes on occipital area and anodal electrodes positioned on the primary motor areas (sham/active sessions lasting 20 minutes) and we followed up patients for 28 days. We also recorded 64-channel EEG at day 1 (pre-stimulation) and day 5 (end of stimulation). We analyzed change in monthly migraine days, clinical scales, and EEG changes in spectral power in the delta (2-4Hz), theta (5-7Hz), alpha (8-12Hz) and beta bands (13-30Hz).

Results: At state of art, we included 13 patients (mean age=46.2 ±12.5, 92.0% female), 7 in active session and 6 in sham. tDCS led to a decrease in monthly migraine days that was more pronounced – although not significant – in the active group (mean difference 3.57, standard error (SE)=1.91, p=0.089). An improvement in the HADS-D scale for depression was found in the active group (mean difference 2.85, SE=0.85 p=0.007) compared with sham (mean difference 1.3, SE=0.92, p=0.17). tDCS induced a significant reduction in the alpha band power – representing most of the occipital cortical activity with eyes closed – and a decrease in delta power over the motor areas only in the active stimulation group (both $p<0.05$); no difference was found in the sham group. No adverse events were reported.

Discussion and conclusions: We described scarce clinical effect of tDCS when combined with CGRP-MAbs. The strong peripheral action of CGRP-MAbs might hinder subtle clinical effects of tDCS. These results must be taken with caution due to the small sample size recruited to date or to the short duration of the stimulation period. According to our preliminary results, tDCS changed basal cortical activity on stimulated areas without any significant improvement in headache in patients treated with CGRP-MAbs.

Reference:

– Ornello R, Rosignoli C, Caponnetto V, Pistoia F, Ferrara M, D'Atri A, Sacco S. Effectiveness of Transcranial Direct Current Stimulation and Monoclonal Antibodies Acting on the CGRP as a Combined Treatment for Migraine (TACTIC): Protocol for a Randomized, Double - Blind, Sham - Controlled Trial. Front Neurol. (2022)

## THE EPIDEMIOLOGY AND UNMET NEEDS OF DIAGNOSED MIGRAINE RESPONDENTS USING THE NATIONAL HEALTH AND WELLNESS SURVEY IN ITALY

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Background: Migraine is a prevalent disease in Italy impacting the quality of life (QOL) of a relatively young age group, making it a public health priority.

Objectives: We aimed to leverage a retrospective cross-sectional database including self-reported migraine status and health covariates within the Italian subgroup of a European survey, to observe the epidemiology and migraine burden in the Italian population.

Methods: We descriptively analyzed a sample of the 2020 EU National Health and Wellness Survey (NHWS, Cerner Enviza) [1], capturing adult patient-reported data on health indicators including migraine disease status. We included only respondents with a self-reported physician's diagnosis of migraine and stratified their disease impact based on the Migraine Disability Assessment Test (MIDAS) scores and the frequency of attacks in the previous 30 days (1 to 3: acute; 4 to 7: low-frequency episodic, 8 to 14: high-frequency episodic and >15 days: chronic). Additionally, we examined their reported medication use for managing migraines, psychiatric comorbidities and mental wellbeing.

Results: There were 10'026 total survey respondents in Italy of which 1'287 had a diagnosis of migraine. This translated to a prevalence of 12.8% (65% females). The proportion of acute, low-frequency episodic, high-frequency episodic and chronic sufferers were 52%, 27%, 13% and 7%, respectively. More than 43% reported a MIDAS grade of III thus indicating an important disease burden. The most frequently used medications were OTC NSAIDs (66%), followed by OTC paracetamol (28%), triptans (19%) and other medications (22%). The corresponding treatment satisfactions for these migraine medication classes were 27%, 22%, 29% and 35% (where the respondents were extremely or very satisfied). With increasing migraine frequency and MIDAS score, the prevalence of psychiatric comorbidities also increased, for example depression (greater than 5 in PHQ-9 questionnaire) was reported by 64% of MIDAS grade I and 78% of MIDAS grade IV migraine sufferers. All psychiatric comorbidities were reported at higher frequencies in the migraine group than in the general population, for example anxiety was reported by 57% of migraine sufferers vs 28% of non-migraine sufferers, and depression by 36% and 14%, respectively.

Conclusions: In the Italian landscape, migraines cause significant disability and disease burden, especially when comorbid with psychiatric disorders. There are still unmet needs to be addressed in the migraine patient population, such as improving the satisfaction to medications by reducing the frequency and intensity of the attacks and assessing the bidirectional impact between migraines and the patient's mental health.

Reference:

1. Cerner Envisia - National health and wellness survey - https://www.cernerenviza.com/real-world-data/national-health-and-wellness-survey-nhws (2020)

## EVALUATION OF THE EFFICACY AND TOLERABILITY OF FREMANEZUMAB: REAL LIFE SINGLE-CENTRE EXPERIENCE

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Objectives: Aim of the present study was to evaluate the efficacy and tolerability of Fremanezumab 225 mg/monthly in migraine prevention following three months of treatment.

Materials and Methods: This retrospective study was conducted at the Headache Centre - ASST Spedali Civili of Brescia. Data were collected between January 2019 and June 2022. Inclusion criteria were the following: age ≥ 18 years old, migraine frequency ≥ 8 migraine days per month, MIDAS score ≥ 11, monthly treatment with fremanezumab 225 mg. The following variables were evaluated: mean monthly headache days (MHDs), mean monthly migraine days (MMDs), analgesics consumption, pain intensity (Numerical Rating Scale – NRS), MIDAS and HIT-6 scores. Patients were assessed at baseline (T0) and following three months (T3). Tolerability and side effects were also recorded at T3. Possible response predictors were also analysed.

Results: Fifty-four consecutive patients were enrolled, of whom 43 (79.6%) females. Mean age at baseline was 48.0 years (±12.6; range 20-67). 16 patients (29.6%) had a diagnosis of episodic migrain, whereas 38 patients (70.4%) of chronic migraine. On average, disease duration was 26.0 (±12.6) years. Twenty-one patients (38.9%) have a psychiatric comorbidity (major depressive disorder, bipolar disorder type II and generalized anxiety disorder). Medication overuse was observed in 29 patients (53.7%). Compared to baseline, at T3 a significant reduction in MHDs (19.8±6.96 vs 10.56 ± 9.04; p<0.001), MMDs (11.1±6.06 vs 4.22±5.43; p<0.001), monthly analgesics consumption (17.4±12.45 vs 6.66±6.90; p<0.001), pain intensity (NRS - 7.7 ±0.85 vs 6.25±1.56; p<0.001), MIDAS score (104.6±63.48 vs 29.34±27.69; p<0.001) and HIT-6 (64.98±5.76 vs 57.80±8.27; p<0.001). At T3, 34 patients (63%) documented a > 50% reduction of baseline MHDs, whereas 5 (9.2%) documented a partial response (30-50% reduction). Side effects were reported by 5 patients (9.2%), mainly constipation. A significant clinical response to fremanezumab was more frequent in triptans responders (90.6%) compared to triptans non responders (9.4%, p=0.006).

Discussion: Fremanezumab is an effective prophylactic treatment in patients with migraine, both episodic and chronic. A significant response in terms of migraine associated disability and analgesics consumption was also observed. A significant response to fremanezumab response was more frequent in patients who also document a significant response to triptans for migraine acute treatment.

Conclusion: Our real-life data supports previous clinical trials [1] regarding the efficacy and tolerability of Fremanezumab as a prophylactic treatment in patients with migraine.

Reference:

1. MD Ferrari, HC Diener, X Ning, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. The Lancet (2019);394(10203):1030-40

## RECEPTOR ENRICHED FUNCTIONAL CONNECTIVITY ABNORMALITIES OF DOPAMINERGIC AND NORADRENERGIC CIRCUITS IN PARKINSON'S DISEASE RELATED-FATIGUE

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Background: Fatigue affects up to 50% of patients with Parkinson's disease (PD), significantly decreasing their quality of life [1]. Unfortunately, pathophysiological mechanisms and treatment options for fatigue are largely unknown. Functional MRI studies have shown abnormal connectivity of brain areas involved in sensory-motor integration in de-novo PD, and multiple neurotransmitter systems have been involved in the pathogenesis of fatigue [2, 3].

Aim: We aimed to investigate associations between fatigue and functional connectivity within dopamine and noradrenaline functional networks in PD patients.

Methods: We enrolled 29 patients with PD, Hoehn and Yahr stages I-III, without significant cognitive decline or severe neuropsychiatric symptoms. Fatigue was measured with the Fatigue Severity Scale (FSS). We used resting-state MRI data and functional connectivity within dopamine transporter (DAT) and noradrenaline transporter (NET)-defined functional networks by applying a recently developed multimodal framework: "Receptor-Enriched Analysis of Functional Connectivity by Targets."

Results: We found a negative linear correlation between fatigue and noradrenaline-enriched functional connectivity in regions of the sensorimotor and salience networks and a positive linear trend between fatigue and dopamine-enriched functional connectivity in regions of the default mode network. FSS scores and NET-enriched functional connectivity were anticorrelated (Pearson's r=-0.48), while a positive correlation was found between FSS scores and DAT-enriched functional connectivity (Pearson's r=0.33).

Conclusions: These preliminary findings might suggest that fatigue in Parkinson's patients is sustained by a disruption in the sensory-motor circuits and a dysfunction of monoaminergic NET and DAT-related connectivity. Medication involved in noradrenergic modulation might open new avenues for targeted-treatment of this disabling and poorly responsive symptom.

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## REFRACTORY MIGRAINE PROFILE IN CGRP-MONOCLONAL ANTIBODIES SCENARIO

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Objective: Despite the advent of even more novel and specific therapeutic strategies, refractory migraine (Ref-M) still represents a conundrum that headache experts have to face with. Indeed, it has been estimated

that from 5 to 30% of migraine patients could be considered as refractory. Nevertheless, the pathophysiological mechanisms underlying Ref-M are still matter of debate, although the prominence of pathways on which the existing drugs seem not to act has been suggested. Among these, the dopaminergic pathway, poorly targeted by current preventive migraine medications, seems to play a critical role in more resistant migraine endophenotypes. We aim to investigate whether a peculiar profile may characterize patients with Ref-M according to 2020 European Headache Federation criteria. Furthermore, to substantiate a dysfunctional dopaminergic pathway involvement in these patients, we explored the effectiveness of olanzapine.

Materials: Eighty-four patients (fitting previous Ref-M criteria of the 2014) were treated with erenumab for six months. In fifteen patients with Ref-M not-responders to CGRP-mAbs, olanzapine was administered (5 mg/die) for 3 months.

Methods: Differences between demographic and clinical features of responder (Ref-M according to 2014 criteria) and not-responder (Ref-M according to 2020 criteria) to CGRP-mAbs were investigated after 6-months of treatment with erenumab and their predictive values assessed. Furthermore, clinical parameters of disease severity such as headache days per month, pain intensity and acute pain medication intake were evaluated in patients with Ref-M treated for three months with olanzapine.

Results: Patients with Ref-M not-responsive to CGRP-mAbs (29/84) when compared with Ref-M responsive to CGRP-mAbs showed higher baseline frequency of migraine attacks, medication overuse and pain catastrophizing scale (PCS) scores. Logistic regression analyses showed that frequency of attacks, medication overuse and PCS score represent independent negative predictors of CGRP-mAbs response. A ≥50% reduction of headache days/month was observed after olanzapine treatment in 67% of patients with Ref-M not-responsive to CGRP-mAbs.

Discussion: We outline that higher frequency of migraine attacks, medication overuse and pain catastrophizing characterize patients with Ref-M not responsive to CGRP-mABs. In this frame, olanzapine effectiveness on frequency and pain intensity of migraine attacks supports the hypothesis that migraine refractoriness may be subtended by a prominent involvement of the dopaminergic pathway.

Conclusion: Future specific therapies able to modulate also dopaminergic pathways could be employed in migraine treatments, further reducing the percentage of patients falling into the category of Ref-M.

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## LONG TERM (1-YEAR) EFFECTIVENESS, SAFETY AND TOLERABILITY OF FREMANEZUMAB IN MIGRAINE: A REAL-LIFE, PROSPECTIVE, COHORT, MULTICENTER STUDY


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Objectives: Results from randomized controlled trials (RCTs) need to be confirmed by real life studies because of their close association with routine clinical practice. We aimed to assess the long-term effectiveness, safety, and tolerability fremanezumab in patients affected by high-frequency episodic (HFEM: 8-14 days/month) or CM in in real-life.

Material and Methods: This is a multicenter (n=9), prospective, cohort, real-life study. We considered all consecutive HFEM or CM patients with ≥3 prior preventive treatment failures, who were prescribed fremanezumab (225 mg monthly/675 mg quarterly) for ≥ 48 weeks. Primary endpoint was the change in monthly migraine days (MMD) in HFEM and monthly headache days (MHD) in CM at weeks 45-48 compared to baseline. Secondary endpoints were variation in monthly analgesic intake (MAI), Numerical Rating Scale (NRS), Headache Impact Test-6 (HIT-6) and Migraine Disability Assessment Scale (MIDAS) scores, and ≥50%, ≥75% and 100% responder rates at the same time intervals.

Results: 470 migraine patients received ≥1 subcutaneous fremanezumab dose and were considered for safety analysis, while 54 patients completed 48 weeks of treatment and were included also in the effectiveness analysis. In both HFEM and CM, fremanezumab significantly ($p<0.001$) reduced MMD (-6.8±3.9), MHD (-14.3±7.3), MAI (-7.4±3.7, 15.0±11.4), NRS (-2.8±2.6, -2.5±2.6) and HIT-6 (-10.0±6.8, -11.6±11.3). The proportion of ≥50%, ≥75% and 100% responders were 72.2%, 38.9% and 16.7% in HFEM and 86.1%, 55.6 and 5.6% in CM. Adverse events emerged in 12.9% (7/54) of the patients: injection site erythema (3.7%), asthenia (3.7%), constipation (1.9%), amenorrhea (1.9%) and nausea (1.9%). No patient discontinued fremanezumab for any reason.

Discussion and conclusions: Long-term (48 weeks) fremanezumab treatment provides sustained effectiveness, safety and tolerability in real-life patients affected by HFEM or CM with multiple prior therapeutic failures. Fremanezumab's long-term effectiveness/tolerability ratio in real-life is considerably greater than that documented in the corresponding RCT.

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## SAFETY AND TOLERABILITY OF ANTICGRP MABS IN REAL-LIFE: A MULTICENTER, PROSPECTIVE, OBSERVATIONAL STUDY ON 1635 MIGRAINE PATIENTS

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Objective: Randomized controlled clinical trials (RCTs) with antiCGRP monoclonal antibodies (mAbs) document that treatment emerging adverse events (TEAEs) occur in 42% to 55% of migraine patients, and serious adverse events (SAEs) in 0.9%-2%. We aimed to assess safety and tolerability of antiCGRP mAbs in a large series of patients affected by high-frequency episodic migraine (HFEM: 8-14 days/month) or CM.

Material and Methods: Multicenter (n=26), prospective, cohort, real-life study across 9 Italian regions. We enrolled all patients affected by HFEM or CM who had previously failed >3 preventive medications classes (according the rules of the Italian Medicines Agency) receiving >1 dose of erenumab (70 mg or 140 mg), galcanezumab (120 mg) or fremanezumab (225 mg monthly or 675 mg quarterly) from 01/02/2019 to 31/03/2023. All patients were visited by specifically trained headache specialists using a shared web-based semistructured questionnaire. Patients asked to record any adverse event on a paper pencil diary.

Results: A total of 1635 patients had received >1 dose of erenumab (928 pts; 56.8%), fremanezumab (479 pts; 28.7%), galcanezumab (237; 14.5%). Sixty-three patients (3.8%) reported >1 TEAE. The most common were constipation (2.5%), injection site erythema (0.6%) and back pain (0.6%), followed by alopecia (0.2%), dyspepsia (0.1%), asthenia (0.1%), nausea (0.1%), amenorrhea (0.06%), and paresthesias (0.06%). TEAEs occurred more frequently in patients treated with erenumab (5.0%) compared to those receiving galcanezumab (4.2%) or fremanezumab (1.6%). SAEs events occurred in 3 patients (0.18%) treated with erenumab who discontinued the treatment. Two individuals witn CM and medication overuse manifested non-ST segment elevation myocardial infarction unrelated to the treatments. A 58-year-old woman presented with an acute coronary syndrome (7 days after the fifth erenumab 70 mg administration) while learning that her apartment was on fire. A 54-year-old, man with a positive family history for cardiovascular disorders, overweight, affected by hypercholesterolemia and hypertension, developed a myocardial infarction 10 days after the seventh erenumab 140 mg administration. A 58-year-old man suffering from CM and medication overuse developed a treatment-related paralytic ileus 20 days after the injection of the first erenumab 70 mg dose.

Discussion and Conclusion: This real-life prospective study confirms that antiCGRP mAbs are safe and well-tolerated. The occurrence of TEAEs and SAEs is much lower than in RCT.

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## BOTULINUM TOXIN AS AN EFFECTIVE TREATMENT IN ANTI-CGRP MONOCLONAL ANTIBODIES FAILURE

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Goal: Anti-CGRP monoclonal antibodies (anti-CGRPAb) represent a highly effective prophylactic treatment for chronic migraineurs, but in some rare cases they are ineffective. Our case series aims to determine whether patients that did not respond to anti-CGRPAb could benefit from OnabotulinumtoxinA (BoNT/A) treatment.

Materials: We collected data from eight chronic migraineurs that attended our headache tertiary center and did not benefit from anti-CGRPAb treatment. Before this therapy, six of them had never been previously treated with BoNT/A, whereas three patients had already made use of it without achieving a good control over headache symptoms. After anti-CGRPAb failure, all these patients underwent at least one BoNT/A treatment according to the PREEMPT protocol.

Methods: We compared the reduction in migraine days, intensity, and symptomatic medication intake obtained before and after anti-CGRPAb therapy and BoNT/A treatment. Results: all patients did not benefit from anti-CGRPab therapy in terms of days of headache (19.566±8.546 days vs 19.111±9.584; p=0.977), pain intensity (NRS 7.444±0.527 vs 7.000±1.000; p=0.346) and the number of symptomatic intake (46.667±58.496 assumptions vs 48.667±59.569; p=0.675). All of them started BoNT/A therapy after discontinuing anti-CGRPAb; there was a significant reduction in migraine frequency (21.67±6.65 vs 9.000±5.701 days per month, p=0.002) and symptomatic medication intake (48.667±59.569 vs 19.000±23.749, p=0.022) while pain intensity NRS did not improve significantly (7.444±1.236 vs 6.222±1.481, p=0.057).

Discussion: BoNT/A improved migraine frequency and symptomatic drug intake; the difference in pain intensity resulted in borderline

significance. It is not well established on which basis pharmacological resistance to anti-CGRPAb exists, but in these cases BoNT/A seems to be effective by bypassing a purely CGRP-mediated pathogenetic mechanism of pain, thus being a good rescue therapy in resistant headache management.

Conclusions: BoNT/A could be useful in chronic migraineurs when anti-CGRPAbs are ineffective.

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## COMPLICATIONS AFTER LUMBAR PUNCTURE PERFORMED AT THE OUTPATIENT NEUROLOGY FACILITY: A SINGLE CENTER EXPERIENCE

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Objectives: To report and discuss post-lumbar puncture (LP) complications observed in our outpatient neurology facility.

Materials and Methods: We report post-LP complications of patients who underwent diagnostic LP according to standard healthcare guidelines and regulations from the 15th of November 2020 and the 30th of May 2023 at the Neurology Day Hospital of Fondazione Policlinico Universitario Campus Bio-Medico. LP was performed conforming to international consensus guidelines (ref.1). We used a 22-gauge 0,7x90mm cutting bevel spinal needle and ice spray as topical analgesia. Before home discharge, patients remained on bed rest, monitored for 3 hours, with saline infusion. Patients were advised not to perform any heavy activity or exercise for at least two days after the procedure and to stay hydrated.

Results: 96 subjects (46F, 50M) of age (mean+SD) 56.60+17.15 years underwent diagnostic LP with our standard-of-care procedure. Indications for LP were inflammatory central nervous system disease (45,83%), polyneuropathy (30,20%), motor neuron disease (12,5%), and cognitive decline (11,5%). LP was performed in the left lateral recumbed position in 79,17% of cases and in the sitting position in the remaining cases. The number of LP attempts was 1.74+0.59. The amount of cerebrospinal fluid (CSF) withdrawn was 7,50+0,89 mL/subject. Complications were reported by fourteen (14,58%) subjects; none were serious. Post lumbar puncture headache (PLPH, ref.2) was the most frequent complication, with an incidence of 11,46%. Mean time of PLPH onset after LP was 28,4+14,29 hours; mean PLPH duration was 83,63+52,14h (range 24–168). Subjective pain intensity ranged from mild to moderate (managed with bed rest and hydration only) in 63,63% of cases and from moderate to severe (requiring over-the-counter medications) in 36,36% of cases. PLPH was associated with low back pain (LBP) in 18,18% of cases, orthostatic dizziness (OD) in 9,00%, and nausea in 18,18% of cases. Other post-LP complications were isolated LBP (incidence 2,08%, onset time 13,5+12,37h, duration 45,6+45,22h), isolated OD (one case, incidence 1,04%, onset time 24,5h, duration 84,0h), and one case of skin ice burn. Total LBP incidence (LBP associated with PLPH or isolated) was 4,17%. The presence of PLPH correlated with age (r=0,348; p<0,001) being more frequent in younger subjects, female gender (chi2=4,604; p=0,03), number of LP attempts (chi2=6,150;p=0,04) and was higher in subjects who reported not having followed rest instructions after discharge (chi2=10,500;p=0,001).

Discussion and conclusions: Acting on procedural risk factors (number of LP attempts) and on patient education (avoiding heavy activity or exercise after LP) may reduce the incidence of PLPH.

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## LONGITUDINAL SALIENCE NETWORK CONNECTIVITY CHANGES ASSOCIATED WITH MINDFULNESS-BASED TREATMENT ADDED TO TREATMENT AS USUAL IN MEDICATION OVERUSE HEADACHE PATIENTS (MIND-CM STUDY)

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Aims: Mindfulness-based therapy has recently gained considerable interest in the management and treatment of migraine [1]. Increasing evidence suggests that mindfulness practice induces a modulatory effect on the Default Mode Network (DMN) and the Salience Network (SN) functional connectivity [2]. Our longitudinal study tested SN and DMN connectivity changes associated with a mindfulness-based therapy added to pharmacological treatment as usual in a group of patients with Medication Overuse Headache (MOH).

Materials: 34 well-matched adult MOH patients were randomized in 17 patients following Treatment as Usual (TaU group, 15 F) and 17 patients practicing mindfulness added to Treatment as Usual (MIND group, 15 F). All partecipants were scanned with a 3T scanner with a rs-fMRI sequence before the treatment (T0) and after one year (T1). Clinical and psychiatric variables were collected for all patients at T0 an T1.

Methods: Functional data were analysed with CONN toolbox. Longitudinal comparisons of DMN and SN seed-to-voxel connectivity were performed between MIND and TAU groups. Age and sex were considered as covariates. All results were corrected for multiple comparisons. Longitudinal connectivity modifications were correlated with changes in clinical variables.

Results: Both groups showed an improvement in all the main clinical variables. After one year of mindfulness practice, MIND patients showed increased SN functional connectivity with the left posterior insula and sensorimotor cortex compared to TaU patients. Moreover, in MIND patiens only, greater SN-insular connectivity was associated with improved depression scores (Beck Depression Inventory) at follow-up.

Discussion: Mindfulness is characterized by present-moment self-awareness and relies on attention control and emotion regulation, possibly allowing a better headache-related pain management [2]. We observed a longitudinal functional connectivity change only in the SN of MIND patients. This network, mainly anchored in the bilateral insula and cingulate cortex, helps in directing attention to relevant information and filtering out irrelevant or distracting information. Enhanced SN-sensorimotor connectivity might represent improved body-awareness of painful sensations. Moreover, the increase of SN functional connectivity with the posterior insula, might be involved in chronic pain and emotional processing of nociceptive input [3], and could suggest that mindfulness practice may improve the management of negative emotions associated with pain.

Conclusions: Our results highlight the beneficial effects of the Mindfulness therapy in patients with MOH, potentially paving the way for future research on non-pharmacological interventions in chronic headache treatement.

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## MIGRAINE HEAVILY IMPACTS HEALTHCARE RESOURCE USE IN ITALY: RESULTS FROM THE ITALIAN MIGRAINE REGISTRY (I-GRAINE)

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Objective: The Italian Migraine Registry (I-GRAINE) is aimed at collecting detailed information on socio-demographic characteristics, patient's journey, clinical government and healthcare resource use of people with migraine. Here we detail diagnostic investigations and specialist visits performed by migraine patients in Italy, considering their impact on our National Health System (NHS)

Material and Methods: The Italian Migraine Registry (I-GRAINE) is a multicenter, prospective, observational, non-interventional study whose aim is to ensure a proper disease management, according to scientific and sustainability criteria. Consecutive patients affected by episodic or chronic migraine seen between 19/4/21 and 31/12/22 at 39 participating center were enrolled according to the systematic random method. Information on sociodemographic characteristics, migraine features, patient's journey and healthcare resource use were collected by specifically trained headache specialists with face-to-face interviews using a shared semistructured web-based questionnaire.

Results: At the date of 31 December 2022, we enrolled 867 patients. Most of them were females (85.5%), had high migraine frequency (9.3 ± 7.8 days/month) and severe disability (MIDAS score: 48.3 ± 50.7; HIT-6 score: 60.9 ± 9.1). Two-thirds of patients (63.1%) underwent at least 2 specialist visits (2.4 ± 0.2) over the last 3 years. The specialists most frequently consulted were neurologists (85.6%), ophthalmologists (33.6%) and dentists (15.9%). The number of different neurologists, ophthalmologists and dentists consulted by each patient were 3.5 ± 3.9, 1.5 ± 0.9 and 1.8 ± 4.0. The proportion of specialists visits subsidized by the NHS were 52.9%, 21.5% and 7.5%, respectively. Patients who underwent diagnostic investigations for migraine during lifetime were 81.8% (68.8% over the last 3 years). Brain neuroimaging was the most common investigation (95% of the patients; self-prescribed in 12.5% of the cases) followed by spine MRI/X-Rays (22.8%; self-prescribed in 17.2%) and EEG (11.4%; self-prescribed in 2.8%). The number of diagnostic investigations performed by each patients were 5.3 ± 3.5 (brain neuroimgaging), 2.2 ± 0.6 (spine MRI/X-rays) and 1.8 ± 1.4 (EEG). Investigations subsidized by the NHS in >50% of the cases were 27.7%–86.3% for brain neuroimaging, 67.6% – 81.3% for spine MRI/X-Rays, and 84.7% for EEG.

Discussion and Conclusion: A large number of diagnostic investigations and specialist visits for migraine are inappropriate, redundant, self-prescribed and subsidized by the NHS. Despite current guidelines, almost all patients undergo brain neuroimaging. The I-GRAINE registry is expected to contribute to improve the clinical management of migraine, rationalizing healthcare resource allocation, and reducing its economic burden.

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## VERY-LOW-CALORIE KETOGENIC DIET VS HYPOCALORIC BALANCED DIET IN THE PREVENTION OF HIGH-FREQUENCY EPISODIC MIGRAINE: THE EMIKETO RANDOMIZED CONTROLLED TRIAL

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Objective: To compare the effects of Very-Low-Calorie Ketogenic Diet (VLKD) vs Hypocaloric Balanced Diet (HBD) in the prevention of high-frequency episodic migraine (HFEM: 8-14 days/month).

Material and methods: Prospective, 24-weeks, single center, randomized, controlled study. HFEM patients with a Body Mass Index (BMI) ranging from 27 to 35 kg/m2 were randomly assigned (1:1) to VLCKD or HBD. Patients on the VLCKD treatment arm used VLCKD during the first 8 weeks, shifting to a low calorie diet (LCD) containing carbohydrates during weeks 9-12, and to a HBD during weeks 13-24. Patients assigned to HBD remained on the same dietary regimen for all 24 week. Anthropometric indexes, urine and blood chemistry were assessed at enrollment (-28 days), baseline, 10 days after treatment onset and at weeks 4, 8, 12, and 24. Migraine characteristics were evaluated at baseline, weeks 8, 12 and 24. Change in monthly migraine days (MMD) at weeks 5-8 compared to baseline was the primary endpoint. Secondary endpoints encompassed change in MMD at weeks 9-12 and 21-24, and change in Numerical Rating Scale (NRS), Headache Impact Test-6 (HIT-6) and Short Form Health Survey-36 (SF-36) scores at weeks 5-8, 9-12 and 21-24 compared to baseline.

Results: We enrolled 57 patients (VLCKD: 29; HBD: 28). Patients assigned to VLCKD showed a greater MMD reduction than those allotted to HBD at weeks 5-8 (-6.4±4.8 vs -2.2±5.0, p=0.008), weeks 9-12 (-7.2±5.42 vs-3.13±3.58, p=0.007) and weeks 13-24 (-6.8±6.42 vs-3.6±3.3, p=0.042). No difference emerged in MIDAS, HIT-6 and NRS scores between the two groups at weeks 5-8 and 9-12. SF-36 score significantly improved at week 8 in VLCKD group and at week 12 in the HBD. Weight-loss and BMI reduction were significantly higher in VLCKD compared to HBD at week 8 (-8.2±4.5 vs -4.3±2.9, p=0.002; -3.0±1.6 vs-1.5±1.1, p=0.002) and week 12 (-9.1± 6.4 vs -4.9 ±2.7, p=0.020; -3.3 ± 2.2 vs -1.8±1.0, p=0.016). At week 24, weight loss was maintained in VLCKD (-9.1± 6.4) whereas a slight increase (-4.3 ± 2.9) was found in HBD. Inflammatory indexes, were significantly reduced ($p<0.05$) in VLCKD group at week 12.

Discussion and Conclusions: VLCKD is more effective than HBD in reducing MMD, BMI and inflammatory indexes. VLCKD superiority over HBD in MMD reduction persists for 16 weeks after VLCKD discontinuation, suggesting that VLCKD could positively influence not only neuronal metabolism but also brain dysexcitability in migraine patients.

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## PERSISTENT FAMILIAL HEMIPLEGIC MIGRAINE AURA DUE TO PRRT2 GENE DELETION: THE FIRST CASE REPORT

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Background: Familial Hemiplegic Migraine (FHM) is a rare genetical disorder in which migraine pain is accompanied or followed by stroke-like symptoms, frequently long-lasting, and at least one first- or second-degree relative suffers from migraine aura with motor weakness. The majority of FHM cases have been attributed to mutations of three genes, CACNA1A, ATP1A2 and SCN1A. Recently, alterations of PRRT2 gene have been highlighted as another main cause of FHM. The different PRRT2 mutations induce a loss of function of the encoded protein, which is implicated in neurotransmission.

Objectives: Aim of this study is to describe the first case of a sensorimotor persistent aura related to PRRT2 gene deletion.

Results: A 27-year-old male migraineur afferent to the Headache Centre of Trieste was evaluated. He has suffered from migraine since he was 4-year-old. His sister was hospitalized for stroke-like symptoms and subsequently clinically diagnosed at the Headache Centre as having hemiplegic migraine. At its onset, patient's headache presented with typical migraine without aura symptoms. Since he was 15, a right hemibody strength deficit starting about 15 minutes after the onset of pain and during up to 12 hours has been associated. Since he was 21, a right hemibody hypoesthesia has also developed. Then, strength and sensitive deficits have always been temporarily associated and had approximately the same duration, up to 12 hours. Seldom, speech and visual disturbances were added. Frequency of attacks were up to 3 days/month. Due to a weakness and hypoesthesia in the right limbs started three months before, at 27 he was neurologically evaluated and a right sensorimotor hemisyndrome was objectified. Cerebral CT, brain MRI and EEG were normal. He was treated with lamotrigine 50 mg bid and he began to improve, but after two months the drug was stopped because of suicidal ideation. Lamotrigine was replaced with valproic acid 300 mg bid and the resolution of aura symptoms was reached after two months. Genetic MLPA analysis detected a heterozygous deletion of the whole PRRT2 gene both in patient and in his sister.

Conclusion: We described the first case of sensorimotor persistent aura related to PRRT2 gene deletion. Lamotrigine and valproic acid were effective.

## LONG TERM EFFECTIVENESS AND TOLERABILITY OF GALCANEZUMAB AND FREMANEZUMAB ON COMORBID CHRONIC CLUSTER HEADACHE AND MIGRAINE: A PROSPECTIVE CASE SERIES

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Background: Cluster headache (CH) and Migraine (M) are considered distinct primary headaches as they differ in multiple aspects such as gender-relation, specific headache features and therapies. However an overlap between CH and M has been reported [1]. In fact CH may occur with migrainous symptoms such as nausea, photophobia, and phonophobia while M can manifest itself with symptoms of trigeminal-autonomic activation. Moreover CH and M can be comorbid in the same individual. Up to now some cases of patients with CH and M treated with antiCGRP antibodies (antiCGRP mAbs) and observed for short periods have been described [2,3].

Case Series: We describe five adult patients, one female and four males, with both CH and M treated with antiCGRP mAbs (2 with Galcanezumab and 3 with Fremanezumab), for a period ranging from one to three years. Four of these patients had high-frequency M, one

had chronic M and all of them were also affected by chronic CH. All patients underwent baseline and quarterly follow-up visits with clinical evaluation and administration of Migraine Disability Assessment Score Questionnaire (MIDAS) and Headache Impact Test -6 item score (HIT -6 Fremanezumab and Galcanezumab both reduced in all patients the monthly number of migraine days, of CH attacks, the number of days with acute medications use and the patient's disability as measured by MIDAS and HIT-6 showing sustained long-term efficacy. No adverse events were reported by 4 patients. Only the female patient reported a slight slowdown in hair growth rate after Fremanezumab but this adverse event was not so serious to interrupt the treatment.

Results and Discussion: Our results are in agreement with those of previous studies conducted on similar case series for shorter observation periods, and demonstrate the long-term efficacy and well tolerability of antiCGRP mAbs in case of comorbidity between M and CH. Common pathophysiological mechanisms including the Calcitonin Gene-Related Peptide (CGRP) role in trigeminal-vascular system activation have been proposed to explain antiCGRP mAbs effectiveness in both CH and M. Further studies on large case series are needed to provide stronger evidence for the use of antiCGRP mAbs as first-line therapy in CH and M comorbidity.

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## TRIGEMINAL INVOLVEMENT IN CONVENTIONAL MRI IS UNDISTINGUISHABLE BETWEEN TRIGEMINAL NEURALGIA AND SUNCT SYNDROME

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Objectives We compare neuroradiological findings in two couple of patients with the same structural abnormalities but with different clinical pictures. Two patients presented a short-lasting unilateral neuralgiform headache attacks with conjunctival injection (SUNCT) while the others were affected by trigeminal neuralgia (TN). Our aim was to identify any difference in neuroradiological picture that could influence clinical presentation.

Materials and methods: The first couple presented a pontine lesion involving trigeminal root entry zone, due to multiple sclerosis. First patient was a 68-years-old man who developed a SUNCT syndrome, characterized by shooting pain in the orbital region associated with prominent ipsilateral autonomic symptoms. Attacks, that were both spontaneous and triggered by tactile stimulation, disappeared after the introduction of lamotrigine. The second MS patient, with an indistinguishable lesion at MRI, reported electric shock like triggered pain in the maxillary region, with occasional ipsilateral autonomic symptoms, that responded to carbamazepine. In the second couple, brain magnetic resonance imaging (MRI) showed a neurovascular contact in which the superior cerebellar artery dislocated the fifth nerve without clear signs of atrophy; brainstem lesions were absent. Patients developed two different clinical pictures, consistent respectively with a SUNCT syndrome and a trigeminal neuralgia.

Results: Routine neuroradiological exams of our cases showed no apparent difference between SUNCT and TN patients.

Discussion: SUNCT and TN significantly overlap. Both conditions are characterized by similar pain pattern, typically very short lasting and strictly unilateral. Presence of pain paroxysms triggered by innocuous stimuli is a hallmark of TN and it is also reported in SUNCT; autonomic symptoms, characteristic of SUNCT, are commonly present in TN patients, mainly when V1 territory is involved [1]. These craniofacial syndromes may share a damage in the trigeminal primary afferents at the root entry zone, justifying the strong similarities. On the contrary, slight clinical differences could be explained by the additional role of hypothalamus in SUNCT.

Conclusions: Although SUNCT and TN are traditionally considered as different disorders, shared neuroradiological and clinical features suggest a common pathophysiological mechanism. To better understand the real nature of this link, future advanced neuroimaging studies are necessary.

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## SUBCUTANEOUS INJECTION OF BOTULINUM NEUROTOXIN TYPE A IN REFRACTORY CHRONIC MIGRAINE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Aims: In this randomized, double-blind, placebo-controlled study, we evaluated the efficacy of an individualized technique of subcutaneous injection of botulinum toxin type A (BoNT-A) targeted (SjBoT) to the occipital or trigeminal skin area in non-responder patients with chronic migraine (CM).

Methods: Patients who had not previously responded to at least two treatments of intramuscular injections of BoNT-A were randomly assigned (2:1) to receive two subcutaneous administrations of BoNT-A (up to 200 units) with the SjBoT injection paradigm or placebo. Following the skin area where the maximum pain began, treatment was given in the trigeminal or occipital region bilaterally. The primary endpoint changed in monthly headache days from baseline to the last 4 weeks.

Results: Among 139 randomized patients, 90 received BoNT-A and 49 received placebo, and 128 completed the double-blind phase. BoNT-A significantly reduced monthly headache days versus placebo ($-13.2$ versus $-1.2$; $p < 0.0001$) in the majority of patients who had cutaneous allodynia. Other secondary endpoints, including measures for disability (Migraine Disability Assessment questionnaire from baseline 21.96 to 7.59 after treatment, $p = 0.028$), also differed.

Conclusions: In non-responder patients with CM,[1] BoNT-A significantly reduced migraine days when administered according to the "follow the origin of maximum pain" approach using SjBoT injection paradigm. This is the first randomized, double-blind, placebo-controlled study demonstrating the efficacy and safety of the "follow the origin of maximum pain" approach using subcutaneous injections of BoNT-A targeted (SjBoT) to the occipital or trigeminal skin area in patients with chronic migraine.This is a new injection strategy developed by F.B. for the preventive treatment of chronic migraine.

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## SEX DIFFERENCES IN RESPONSE TO TREATMENT WITH ANTI-CGRP DRUGS IN PATIENTS WITH MIGRAINE AFTER 1 YEAR: A PILOT STUDY OF REAL LIFE

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Introduction: Recent evidence shows sex differences in migraine characteristics [1]. However, there is a lack of data comparing over a long period the response to treatment with anti-CGRP mAbs in relation to sex [2].

Aims: We conducted a single center prospective observational study to evaluate sex differences in response to treatment with anti-CGRP mAbs for migraine prevention after 1 year.

Methods: Patients with chronic migraine (according to the criteria of International Headache Association) were treated with anti-CGRP mAbs and followed up for 12 months. The outcomes were: decrease in monthly headache days (MHD), rate of treatment stopping, monthly days of acute medication use, Headache Impact Test 6 (HIT-6) score and intensity of headache pain assessed with the visual analogue scale (VAS 0-10). Decrease of MHDs was evaluated on percentage of decrease and classified in four classes of response: 0-29% (low responders), 30-49% (medium-low responders), 50-74% (medium-high responders) and ≥75% (high responders). Patients who interrupted the treatment were considered as non-responders. All included patients were followed for 12 months, regardless of treatment discontinuation. Baseline was considered as the 4 weeks before the start of treatment with monoclonal antibodies (erenumab, fremanezumab, galcanezumab), while outcomes were assessed at 12 months after the start of treatment and compared with baseline.

Results: We recruited 208 patients with chronic migraine (169 F; 39M) treated with anti-CGRP mAbs. After one year of treatment, we found that 25% of men were low responders, 17,9% were medium-low responders, 24% were medium-high responders, 15,3% were high responders, while 17% interrupted the treatment. On the other hand, 20,7% of women had low responders, 14,2% had medium-low responders, 43,7% had medium-high responders, 16,5% had high responders, while 4,7% interrupted the treatment.

Conclusion: Our pilot study demonstrates the presence of sex differences to anti-CGRP treatment for migraine after 1 year. These results can be explained by the relationship that exists between estrogen receptors and CGRP in the trigeminal vascular system, and they suggest the development of sex-specific therapies in migraine.

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## RECURRENT IDIOPATHIC INTRACRANIAL HYPERTENSION TREATED BY BARIATRIC SURGERY: A CASE REPORT

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Introduction: Idiopathic intracranial hypertension (IIH) or pseudotumor cerebri is a debilitating condition that causes severe headaches, tinnitus, radicular pain and progressive visual loss, that typically affects young overweight females. The standard of care is weight loss and acetazolamide; also, in severe or refractory cases may be needed invasive procedures, such as spinal fluid diversion, optic nerve sheath fenestration or venous sinus stenting. However, losing weight is often very difficult to achieve and acetazolamide carries numerous undesirable side effects that can result in medical noncompliance. Bariatric surgery is a safe and effective treatment modality for IIH, leading to excellent weight loss and reversal of related comorbidities.

Case report: A 31-year-old female presented at Emergency Department for an episode of syncope, pulsatile tinnitus, nausea and headache for 2 weeks. Her BMI was 40.5 and she took estroprogestinic medications for an endometrial polyp. Neurologic examination was negative except for headache, while neurophthalmological evaluation revealed bilateral papilledema. Cerebral computerized tomography (CT) and cerebral CT angiography detected a partial empty sella and patency of transverse venous sinuses; while brain magnetic resonance (MR) with gadolinium showed minimal distention of optic nerve sheaths. We performed a lumbar puncture withdrawing 35 ml of cerebrospinal fluid (CSF) and we detected an opening pressure of 65 mmHg and a closure one of 50 mmHg. Hence, we made diagnosis of IIH and set treatment with acetazolamide and weight loss. Four months later, despite the medical treatment and the diet, the patient had not lost weight and presented a return of clinical symptoms of IIH associated with papilledema and an increase of CSF pressure. After the evaluation by a multidisciplinary team, she underwent sleeve gastrectomy surgery, without complications. At her six-month follow-up after bariatric surgery, she had lost a total of 20 kg with a significant reduction in headache, the absence of clinical signs of intracranial hypertension and no evidence of papilledema at the neurophthalmological evaluation.

Discussion: Current literature about the efficiency of bariatric surgery for the treatment of IIH has been raising over the course of the past years, suggesting that bariatric surgery is superior compared to medical management and cerebrospinal fluid pressure reducing procedures which have high rates of recurrence.

Conclusion: The case demonstrate that bariatric surgery could be an effective and long-lasting method of treating idiopathic intracranial hypertension. It should be considered in overweight patients with typical features of IIH who don't respond to life-style modification and medical treatments.

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## ASSESSMENT OF CEREBRAL HAEMODYNAMICS DURING KINETIC OSCILLATION STIMULATION (KOS) TREATMENT ON CHRONIC MIGRAINE: A PILOT STUDY

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Objectives: KOS is a minimally invasive method of neuromodulation able to regulate the trigeminal-autonomic reflex (TAR), which is believed to play a significant role in migraine pathophysiology. The sphenopalatine ganglion stimulation through the mucous membrane of the nasal cavity with low-frequency mechanical vibrations has been shown to be effective in both tempering acute pain and reducing the number of monthly headache days from baseline to week 6 of treatment compared to sham stimulation. The aim of this study was to verify any changes ongoing or at the end of a six weeks treatment cycle with KOS, as well as to correlate any improvement obtained from the treatment to any changes in the hemodynamic indices.

Materials: We enrolled four patients with refractory chronic migraine and we offered them a six weeks treatment with the Chordate System S220 at weekly intervals.

Methods: In the first and last week, and halfway through the course of treatment, patients underwent non-invasive Doppler tests to record cerebral blood flow parameters (mean flow velocity, pulsatility index, resistance index) in the middle cerebral artery (MCA) during the period of KOS stimulation. Before each session and during the follow-up period each patient was requested to fill in a questionnaire with validated clinical scales (BS-11, PPI, BRS-6, SF-MPQ, H.A.D.S.) to evaluate any benefits occurred during and after the treatment.

Results: We recorded a downward trend in the resistance index of the MCA during the stimulation period in 3 of the 4 enrolled patients. No significant difference in any other derived index was observed intersubjectively at different times of the treatment cycle, nor remarkable modifications in the clinical scales emerged between T0 and T6, apart from a single patient in which the scores related to the subjective intensity of pain and the effects of pain on behaviour (BS-11, BRS-6) were significantly reduced from the beginning to end of the treatment cycle.

Discussion: Albeit on a smaller scale, we have not confirmed the preliminary data regarding the improvement of chronic migraine after a six-week treatment with KOS. The activation of TAR could be responsible for the acute variation of the resistance index during stimulation, as in response to compensatory vasodilatation secondary to activation of the trigeminovascular system by brainstem afferents.

Conclusions: Although KOS may be a viable alternative for migraine treatment, the precise mechanism by which it modulates the TAR is still speculative and further studies on a larger cohort will be needed.

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## ANTI-CGRP MONOCLONAL ANTIBODIES IN MIGRAINE PREVENTION: REDUCTION OF THE FREQUENCY OF ADMINISTRATION DOES NOT MODIFY EFFICACY. PROPOSAL FOR A TAILORED THERAPY


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Background: Anti-CGRP monoclonal antibodies (CGRP-mAbs) enlarged migraine prevention options and modified global health condition of patients with migraine. These drugs are specifically targeted and work safely and efficiently in many patients with the standard dosing schedule.

Objective: To identify if a progressive reduction in the frequency of administration may modify the efficacy of anti-CGRP-mAbs migraine prophylaxis.

Methods: We evaluated headache frequency (monthly headache days – MHD) in patients treated with an anti CGRP or antiCGRP-R molecule. Patients were classified as: i) non-responders (nonR) when the reduction was <30% vs. baseline; ii) partially responders (PR) (30-49% reduction); iii) normal responders (NR) (reduction 50-74%) and iv) super responders (SR) (>75% reduction). The entity of reduction was evaluated after 3 months of standard schedule and 6-9 months after a reduction in administration frequency.

Results: 38 patients (6M and 32F, mean age 48yrs) changed their dosage schedule from the standard monthly injection to a one performed every 40 days (26 directly and 12 through a 3-month period at the intermediate schedule, i.e., one shot in 35 days). At the standard schedule, 20 patients were SR, 13 NR, 4 PR, and 1 NonR. After a 3-month period with the reduced administration frequency schedule (1 injection / 40 days), 21 were SR, 10 NR, 5 PR, and 1 NonR.

Discussion: A progressive partial reduction in administration frequency seems to be possible without a reduction of efficacy in the larger proportion of patients, at least among good responders. It may be an option when side effects, although globally few and not particularly relevant, have to be minimized.

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## FAMILIAL HEMIPLEGIC MIGRAINE: IS CARDIAC INVOLVEMENT POSSIBLE?


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Purpose: Hemiplegic migraine (HM) is a rare subtype of migraine with aura, characterized by motor weakness as aura manifestation, often accompanied by impairment in vision, speech, or sensation. Symptoms typically last 4–72 hours. HM is a clinically and genetically heterogeneous condition that can simulate more severe neurological diseases like stroke. The familial variant is associated with 3 main genes (CACNA1, ATP1A2, SCN1A) [1]. The mechanism of cortical spreading depression (CSD) for the development of the aura is known, however there are few data regarding a possible concomitant cardiac involvement. Materials: We report a case of familial hemiplegic migraine with prolonged motor-sensitive aura lasted 21 days, showing also cardiac involvement.

Methods: We performed a Pubmed search using the following MeSH terms "(Hemiplegic migraine) AND (electrocardiographic

changes)", looking for articles in which influence of CSD on heart rate has been explained.

Results: A 24-year-old girl was admitted to the ED of the Hospital of Trento with an acute onset of right hemiparesis, right lateral hemianopia and aphasia, concomitant severe headache. She had a past history of paediatric hospitalizations for questionable clear liquor encephalitis with symptoms of right motor-sensory hemiplegia and aphasia. At the time of admission, brain CT scan, CT angiography and MRI perfusion did not show any focal lesion, vessel occlusion or areas of restricted diffusion on diffusion-weighted imaging sequences. In the suspicion of a HM she was kept under observation and treated with Methylprednisolone 100 mg/kg/day [2]. Cardiac involvement was immediately suspected as she presented significant hypotension, bradycardia (35 bpm) and T-wave abnormalities. Troponin levels and echocardiography didn't show any abnormalities. The patient's symptoms persisted with mild improvement of the aphasia for 21 days. The ECG, on discharge, was characterized by negative T waves in the anterolateral and inferior areas. Heart MRI was normal. Genetic analysis was positive for the SCN1A gene.

Discussion: We report the case of HM and concomitant cardiac involvement. In literature, there are no direct correlations between HM and cardiac involvement, less is known about how long the ECG changes last after aura resolution and whether there are any permanent changes [3]. A mechanism linked to the membrane channels involved both in the brain and in the heart has been postulated.

Conclusions: HM is an uncommon subtype of migraine; it would be interesting to study whether this syndrome could also be considered a heart-brain syndrome as a univocal entity.

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## PREDICTORS OF EARLY EFFICACY OF MONOCLONAL ANTIBODIES THERAPY IN MIGRAINE: INVESTIGATING THE CENTRAL ROLE OF GCRP THROUGH STRUCTURAL EQUATION MODELLING

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Aim: Migraine represents nowadays one of the leading causes of disability and loss of working days in the world. Innovative therapies targeting the CGRP signaling opened and established a new era in preventive treatment of migraine. Post marketing efficacy evidences are convincing, although a large variability in treatment response could be observed. Emerging evidences suggest a role of circulating factors to unravel the neurobiological causes of this variability. This study aim to combine the use of baseline biochemical (plasmatic neuropeptides) and clinical factors to develop a prediction model of response to anti-CGRP monoclonal antibodies (mAbs).

Materials: We enrolled 41 patients (34 females, 7 males; age 52.16 ± 12.47 years; 24 diagnosed with chronic migraine, and 17 with episodic migraine) who started mAbs therapy (7 Erenumab, 17 Galcanezumab and 17 Fremanezumab). During the first visit (T0) they underwent plasmatic CGRP, Orexin-A (OxA) and PACAP-38 measurement and collection of clinical-anamnestic information. The clinical course was re-evaluated at 3 months (T3), based on monthly migraine days (MMD), monthly medication use, mean pain intensity (NRS) and MIDAS.

Methods: Data were analyzed by S.E.M. (Structural Equation Modeling) to develop a predictive model of treatment response based on T0 clinical and biochemical characteristics. This multivariate analysis defines new composite variables (called latent variables) through quantitative relationships with the observed variables. Thus, we obtained the latent variables NeuP, i.e. "Neuropeptides" (CGRP, PACAP-38 and Orexin-A) and MigBurd T0 i.e. "Migraine burden" (MIDAS and MMD at T0). Then, via S.E.M., we correlated them with T3 clinical outcome.

Results: CGRP plasmatic concentration at T0 emerged as a unique independent predictor of therapeutic response at T3 through direct correlation with MMD (100 pg/ml per 1,7 MMD at T3; $p = 0.032$). Through S.E.M. we found a similar correlation also with monthly medication use and MIDAS at T3. The latent variable MigBurd T0 was directly correlated with all three above mentioned parameters, while baseline CGRP prevailed over NeuP latent variable as predictor of MMD and MIDAS at T3.

Discussion and conclusions: The neurobiological setting may be crucial in the variability of clinical response to mAbs therapy even in the short term (first trimester). Though further data are needed to generalize these results, the present study confirms our previous findings about the predictive role of baseline GCRP plasmatic concentration in the context of preventive anti-CGRP therapy.

## HYPOTHALAMIC INVOLVEMENT IN THE MIGRAINE CYCLE: A TASK-FREE FMRI ANALYSIS DURING NITROGLYCERIN-INDUCED ATTACKS

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Objective: The hypothalamus plays a crucial role in migraine pathophysiology, contributing to pain perception modulation, circadian rhythm disturbances, autonomic dysfunction, and neuroendocrine alterations. [1] In this resting-state functional magnetic resonance imaging (rs-fMRI) study, we assessed the relationship between the hypothalamus and the cortex during various phases of a nitroglycerin-induced migraine attack (NTG).

Material and Methods: Ten episodic migraine patients (EM) and 10 healthy controls (HC) underwent 3T MRI scans during subsequent phases of the NTG migraine attack (baseline, prodrome, full-blown attack, recovery). A seed-based correlation analysis assessed the relationship between the hypothalamus and the cortex during the different phases of the attack in EM and at pre-specified time points in HC. A comparison between each scan and the baseline (pain-free) condition was performed, also testing whether there was a correlation between mean functional connectivity (FC) and anamnestic features.

Results: At baseline, compared to HC, EM presented a reduced FC between the hypothalamus and supramarginal gyrus, middle frontal gyrus and angular gyrus, and left crus II; FC was increased with the posterior cingulate cortex. No significant FC changes were detected during the prodromal phase when compared to the pain-free condition at baseline. In the full-blown phase instead, EM expressed increased FC between the hypothalamus and right frontal lobe (orbitofrontal and

middle frontal gyrus, frontal pole), pons and crus II. These alterations persisted during the painful and the recovery phases. The FC alteration observed during the full-blown phase correlated with the presence of nausea in EM at the time of the scan.

Discussion: These findings help to highlight the disease-specific and phase-specific contribution of the hypothalamus in migraine attacks [2]. In our experimental setting, the hypothalamus did not show a role in attack initiation, given the lack of changes observed in the prodromal phase. Contrary, during the ictal phase of the attack, the disruptions in the FC between the hypothalamus and the frontal lobe may contribute to pain perception, autonomic dysfunction, such as nausea, and emotional disturbances, which persist over the painful experience. The hypothalamus relationship with the crus II suggests the role of this latter in pain processing, modulation of pain perception, and integration of sensorimotor information, possibly playing a crucial role in the definition of the attack end.

Conclusions: fMRI studies [3] have shown increased hypothalamic activation during migraine attacks, suggesting its involvement in generating pain. This study focuses on its role in pain maintenance and its impact on the autonomous system.

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## THE REGIONAL OUTREACH PROGRAMME OF THE INTERNATIONAL HEADACHE SOCIETY IN SUB-SAHARIAN AFRICA IN PARTNERSHIP WITH THE DREAM PROGRAM: FIRST ON-SITE COURSE IN MALAWI

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Objectives: Recent studies confirm that headache disorders are highly prevalent in sub-Saharan Africa (SSA) countries as Malawi [1]. Due to doctors' shortage in SSA, primary care non-physician clinicians (NPC, called clinical officers, (CO)) provide most of the care to the population but their education on headaches is poor. In November 2022, the Regional Outreach Programme of the International Headache Society (IHS) organised the first on-site teaching course in Malawi "Headache, head pain syndromes, migraine and related disorders" in partnership with the Disease Relief through Excellent and Advanced Means (DREAM) program to improve CO headache education and headache management in SSA.

Material: A 2-day course was organised in Blantyre, Malawi, and was attended by COs from several primary care facilities. The teaching modules foresaw a high degree of interaction with the audience; the treatment approach was focused on the use of the WHO list of essential drugs. The final session involved the group discussion of multiple clinical cases.

Methods: Here we report the results of a survey to evaluate the participants' education and needs, and their knowledge about headache before and after the course.

Results: Thirty-four CO (10 women), who had been practising medicine for an average of 9 years, participated (median age 37 years; median duration of education 3 years). The pre-course survey highlighted the lack of proper training and experience in neurology, headache and pain. After the course, trainees demonstrated much-improved knowledge of both neuroanatomy and headache science as well as skills in differential diagnosis and treatment of primary and secondary headaches. The trainees were highly satisfied and appreciated the lectures and the provided practical tips. They strongly recommended the course and wished to change their approach to headache patients.

Discussion: In Malawi, there are no teaching courses on headache disorders notwithstanding their high prevalence. Our study shows that tailored teaching courses improve headache knowledge of primary healthcare CO. Comprehensive CO training in diagnosing and managing headaches effectively is a crucial step to address the huge treatment gap of highly prevalent non-communicable diseases in SSA.

Conclusions: The partnership between the IHS and the DREAM program in Malawi is effective in providing headache education at the primary care level where most patients are seen and managed. Long-term follow-up, tailored task-shifting and task-sharing are necessary. The IHS-DREAM program in SSA adheres to and contributes to the objectives of the WHO Intersectoral Global Action Plan. [2]

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## WHEN A CAVERNOUS ANGIOMA MIMICS MIGRAINE: A CASE REPORT

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Background: Cavernous angioma (CCM) is a cerebral vascular malformation that may occur sporadically or in a familial pattern, characterized by clusters of dilated, thin-walled blood vessels. CCMs are often asymptomatic, but they can occasionally present with seizures, focal neurological deficits, and headache, with or without associated hemorrhage.

Case report: A 37-year-old man, with unmarkable medical history except for detection of MORC2 mutation, of which the patient is a healthy carrier, had never experienced headaches until the age of 30, when the first sporadic episodes of throbbing headache appeared. The pain started in the right temporo-occipital region, radiating bilaterally to the frontotemporal regions, more severely on the right side, and was accompanied by photophobia, phonophobia, sometimes nausea, vomiting, dizziness. The first pain episodes were responsive to medical therapy, occurring approximately five times a year in the absence of clear triggering factors. On prescription from the family doctor the patient underwent an electroencephalogram reporting normal results. The last two episodes, that lasted approximately 3 days, were more severe and disabling and they were followed by intense fatigue, photophobia, and objective vertigo forcing the patient to stay in bed for a week. After a few days from the last episode, the patient underwent neurological consultation. Neurological examination was unmarkable.

A brain magnetic resonance imaging (MRI) showed a right temporal region cavernoma with signs of recent intracerebral hemorrhage.

Discussion: The first headache episodes were suggestive of migraine without aura. Due to the sporadic occurrence of the episodes and the good response to medical therapy, further diagnostic investigations were not performed. However, some atypical characteristics, such as persistent fatigue and an increase in severity prompted further investigation with MRI. The identification of a cavernous angioma in the right temporal region explained the patient's symptoms. Reports of isolated cases suggest that some cavernous angiomas can trigger migraine-like attacks. In a series of 126 symptomatic patients with cavernous angioma and KRIT1 mutation, only 4% reported headache as a presenting symptom, while headaches are commonly reported as a consequence of cerebral hemorrhage or epileptic seizures in patients with cavernous angiomas.

Conclusions: This case report highlights the importance of considering alternative diagnoses in patients presenting with atypical or refractory migraine symptoms. CCMs can mimics migraine, leading to diagnostic challenges. MRI plays a critical role in identifying structural lesions and ensuring appropriate management.

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## DENTATE NUCLEUS CAVERNOMA AS A CAUSE OF TINNITUS AND VERTIGO: A CASE REPORT


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The dentate nucleus is the largest deep cerebellar nucleus. It is responsible for the planning, initiation and control of voluntary movements, but it also involved in nonmotor function, such as cognition and visuospatial function. Furthermore, it represents a short-latency relay of a primary auditory transmission pathway since cochleovestibular fibers pass through this station to go to the contralateral side of the auditory cortex. Consequently, every damage affecting dentate nucleus could potentially cause contralateral auditory problems such as tinnitus. In this paper, we report the case of a patient presenting 10-year-lasting tinnitus caused by a dentate nucleus cavernoma. A 33-old-year woman suffering from arterial hypertension was admitted to our clinic because of a left tinnitus for ten years and history of headache. In the last three months, she also complained daily transitory episodes of vertigo. Her neurological exam, blood tests and audiological and vestibular assessment were unremarkable. Brainstem Auditory Evoked Potentials did not show any alterations. Brain Magnetic Resonance Imaging (MRI) showed a circular signal of hyperintensity in Fluid Attenuated Inversion Recovery (FLAIR) sequences and spotting hypointensity inside the area of the lesion in Gradient Echo (GRE) sequences affecting the right dentate nucleus; brain imaging did not highlight the presence of gadolinium enhancement. MRI allowed us to make a diagnosis of tinnitus secondary to a contralateral dentate nuclei cavernoma, probably complicated with vertigo due to a blood pressure peak in the last months which had caused bleeding of the lesion. This is the first reported case of dentate nucleus cavernoma presenting with tinnitus and vertigo. We hypothesize that tinnitus and vertigo were due to the selective involvement of the cochleovestibular fibers. We suggest the clinician to consider a pathological involvement of the dentate nucleus in case of vertigo or tinnitus.

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## THE EFFECT OF ERENUMAB ON BRAIN NETWORK FUNCTION IN EPISODIC MIGRAINE PATIENTS: A RANDOMIZED, PLACEBO-CONTROLLED CLINICAL TRIAL


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Objective: Monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway, like erenumab, are believed to prevent migraine attacks via the block of CGRP activity in the periphery. In this study, we explored the effect of erenumab treatment on the functional connectivity (FC) of brain networks involved in migraine and investigated the persistence of such an effect following treatment discontinuation.

Materials: This was a randomized, double-blind, placebo-controlled, multicenter trial with a crossover design performed in adult episodic migraine patients with previous treatment failure. Patients were randomized (1:1) to 12 weeks of treatment with erenumab 140 mg or placebo, followed by a 12-week crossover. Clinical and safety outcomes were assessed every 4 weeks.

Methods. Resting state (RS) FC changes of brain networks were investigated at baseline, week 12 and week 24 using a seed-based correlation approach.

Results: Sixty-one patients were enrolled and randomized to treatment. In each treatment sequence, 27 patients were included in the analyses. We observed a carry-over effect of erenumab treatment on

clinical and MRI variables during the placebo treatment and therefore data analysis was performed as a parallel comparison of erenumab vs placebo for the first 12 weeks of treatment. From baseline to week 12, compared to placebo, patients receiving erenumab showed RS FC changes within the cerebellar, thalamic and periaqueductal gray matter networks, significantly associated with clinical improvement. Compared to non-responders, patients achieving a 50% reduction in migraine attack frequency had distinct patterns of thalamic and visual network RS FC. Brain RS FC changes tended to revert when erenumab was stopped. A lower baseline RS FC of the pontine network identified patients responding to erenumab. No safety concerns emerged during the study.

Discussion: This study showed that in episodic migraine the clinical efficacy of a 12-week erenumab treatment is associated to RS FC changes within clinically relevant brain networks mediating migraine manifestations. In line with previous clinical studies, we showed that ereunmab-related brain functional changes are temporary and tend to revert when erenumab is stopped.

Conclusion: Erenumab modulates RS FC of networks involved in migraine pathophysiology. These functional changes are temporary and strictly related to erenumab administration. Funding. Novartis Pharma Acknowledgments. The authors thank Donatella Vassellatti of Novartis Farma for the oversight of all the aspects related to the conduction of the clinical study and OPIS for providing clinical trial support as CRO assigned to the study.

## EFFICACY OF MINDFULNESS ADDED TO TREATMENT AS USUAL IN PATIENTS WITH CHRONIC MIGRAINE AND MEDICATION OVERUSE HEADACHE: A RANDOMIZED CLINICAL TRIAL, EARLY RESULTS

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Objective: To assess the efficacy of a six-session mindfulness-based treatment added to treatment as usual (TaU) on headache frequency reduction and medication intake.

Materials: 177 patients from the third-level headache center IRCCS "C. Besta", with Chronic Migraine and Medication Overuse Headache (CM and MOH) were enrolled in between November 2018 and December 2021.

Methods: This is a phase-III single blind RCT single-center study. Patients were randomized 1:1 to either TaU or mindfulness added to TaU (TaU+MIND) and followed-up for 12 months. Exclusion criteria were psychiatric comorbidities; pregnancy; secondary headaches; withdrawal from MOH at least twice in the previous two years; previous experience with mindfulness. TaU consisted of withdrawal from overused drugs, patients' education, and prescription of prophylaxis. Patients attending mindfulness sessions were taught to focus their attention on the present and enhance awareness of body sensations, which enabled tackling the pain-pill automatism, and were encouraged to engage in a 7-10 minute/day self-practice. The primary endpoint was the achievement, at 12 months of ≥50% headache frequency reduction compared to baseline. Secondary endpoints included medication intake.

Results: Out or the 177 participants (median age 47.9 years [Q1-Q3: 40.1-54.2]; 19 [11.3%] males; median CM duration 14.6 years [Q1-Q3: 4.9-22.2]) 89 were randomized to TaU and 88 to TaU+MIND. Patients in the TaU+MIND group outperformed those in TaU for the primary endpoint, achievement of ≥50% headache frequency reduction (78.4% vs 48.3%; $p<0.0001$). They also showed superiority in some secondary endpoints, namely headache frequency and medication intake.

Discussion: Our results demonstrated that adding on a mindfulness-based protocol to TaU implemented for the treatment of CM associated to MOH produced a superior and statistically significant reduction in headache frequency, all-drug intake and NSAIDs intake.

Conclusion: These findings show that a six-week mindfulness-based treatment as add on to TaU is superior to TaU for the treatment of patient with CM and MOH.

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## FEASIBILITY AND EFFECTIVENESS OF A SPECIFIC APP TO DELIVERY MINDFULNESS SESSIONS TO PATIENTS WITH DIFFERENT KINDS OF PAIN CONDITION: A PILOT STUDY

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Objective: Chronic pain is a difficult condition to manage, affecting a significant percentage of population; in particular, neuropathic pain and chronic migraine are problematic diseases that imply disability, medication overuse and low response to preventive pharmacological therapies. Clinical results can be improved when traditional therapies are combined with behavioral approaches, in particular mindfulness, that help patients to become more conscious about their symptoms and able to manage pain avoiding medications. Also, this practice can be effective to reduce anxiety related to pain condition. In the last years different clinical experiences reported that intervention like advice or brief interview and education of patients and behavioral approaches like mindfulness can improve significantly clinical benefit and the efficacy of pharmacological treatments, also in telemedicine or web modality. Mindfulness in particular is a perfect tool for patients to learn management of pain, to be educated to the adequate use of medications, to arrange correct life habits that can improve wellbeing and good health.

Material and Methods: We propose a pilot study to enforce the application of a Home-program for patients with pain conditions, to learn mindfulness practice, by using technology with android to deliver mindfulness sessions for daily practice. This study has been conducted on 60 patients (30 naïve for mindfulness practice; 30 familiar with mindfulness practice) with diagnosis of Neuropathic Pain or Chronic Migraine, diagnosis performed at our institute after a regular visit at our hospital. They received a specific APP for mindfulness practice on their phone. Daily standardized guided 12-minutes mindfulness sessions delivered on mobile phones recorded by the experts who generally manage sessions at the hospital. Patients have been evaluated for different outcomes.

Adherence: patients have been asked to practice every day by recording time of their practice; adherence tested and measured a specific questionnaire (MORISKY scale for adherence -adapted for this study). Moreover, FFMQ questionnaire to determine mindfulness competence (Baer, 2006) before and after the APP application. SUS scale: the usability scale (Brooke, 1996) to measure the usability of the APP. GSE: global self-efficacy questionnaire (Scholz, 2002; Sibilia, 2021). Pain level (NRS scale) and Medication intake on the daily diary. The outcomes have been evaluated at the end of the training at 2 months.

Conclusions: Data collected demonstrated that the APP is an effective and helpful tool to reduce pain and to induce the adherence the mindfulness practice.

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## HEADWORK AS INNOVATIVE TOOL FOR MONITORING MABS EFFICACY IN MIGRAINE AND THEIR INFLUENCE ON WORK ACTIVITY: A MULTICENTRIC EXPERIENCE


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Objective: The efficacy of monoclonal antibodies (mAbs) anti-CGRP is generally rated with disease related metrics, but the impact of treatment on the global burden of disease needs to be assessed. HeadWork (HW) is a new evaluation tool developed to assess the impact on work tasks and reduced productivity of migraineurs. Aim of this study is to test the validity of HW and to compare its performance with usually used clinical indexes.

Materials: We enrolled 108 patients receiving mAbs treatment at the Headache Centres of IRCCS C. Besta (Milan), IRCCS C. Mondino (Pavia) and Campus-Biomedico (Rome).

Methods: Patients were followed up on a three-month basis, at each time point they filled in diaries about headache frequency (MMD), medication intake (MMI) and HW. HW questionnaire consists of two sections: "Work-related difficulties"(HW1), 11 items dealing with the degree of difficulty in general skills, problems solving or starting new task; "Factors contributing to work-related difficulties"(HW2), 6 items to address the degree to which some factors, such as noise and brightness of the workplace, negatively impact work-related tasks. Friedman and Wilcoxon repeated measure tests were used for the analysis ($p<.005$). We assessed the presence of a correlation between T0-T3 and T0-T6 deltas with SpearmanRho.

Results: 108 patients (79%females, age 50y±9, disease duration 16±8, age at onset of disease 18y±8) completed the 6-months evaluation. For each of the parameters a significant reduction was observed in the first three and six months of treatment ($p<.001$). MMD decreased from 16.8±6.5 days to 8.1±6.2; MMI from 17.8±9.7 to 7.8±6.5; HW1scale from 23.8±10.5 to 15.2±10.0; HW2scale from 11.3±6.3 to 8.1±5.4. 60 patients out of 108(56%) reduced monthly headaches by 50% or more, and 29(27%) by 75% or more. Correlation for HW1 is moderate and significant with deltas 0-3 and 0-6 for MMD and MMI; for HW2 it is significant for 0-3 changes for MMD, and only with MMI for 0-6 change.

Discussion: Our results confirm the strong efficacy of mAbs as early as 6 months of treatment. HW has a parallel reduction with indexes usually used to monitor treatment efficacy in clinical practice, suggesting good reliability and fidelity. We observed that the reductions in headache frequency, medication intake and HW scales were generally moderately correlated: although a causal direction cannot be stated, it is reasonable to presume that improvement in work-related activities might be due to improved clinical course.

Conclusion: HW seems can evaluate the effectiveness of these treatments on work productivity.

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## REAL-WORLD EFFECTIVENESS OF ANTI-CGRP MONOCLONAL ANTIBODIES COMPARED TO ONABOTULINUMTOXINA. THE RAMO STUDY: EARLY RESULTS


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Objective: Chronic migraine (CM) is a disabling condition with huge impact on the quality of life. OnabotulinumtoxinA (BoNT-A) is an effective treatment for CM. Recently, monoclonal antibodies (mAbs) against calcitonin gene related peptide (anti-CGRP) pathways have been approved to. Aim of this study is to compare the effectiveness and safety of anti-CGRP mAbs and BoNT-A after 6 and 12 months of treatment.

Materials: We enrolled patients from IRCCS Neurologic Institute C. Besta and Bio-Medic Campus University.

Methods: This is an interim, preliminary analysis, of an ongoing retrospective, observational, multicentre, cohort study. Inclusions criteria: diagnosis of CM, received anti-CGRP mAbs or BoNT-A, with at least 6 months follow-up, age 18-65y≥2 preventive treatment failures, starting MIDAS ≥11. Exclusion criteria: serious psychiatric diseases, received BoNT-A before anti-CGRP mAbs treatment (for mAbs arm). Study outcomes: difference from baseline in monthly migraine days (MHD), number of monthly acute medications (MAM) and MIDAS.

Safety assessment: report of serious adverse events (SAE), treatment discontinuation. Wilcoxon rank-sum and Fisher's exact tests were used for the analyses($p<0.05$).

Results: At the time of this interim analysis, we screened 140 patients:110 included,43 mAbs arm,67 BoNT-A arm. Population: mean age 51.1(8.6) y,80 female,90 medication overuse (non-significant differences between groups). At baseline the BoNT-A group presented significantly higher mean MHD (23.0[6.3]vs17.4[32.2]), MAM (24.1[13.7]vs16.5 [2.8]), and MIDAS (93.0[66.8]vs55.6[36.8]) compared to mAbs group. MHD reduction was significantly greater in the mAbs group (-12.4[4.8]vs -9.0[8.8]) at 6 months compared to BoNT-A. Adverse events'(AE) discontinuation: 1(4.8%) patient mAbs arm, 3(4.5%) patients BoNT-A arm.

Discussion: Our preliminary results show a comparable effectiveness between mAbs and BoNT-A at 12months follow-up, with significantly higher efficacy for mAbs at 6 months. Discontinuation due to AE were similar.

Conclusion: From these preliminary data the effectiveness and sustainability of the two treatments appear to be overlapping.

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## BENEFIT-RISK ASSESSMENT OF ATOGEPANT: A POST HOC ANALYSIS OF THE ADVANCE TRIAL

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Objectives: The number needed to treat (NNT) and number needed to harm (NNH) are clinically relevant measures of treatment efficacy and safety, and can help inform treatment decisions. The NNT and NNH for atogepant for the preventive treatment of migraine have not yet been reported. This analysis aims to determine the NNT and NNH for atogepant for the preventive treatment of episodic migraine (EM).

Materials: Atogepant is an oral calcitonin gene–related peptide receptor antagonist approved for the preventive treatment of EM in adults. NNT and NNH are clinically relevant assessments of effect size that can inform management. The Migraine-Specific Quality of Life Questionnaire (MSQ v2.1) Role Function-Restrictive (RFR) domain assesses impacts of migraine on daily functioning that are important to people with migraine.

Methods: The ADVANCE trial (NCT02848326) was a 12-week, randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of atogepant for the preventive treatment of EM. The NNT was calculated based on achievement of a $\geq$50% decrease in mean monthly migraine days (MMDs) (NNT$\geq$50%) across 12 weeks. A second NNT was calculated based on achievement of a $\geq$10.9-point clinically relevant improvement from baseline in MSQ-RFR score (NNTMSQ-RFR) at week 12. NNH was calculated using the proportion of participants reporting a treatment-emergent adverse event (TEAE) leading to discontinuation.

Results: A 50% reduction of MMDs from baseline was achieved by 56%-61% of atogepant participants versus 29% of placebo participants. The calculated NNTs$\geq$50% for atogepant 10 mg, 30 mg, and 60 mg were 3.8, 3.4, and 3.1, respectively. The NNTsMSQ-RFR for the atogepant dose groups were 5.9, 5.7, and 6.3, respectively. TEAEs leading to discontinuation in participants treated with atogepant 10 mg, 30 mg, and 60 mg were reported by 4.1%, 1.8%, and 2.6% of participants, respectively, versus 2.7% of placebo-treated participants. The NNH was 73.0 for atogepant 10 mg. In the atogepant 30 mg and 60 mg dose groups, a lower percentage of participants discontinued versus placebo, resulting in negative NNT calculations ($-105.5$ and $-949.7$, respectively).

Discussion: These findings show a positive benefit-risk profile with atogepant for the preventive treatment of EM.

Conclusions: Atogepant has demonstrated efficacy in the preventive treatment of migraine. As measured by NNT and NNH, a positive benefit-risk profile is associated with atogepant.

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## MESOCORTICOLIMBIC FUNCTIONAL CONNECTIVITY DYSREGULATIONS IN CHRONIC AND EPISODIC CLUSTER HEADACHE PATIENTS

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Aims: Cluster headache is a primary neurovascular headache characterized by excruciating short-lasting unilateral craniofacial pain episodes associated with autonomic oculofacial phenomena. The hypothalamus has been shown to play a major role in the pathophysiology of the disease even if underlying mechanisms need to be better clarified. Converging evidence suggests that functional alterations of the dopaminergic mesocorticolimbic system plays a role in onset and chronification process of pain disorders [1]. Our aim was to study the functional connectivity alterations of the mesocorticolimbic system in both forms of cluster headache (CH), chronic (cCH) or episodic (eCH) CH.

Materials: 24 cCH patients (4 F), 45 eCH patients (6 F) and 26 matched adult healthy controls (CTRL) (5 F) were scanned with a 3T scanner using a rs-fMRI sequence.

Methods: Functional data were analysed with CONN toolbox. The MRI images of patients with attacks on the right side were flipped on the left side. Region of interest (ROI)-to-ROI analyses were performed to investigate connectivity differences between patients and controls in the following structures of mesocorticolimbic system: Frontal Pole, Medial Frontal Cortex (MFC), Frontal Orbital Cortex, Hippocampus, Amygdala, Nucleus Accumbens, Ventral Tegmental Area (VTA) and Hypothalamus. Age and sex were considered as covariates. All results were $p<0.05$ FDR-corrected for multiple comparisons.

Results: In cCH patients we observed decreased connectivity between bilateral hypothalami and the ipsilateral-to-the-pain hippocampus and amygdala, and between frontal regions and the ipsilateral hippocampus and controlateral amygdala compared with CTRL; increased connectivity was observed between the VTA and controlateral-to-the-pain hippocampus and amygdala. In eCH patients, with respect to CTRL, we observed reduced connectivity between the hypothalami and the ipsilateral-to-the pain hippocampus-amygdala complex, and between the MFC and bilateral hippocampi and amygdalae; increased connectivity was observed between VTA and controlateral hippocampus. No differences between eCH and cCH were observed.

Discussion: The present study confirms previous findings of disrupted connectivity between the hypothalamus and brain areas of the mesocorticolimbic circuit in CH [2]. This suggests an imbalance of frontal areas control over dopaminergic pathways [3]. In addition, cCH patients showed specific abnormalities consisting of increased VTA-amygdala connectivity: the latter finding may represent a signature of the disease chronification.

Conclusion: In this study, we confirmed a mesocorticolimbic connectivity dysregulation in both episodic and chronic cluster headache patients.

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## CEREBRAL VENOUS SINUS STENTING IN INTRACRANIAL IDIOPATHIC HYPERTENSION: AN INSTRUCTIVE CASE REPORT

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Introduction: Idiopathic intracranial hypertension (IIH) or pseudotumor cerebri is characterized by clinical findings of intracranial hypertension in the absence of an alternative cause [1]. Despite the usually benign course, IIH can lead to significant morbidity, above all visual loss [1]. The standard treatment includes lifestyle changes, weight loss and intracranial pressure lowering medications, but invasive procedures, such as spinal fluid diversion, optic nerve sheath fenestration or venous sinus stenting may be needed in severe or refractory cases [2, 3].

Case presentation: A 28-year-old female presented at Emergency Department for the subacute onset of diplopia and neck pain irradiated to the left hemicranium. She had a normal BMI, had never smoked nor taken any estroprogestinic medications, tetracycline or vitamin A-derived drugs. Neurologic examination showed diplopia in distant fixation and bilateral abducens palsy. Neurophthalmological evaluation revealed bilateral papilledema and alternating esotropia without visual loss. Cerebral computerized tomography (CT) was normal, while cerebral CT angiography revealed reduced caliber of transverse venous sinuses; magnetic resonance (MR) brain imaging with gadolinium was normal. We performed a lumbar puncture in lateral decubitus and we withdrew 5 ml of cerebrospinal fluid (CSF), detecting an opening pressure of 30 mmHg and a closure one of 15 mmHg. Thus, we made diagnosis of IIH. Notwithstanding the starting of medical treatment with acetazolamide, there was a further clinical deterioration. Cerebral venography with venous pressure measurement was executed, showing bilateral transverse sinuses stenosis with a trans-stenosis pressure gradient of 29 mmHg on the right and 39 mmHg on the left. The right transverse venous sinus, being the dominant, was the one chosen for the endovascular stenting procedure. Whereupon cerebral venous pressure values normalized. At one-month outpatient follow-up, the patient reported improvement of symptoms, neurological examination was normal and papilledema decreased.

Discussion: We report a case of pseudotumor cerebri with finding of venous sinus stenosis undergoing stenting, followed by clinical benefit. There is a debate regarding whether venous sinus stenosis is consequence or cause of increased intracranial pressure and the role of sinus venous stenting is still unsettled [2, 3].

Conclusions: In cases of IIH showing scarce response to medical treatment and venous sinus stenosis on non-invasive neuroimaging, a cerebral venography with venous pressure measurement should be conducted and cerebral venous stenting could be beneficial.

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## MIGRAINE SCENARIO IN ITALY: THE SECOND REPORT OF THE ITALIAN MIGRAINE REGISTRY (I-GRAINE)

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Objective: The Italian Migraine Registry (I-GRAINE) is the first nationwide clinical registry whose core mission is to provide big data on migraine, detailing sociodemographic aspects, patient's journey, disease characteristics and governance, and healthcare resource use. Here, we describe the second annual I-GRAINE report.

Material and Methods: I-GRAINE is an observational, prospective, multicenter (n = 39), non-interventional study. Adults affected by episodic or chronic migraine, seen at each participating headache center, were enrolled. For each outpatient day, the first incident patient (first visit) and the first prevalent patient (follow-up visit), were recruited according to the "systematic random" method. Detailed patient's information was collected by a specifically trained board-certified neurologist using a shared web-based questionnaire.

Results: At the date of 31/12/2022, a total of 867 patients were enrolled (M/F:126/741; age 45.0±12yrs; EM/CM:718/149; medication overuse:131). Most of them had > high school degree (86.8%) and were employed/students (75.7%). Only 8.1% of the patients had consulted (lifetime) a general practitioner due to migraine and 36.2% a headache center (age at first headache center access: 31.5±13.5 yrs; number of centers consulted: 1.3±0.6), whereas 9.2% had been admitted to the Emergency Department within the last 12 months (1.7±1.5 admissions). Age at migraine onset was 17.6 ±8.7 yrs. Comorbidities were present in 41.4% of the patients. Body mass index was 23.1±3.7. Patients referred unilateral pain (70.3%), high migraine frequency (9.3±7.8 days/month) and severe disability (HIT-6 score 60.9±9.1, MIDAS score 48.3±50.7). Many patients complained of migraine-associated symptoms such as photophobia (87.3%), phonophobia (85.8%), osmophobia (42.1%), dopaminergic symptoms (40.4%), allodynia (40.3%), cephalalgiophobia (33.5%), unilateral cranial autonomic symptoms (25.8%) and vertigo (17.1%). Two/thirds of patients (66.7%) used triptans as acute treatment (responders: 74.6%). Migraine prophylaxis was taken by 67.0% of the patients: most of them (46.9%) were treated with anti-CGRP monoclonal antibodies (mAbs) (erenumab 42.4%, galcanezumab 31.7%, fremanezumab 25.4%, eptinezumab 0.5%). The proportion of anti-CGRP mAbs responders ranged from 77.3% to 85.7%.

Discussion: The 2° report of the I-GRAINE registry documents that 1) migraine diagnosis and treatment are delayed due to poor disease awareness; 2) migraine phenotype frequently includes symptoms not listed in the current headache classification; 3) specific/selective acute and preventive drugs (triptans, anti-CGRP mAbs) are now the most frequent treatments among patients visited in the Italian headache centers, and are characterized by high responder rates.

Conclusion: Big data collection is crucial to move migraine out of the shadow cone of marginalization in which it has been relegated up to now.

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## ALTERED NEUROVASCULAR COUPLING WITHIN VISUAL CORTEX IN PATIENTS WITH MIGRAINE WITH AURA: A MULTIDELAY-3D-PSEUDOCONTINOUS-ASL STUDY

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Aim: Converging evidences from advanced neuroimaging studies have identified functional abnormalities of occipital cortex in patients with migraine with aura (MwA). However, several concerns remain about the mechanisms underlying the "tendency" of the visual cortex to allow the beginning of aura phenomenon. Considering that the aura phenomenon triggers are associated with increased global (such as physical activity, stressors and sleep abnormalities) or local (such as bright light visual stimulations) cerebral energy demands, it could be argued that the vascular supply is unable to satisfy the increased energy requirement. We aimed to evaluate whether a dysfunctional neurovascular coupling (NVC) of visual areas could characterize patients with MwA representing the "primum movens" of aura ignition when functional demand increases as following trigger factors.

Materials: 23 patients with MwA and 25 patients with MwoA, naïve for commonly prescribed preventive migraine medications, were recruited. Finally, 20 subjects with less than a few spontaneous non-throbbing headaches per year were recruited as HC. Methods: All patients and HC underwent a 3-Tesla MRI. We considered two multi-delay-3D-pcASL acquisitions, obtaining for each the CBF maps corrected for the transit time. Finally, we combined the two CBF maps into a single statistical analysis by calculating the mean estimated CBF per region and the local NVC from the correlation between the CBF and a functional connectivity measure called REgional HOmogeneity. Results: We observed a reduced NVC in the occipital cortex (ROI 27 and 30) in patients with MwA compared with both patients with MwoA and HC ($p<0.001$). No differences were observed in rCBF comparing patients with MwA with HC ($p=0.36$). Similarly, no differences were observed in rCBF comparing patients with MwA with patients with MwoA except for significantly increased rCBF of ROI 27 and 30 within the visual network in patients with MwA when compared with patients with MwoA ($p<0.001$).

Discussion: The reduced visual cortex NVC could represent the "missing-link" between the exposure to trigger factors and the development of MwA attacks. As a proof of the concept, preventive strategies as antiepileptic drugs exert their antimigraine activity by inhibiting the cortical hyperexcitability probably restoring the trade-off between brain energy demands and rCBF within the visual network.

Conclusion: The inadequate NVC observed in the visual network of patients with MwA, leading to aura phenomenon in response to trigger factors, can shed a light on the mechanisms underpinning the tendency of brain cortex to allow the aura ignition in these patients.

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## GUT MICROBIOTA PROFILING OF PEDIATRIC PATIENTS WITH MIGRAINE

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Objectives: To verify if gut microbiota in children with migraine shows differences in the profiling when compared with age-matched controls. To verify if different migraine phenotype (aura or not aura; presence of nausea/vomiting during the attacks; duration of disease and frequency of monthly days with headache) are associated with differences in the profiles of gut microbiota.

Methods: Patients aged between 6 and 18 years with diagnosis of migraine (ICHD-3 criteria) were recruited. The GM profiling was obtained by the 16S rRNA region sequencing from faecal samples of migraine patients (n = 98) and of HCs (n = 100). QIIME2 v2022.2 software was used to obtain Amplicon Sequence Variants (ASV) with 99% of identity and taxonomic assignations by the sequence matching with Greengenes database. α and β diversity analyses and multivariate and univariate tests were applied to compare the GM profiles by R v4.0.2.

Results: Alpha diversity, assessed by Shannon-Weiner and Simpson indexes, was not significantly different between patients with migraine and HC (Mann-Whitney test, p-value > 0.05). However, the median of these two indices were higher in patients respect to HC. The analysis of β-diversity, which was performed by Bray-Curtis and Unweighted Unifrac algorithms, revealed a dissimilarity statistically significant among two groups (PERMANOVA, p-value = 0.001), suggesting a different gut microbiota profile of patients compared with HCs. The PCA evidenced the presence of gut microbiota fingerprints specific of patients' and HC. Furthermore, the PLS-DA model confirmed the two differential profiles for migraine and HC cohorts, each characterized by different distribution of bacteria. The low Root Mean Square Error value (RMSE = 0.347) and the high R2 (0.525) and Area Under the Receiver Operating Characteristics (AUROC = 0.87) values suggested a high accuracy of the model to predict the subject classification. Finally, the LEfSe test confirmed the presence of features that characterize the gut microbiota composition of patients affected by migraine. By matching the results from these different statistical approaches, we assigned, Bacteroides, Faecalibacterium, Butyricicoccuus, Lactobacillus and Enterobacteriaceae as biomarker of the patient's microbiota, while Bifidobacterium, Akkermansia, Collinsella, Eggerthella, Clostridium, Erysipelotrichaceae, Mogibacteriaceae and Coriobacteriaceae to gut microbiota of HCs.

Conclusions: Our study shows that pediatric migraine patients have a very different GM composition compared to HCs. These differences do not appear to be related to disease characteristics such as duration, presence of aura, or neurovegetative or sensory symptoms.

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## REVERSIBLE CEREBRAL VASOCONSTRICTION SYNDROME: DIAGNOSIS AND TREATMENT MONITORING WITH TRANSCRANIAL ULTRASOUND

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Introduction: Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by sudden onset of thunderclap headache with or without focal neurological deficits, and it is most common among females aged 20-50 years. Typical brain imaging finds multifocal, segmental narrowing of the cerebral arteries, lasting several weeks to months.

Methods: A retrospective chart review of the patient's electronic health record and a literature review were conducted to elucidate the details of this case.

Case report: A young woman with a history of hypertension and medication-overuse headache (MOH) was hospitalized due to bilateral blurred vision followed by total blindness and alteration of consciousness during one of her usual headaches. On admission cerebral CT was unremarkable, conversely MRI documented bilateral occipital ischemic lesions. Fast track Transcranial Ultrasound (TCD) showed multifocal stenosis of both MCA's (PSV 250 cm/s on the right; PSV 280 cm/s on the left) and both PCA's (PSV 220 cm/s on the right; PSV 250 cm/s on the left). Cerebral DSA confirmed the ultrasound findings. Total body CT did not document neoplasias. CSF examination and extensive blood tests including plasma levels of indomethacin, urinary levels of catecholamines and toxicological screening were negative. The diagnosis of probable RCVS was made and infusion therapy with nimodipine, aminic support and anti-seizure treatment were administered. Daily monitoring of cerebral hemodynamics by TCD was performed. At discharge the patient was asymptomatic except for a mild blurred vision. Due to the persistence of a moderate stenosis on the left PCA (Soustiel index > 2.25), oral nimodipine therapy was continued for one month. At follow-up visits TCD showed a complete normalization of blood flow velocities in all major intracranial arteries and treatment was stopped.

Conclusions: Even in a rare disease, such as RCVS, TCD plays a crucial role in early diagnosis and non-invasive monitoring of vasoactive therapy.

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## WHEN THE PAST COMES BACK

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Introduction: Stroke-like migraine attacks after radiation therapy (SMART syndrome) is an uncommon late complication of cerebral radiation therapy. Headache, seizures, focal neurologic deficits are common clinical presentations.

Materials and methods: A retrospective chart review of the patient's electronic health record and a literature review were conducted to elucidate the details of this unusual case.

Case report: A 52 years-old woman, with a history (20 years earlier) of right posterior parietal cerebral ependymoma excision and irradiation, was hospitalized for left faciobrachiocrural weakness, headache and subsequent stuporous status that disappeared after antiepileptic therapy.

On admission cerebral CT excluded recent ischemic lesions and an electroencephalogram showed epileptiform activity on the right fronto-central region. Total body CT revealed no signs of systemic inflammation. Extensive blood tests and cerebrospinal fluid (CSF) examinations were negative. Furthermore, considering a possible inflammatory etiology, a short course of high dose intravenous steroid therapy was administered, followed by gradual tapering. Thickening of the dura mater with swelling of the parietal cortex was documented on cerebral MRI, while an alteration of perfusion was present in the post-radiotherapy area. At discharge persisted a mild cognitive-motor slowing even if the headache had completely resolved. The patient never had new seizures at the last follow up after one months. According to this, serial EEG showed an improvement of the traces.

Conclusions: In summary, in patients with a history of cerebral radiation therapy and a new presentation of neurological deficits, SMART syndrome should be suspected. Given the reversibility of symptoms and radiological findings, an appropriate diagnosis of this syndrome is essential to avoid unnecessary and invasive tests and treatments.

Disclosures: I hereby certify that, to the best of my knowledge, no aspect of my current personal or professional circumstance places me in the position of having a conflict of interest with this presentation.

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## ANTIEPILECTIC DRUGS AND OPERABILITY IN EPILEPSY


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Objectives: It is possible to find an antiepilectic drug without toxic effects?

Material: Patient 45-year-old tracted with levetiracetam, having partial seizures. When generalized it is used fenobarbital.

Method: collateral effects: sedation, atassia, mental confusion. result toxicity in fenobarbital and partial inefficacy in levetiracetam.

Discussion: A sinergic effect is possible using combinated drugs, such as fenobarbital, sodium valproate and diazepam. these drugs act a mechanism of gabamediated inibitory control. Fenobarbital in monoterapy is not the only solution because of the toxic effects.

Conclusion: For the toxic effects of antiepilectic drugs, is possible and correct to choose the surgery.

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## INSOMNIA AND MIGRAINE: HOW HEADACHES AFFECT SLEEP PROFILE


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Background: Migraine and sleep show a complex and bidirectional relationship: migraineurs often report insomnia due to attacks, but poor sleep quality is one of the main triggers for a migraine attack. In migraineurs sleep appears to be characterized by a reduction in quality and efficiency. [1,2]

Methods: Data are collected by a telephonic interview of migraineurs patients, enrolled in Headache center in Policlinico of Palermo. Were asked number of headache days per month, pain intensity ranging from 0 to 10, and were administrated Insomnia Severity Index (ISI). [3] Quantitative variables were analyzed using Pearson coefficient to find any significant correlation. Were asked number of headache days per month, pain intensity ranging from 0 to 10, and were administrated Insomnia Severity Index (ISI). In our study we analyzed the relationship between insomnia and headache's days per month.

Results: We interviewed 157 patients with a mean age of 43±12 years: 88(56%) had chronic migraine and 53 (33%) episodic migraine, 112 without aura. In our migraine patients, sleep disorder ($p<0.001$) the difficulty in falling asleep score (ISI1a) and in staying asleep (ISI1b), were significantly correlated with headache days per month ($p<0.005$). In our sleep profile waking up too early (ISI1c: $p > 0.005$), and interference of the sleep problem with their daily functioning (ISI5: $p >0.005$) were not correlated with headache days. Insomnia was not significantly associated with the intensity of pain.

Conclusion: Our data confirmed the relation between sleep and migraine in particular initial and middle insomnia was significantly related with the number of headache for months. The intensity of the headache didn't affect insomnia. More studies are necessary to demonstrate this relationship between insomnia and migraine.

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## ASSOCIATION OF MONOCLONAL ANTIBODIES FOR DIFFERENT DISEASES: A MULTICENTER STUDY


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Objective: The objective of this multicenter observational study was to evaluate the 6-month effectiveness and tolerability of antibodies targeting the calcitonin gene-related peptide (CGRP-MoAbs) when combined with other MoAb for different diseases.

Materials and Methods: Outpatients included in the "Italian Headache Registry" (RICe) and treated with CGRP-MoAbs for high frequency episodic migraine or chronic migraine, while simultaneously assuming other monoclonal antibodies for additional pathologies, were screened for the inclusion. Patients were included if they had a 6-month follow-up after the start of therapy with the two co-prescribed drugs. Effectiveness outcomes for migraine included reduction from baseline of Monthly Headache Days (MHDs), Migraine Disability Assessment (MIDAS) and HIT-6 questionnaire total scores. The Patients' Global Impression of Change (PGIC) scale was used to quantify the patient's evaluation of the efficacy of treatments. Safety outcomes included the observation of side effects different from those expected in monotherapy.

Results: Twenty-six patients (21 women and 5 men; mean age±SD, 50.3±9.7) were included. In most of cases (n=16; 61%) the CGRP-MoAb (erenumab, galcanezumab or fremanezumab) was added to a previously ongoing treatment with another MoAb (namely adalimumab, ocrelizumab, omalizumab, natalizumab, ustekinumab, risankizumab, tocilizumab, etanabercept, denosumab, certolizumab, evolocumab). The most frequent diseases associated with migraine were psoriatic arthritis (n=6; 23%) and osteoporosis (n=6; 23%), followed by ankylosing spondylitis (n=4; 15%), rheumatoid arthritis (n=3; 11%), multiple sclerosis (n=2; 8%), asthma (n=2; 8%), ulcerative colitis (n=1; 4%), vasculitis (n=1; 4%) and dyslipidemia (n=1; 4%). MHDs significantly decreased from baseline to 6 months (20.7±6.1 vs 11.8±8.0; p<0001) as well as the MIDAS score (75.0±41.9 vs 30.3±27.7; p=0.001) and the HIT-6 score (66.5±10.5 vs 53.4±8.7; p=0.002). The PGIC score was high for both the treatments (anti-CGRP mAbs: mean±SD 5.48±2.6; other MoAbs mean±SD 5.5±2.9). Mild side-effects associated with the introduction of the second MoAb were detected in two cases only: the combination of evolocumab with the previously prescribed erenumab was associated with the appearance of gastrointestinal symptoms while the combination of galcanezumab with the previously prescribed ustekinumab was associated with the appearance of alopecia.

Discussion: Preliminary findings confirm the efficacy and safety of CGRP-MoAbs even when used in combination with other MoAbs. The low incidence of mild side-effects following the introduction of a second MoAb should be better investigated to establish whether a causal relationship between the two events must be suspected.

Conclusions: The combination of different MoAbs may be considered safe and effective in daily clinical practice.

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## PARAMAGNETIC RIM LESION BURDEN AND CHOROID PLEXUS ENLARGEMENT CONTRIBUTE TO COGNITIVE IMPAIRMENT AND FATIGUE IN MULTIPLE SCLEROSIS

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Objectives: Chronic inflammation may contribute to worse cognitive performance and fatigue in multiple sclerosis (MS) patients. Paramagnetic rim lesions (PRLs) and choroid plexus (CP) enlargement have been proposed as markers of chronic inflammation in MS and are associated with a more severe disease course. However, their relation with cognitive impairment and fatigue has not been fully explored yet. In this study we investigated the contribution of PRL number and volume and CP enlargement to cognitive impairment and fatigue in MS patients

Material and Methods: Brain 3T magnetic resonance imaging (MRI), neurological evaluation and neuropsychological assessment, including the Brief Repeatable Battery of Neuropsychological Tests and Modified Fatigue Impact Scale were obtained from 129 MS patients and 73 age- and sex-matched healthy controls (HC). PRLs were identified on phase images of susceptibility-weighted imaging (SWI), whereas CP volume was quantified using a fully automatic method on brain three-dimensional (3D) T1-weighted and FLAIR MRI sequences. Predictors of cognitive impairment and fatigue were identified using random forest.

Results: Thirty-six (27.9%) MS patients were cognitively impaired and 31/113 (24.0%) had fatigue. Fifty-nine (45.7%) MS patients had ≥1 PRLs (median=0, interquartile range=0;2). Compared to HC, MS patients showed significantly higher T2-hyperintese white matter (WM) lesion volume, lower normalized brain, thalamic, hippocampal, caudate, cortical and WM volumes, and higher normalized CP volume (p from <0.001 to 0.048). The predictors of cognitive impairment (relative importance) (out-of-bag area under the curve [OOB-AUC]= 0.727) were lower normalized brain volume (100%), lower normalized caudate volume (89.1%), higher normalized CP volume (80.3%), lower normalized cortical volume (70.3%), higher number (67.3%) and volume of PRLs (66.7%) and higher T2-hyperintense WM volume (64.0%). Higher normalized CP volume was the only predictor of the presence of fatigue (OOB-AUC=0.563).

Discussion: Chronic inflammation, in terms of higher number and volume of PRLs and enlarged CP may contribute to cognitive impairment in MS in addition to atrophy. The contribution of enlarged CP in explaining fatigue supports the relevance of immune-related processes in determining this MS-related manifestation independently from disease severity.

Conclusion: The evaluation of PRL number and volume and CP enlargement may contribute to understand the pathophysiology of cognitive impairment and fatigue in MS. Moreover, they may represent clinically-relevant therapeutic targets to limit the impact of MS on both these clinical manifestations.

## COST-EFFICACY OF A SIX-WEEK MINDFULNESS-BASED TREATMENT ADDED TO TREATMENT AS USUAL VS. TREATMENT AS USUAL IN PATIENTS WITH CM-MOH: THE MIND-CM STUDY

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Objectives: To assess the cost-efficacy of six-week mindfulness-based treatment added to treatment as usual (TaU) vs. TaU, which showed clinical superiority in terms of headache frequency and medication intake reduction [1-3].

Materials: A full protocol evaluating disease cost was implemented, and it accounted for: a) direct healthcare cost (medications, medical consultations, diagnostic procedures, and other treatments connected to headaches, including non-pharmacological ones); b) direct non-medical costs, which included costs of informal care for housework and for baby-sitting; c) indirect costs, which are based upon loss of productive time.

Methods: Phase-III single-blind RCT. 177 patients with CM and MOH were randomized 1:1 to either TaU (withdrawal from overused drugs, education, and tailored prophylaxis) or TaU + Mindfulness, the latter consisting of six group session of mindfulness practice and 7-10 minute daily self-practice. Follow-ups were planned at 3, 6 and 12 months from baseline. We calculated the average three-month cost before and after randomization, and the average cost during the 12 months' follow-up period after randomization. The reimbursement foreseen by Lombardia Region for the implementation of such a group intervention as organized for the MIND-CM project, i.e. 6 group sessions of 6-8 persons each, corresponds to 9.5€ per patient and per session [see note below], i.e. 57€ per patient for the entire period; the analyses were referred to study completers only.

Results: A total of 154 patients (79 of those in TaU and 75 of those in TaU + Mindfulness) completed the study. For those in TaU, the baseline 3-month cost was 2284€ (95%CI: 1059-3399€), after randomization it was 1168€ (95%CI: 469-1951€); the same figures were 2122€ (95%CI: 980-3694€) and 515€ (95%CI: 291-879€) for those in the TaU + Mindfulness group. The total average cost during the 12 months' follow-up period after randomization was 4671€ (95%CI:1875-7805€) for those in TaU and 2062€ (95%CI:1163-3517€) for those in TaU + Mindfulness, the delta being around 217€ per month.

Discussion: The cost-efficacy analysis herein presented thus witnesses that, considering the little cost of implementation in public bodies of Lombardia Region, there is adequate room for implementing a protocol based on the MIND-CM project.

Conclusions: This study showed the cost-efficacy of a six-week mindfulness-based treatment added on to TaU Vs. TaU alone. Note. Lombardia Region "Nomenclatore tariffario di specialistica ambulatoriale". Available at http://normativasan.servizirl.it/port/GetNormativaFile?fileName=18461_Prest_AMB%20DICEMBRE%202022_agg.xlsx (Accessed 30/05/2023)

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## QUALITATIVE MIDAS SCORE AS A NOVEL ALTERNATIVE TOOL FOR TREATMENT EFFICACY EVALUATION IN CHRONIC MIGRAINE

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Introduction: One of the goal of migraine preventive therapy consists in the improvement of quality of life (QoL). MIDAS scale [1] measures migraine-related disability and its score>11 is needed for the reimbursement of the monoclonal antibodies blocking CGRP pathway (mAb-CGRP), according to the Italian Agency of Drug (AIFA). Also, MIDAS reduction rate (MIDAS-RR)>50% has to be documented for treatment continuation. Chronic Migraine (CM) patients usually score high MIDAS and difficulty reach a MIDAS-RR>50%, although they refer therapy benefit. Improvement of 30% has been proposed as a good outcome in CM [2].

Materials and Methods: We proposed to 17 consecutive CM patients undergoing mAb-CGRP treatment a modified MIDAS scale we called "Qualitative MIDAS"(Q-MIDAS). The Q-MIDAS is composed by five question exploring the same five domains of the standard MIDAS (reduction/impossibility to attend work or study and impossibility to his own social affairs). Instead of reporting the number of days with disability within 3 months for each question, the Q-MIDAS prompts the patients to choose an answer in a qualitative manner, indicating the self perceived variation with respect to a previous period (without therapy). To such an answers a point was attributed in the subsequent way: a) zero= (-0.20); b) very diminished (-0.15); c) quite diminished (.-0.10); d)the same(0); e)quite incremented(+0.10); f)very incremented(+0.20). The Q-MIDAS score, ranging between -1 and +1, is assumed to represent MIDAS variation from 100% reduction (-1) to 100% increase (+1). Treatment has been considered effective if Q-MIDAS score was <-0.5. Standard MIDAS and Q-MIDAS were administered after 3 months of mAb-CGRP therapy. A comparison between mean MIDAS-RR and Q-MIDAS was performed as well as the number of responders with MIDAS-RR >50% vs Q-MIDAS< -0.5; concordance between the two scales has been calculated.

Results: Mean MIDAS score was 67,1 (+/-57,4) at baseline and 24,5 (+/-31,4) at 3rd month. MIDAS-RR was -0,54 (+/-0,4) compared to Q-MIDAS that was -0.64(+/-0.22) and this difference was significant (p<0.01). Number of patients reaching MIDAS-RR>50% was 10/17 while whose reaching Q-MIDAS<-0,5 was 13/17 (p<0.05).

Concordance between the two scales was 0,82 with a Cohen Kappa value of 0,61 (good concordance).

Discussion and Conclusions: Q-MIDAS resulted a very easy scale to be applied with a possible advantage to estimate MIDAS variation in a qualitative manner. In 3 out 17 patients there was not a concordance between MIDAS-RR>50% and Q-MIDAS<-0,5. In such a cases the Q-MIDAS revealed a significant self reported improvement in QoL, non demonstrated by standard MIDAS. This experience, if confirmed in a more extensive study, would give the possibility to continue a treatment in a boarder part of patients affected by CM.

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## DIFFERENCES IN PATIENT JOURNEY FOR RESISTANT AND REFRACTORY MIGRAINE: BASELINE DATA FROM THE REFINE STUDY


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Despite advances in migraine treatment, some patients suffer from resistant (RES) and refractory (REF) disease forms [1], which pose a significant social and economic burden. The Resistant and rEFractory migraINE (REFINE) study aims to validate 2020 EHF definitions of RES and REF migraine [1] in the real-world. This analysis aims to detect differences in the journey of RES and REF patients compared with not resistant and not refractory (NRNR). The REFINE is a prospective study including RES and REF patients from 15 European Centres between February 2021 and December 2022. We reported descriptive statistics of baseline and disease characteristics of the entire study cohort and compared RES, REF and NRNR patients through the $\chi 2$ test and Wilcoxon signed rank test. Centres included 671 patients with a median age of 46 years (Interquartile range [IQR] 37-54); 253 (37.8%) were RES, 73 (10.8%) REF, and 345 (51.4%) NRNR. RES and REF patients were older than NRNR (median age of 49, IQR 39-56 vs 51 IQR 43-58 vs 43, IQR 34-52; p<0.001), were more frequently diagnosed with chronic migraine (CM) (70.4% vs 83.6% vs 40%; p<0.001), with a longer CM history (median months of chronification=36, IQR14-96 vs 36, IQR 12-84 vs 24, IQR 12-60; p<0.001). RES and REF patients also had higher rates of medication overuse (47.4% vs 45.2% vs; 20%; p<0.001) that led more frequently to detoxification treatment compared with NRNR (21,9% vs 27.8% vs 9.3%; p<0.001), both home oral (11.9% vs 12.3% vs 4.9%; p<0.004) and hospital day service detoxification (5.5% vs 11% vs1.7%; p<0.001). Furthermore, these patients were more frequently misdiagnosed (30.4% vs 36.4% vs 28.7%; p=0.032), received more frequently inappropriate drug treatments in the past (6.7% vs 8.2% vs 3.2%; p=0.065) and accessed more than once to emergency department (39.1% vs 49.3% vs 28.7%; p<0.001). A higher proportion of RES and REF patients underwent radiological examinations such as brain MRI compared with NRNR patients (48.2% vs 54.8% vs 47.8%; p<0.001). RES and REF patients experienced longer and more complex migraine history and required higher use of health care resources than NRNR. Their management still represents an unmet need and a challenge for migraine experts. Further efforts are needed to detect these patients in advance and optimise their management.

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## PERSISTENT OPHTHALMOPARESIS IN PEDIATRIC ONSET RECURRENT PAINFUL OPHTHALMOPLEGIC NEUROPATHY (RPON). A REVIEW OF THE LITERATURE, A PEDIATRIC CLINICAL REPORT, AND AN ANALYSIS OF THE RELATED CLINICAL FEATURES


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Aim: Recurrent Painful Ophthalmoplegic Neuropathy (RPON) is a rare disorder, characterized by episodes of ophthalmoparesis and ipsilateral headache. The etiology is still debated, and clearcut evidence of treatment efficacy is lacking. Although ophthalmoplegia is typically reversible, there is an unpredictable risk of residual motor deficit. We present a review of pediatric reports published so far and a pediatric clinical report, in order to explore predictive features of residual ophthalmoparesis.

Methods: The literature review was performed on PubMed, using the search terms "ophthalmoplegic migraine" and "Recurrent Painful

Ophthalmoplegic Neuropathy". We selected reports published until 30th June 2022, with onset under 16 years of age.
Review of the literature and clinical report: A nine-year-old boy was diagnosed with RPON after the third episode of III cranial nerve palsy and headache. The first two episodes, preceded by flu symptoms, remitted spontaneously. The third, preceded by a herpes labialis eruption, remitted with corticosteroids. The MRI revealed thickening and gadolinium-related enhancement of the right III cranial nerve. Twenty-two months later the patient presented a fourth episode, treated with intravenous immunoglobulin. Eight months after the fourth episode, a residual motor impairment was observed. To our knowledge, 129 cases of pediatric onset RPON have been reported so far; 35/102 (34%) were reported with permanent oculomotor deficits, after a mean of 15 months since the last episode. Patients with persisting ophthalmoparesis had an earlier age at onset (mean 4,8 years, range 0,3-15) compared to those with complete resolution (mean 5,9 years, range 0,8-13; p 0.044*), and more frequently several recurrences (p 0.003*, 14/57 patients versus 15/25). Gender distribution, age at follow-up, follow-up duration, episodes frequency, other concomitant forms of headache, acute treatment with corticosteroids, prophylactic therapy, preceding infectious symptoms, Schwannoma or vascular disorder detection, did not differ between the two groups.

Discussion: Our findings, show that the age at onset and the number of recurrences represent predictive factors for persisting oculomotor deficit. A correlation among deficit persistence and episode recurrence has been already described even though complete recovery after several episodes has been reported. Age at onset, so far not considered as major risk factor, was earlier (p*0.044) in patients with persistent motor impairment. Acute treatment or prophylactic therapy were not associated to ophthalmoparesis remission.

Conclusion: The age at onset and the number of recurrences represent predictive factors for persisting oculomotor deficit. Future evidence about etiopathogenetic mechanisms would allow better attacks management and a more favourable long-term outcome.
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## PUPILLARY LIGHT RESPONSE IN MIGRAINE PATIENTS: A STUDY OF AUTONOMIC FUNCTION


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Objective: To assess the autonomic function through automated pupillometry, a non-invasive and rapid test able to provide objective and reproducible data on pupil size and reactivity in patients with migraine compared to healthy controls (HC). We investigated whether the measurement of the pupillary light reflex provides further information on the pathophysiology of migraine.

Methods: We performed automated pupillometry in a cohort of patients with a diagnosis of migraine without and with aura in the interictal phase, compared to age-matched HC. The following pupillometric parameters were recorded: Baseline pupil diameter (BPD), Minimum Pupil Diameter (MPD), Constriction Index (CI), Reflex Latency (RL), Constriction Velocity (CV), Maximum Constriction Velocity (MCV), Dilation Velocity (DV) and Neuro-pupillary index (NPi). Demographical and clinical data on migraine were collected. The severity and disability of migraine were assessed through the headache impact test (HIT-6) and the migraine disability assessment (MIDAS) scale.

Results: We included 220 eyes from 110 patients with a diagnosis of migraine and a mean age of 38.1 ±14.0 and 152 eyes from 76 HC with a mean age of 41.0 ±12.8. In the migraine group, we found significantly lower values of NPi ($p < 0.001$), CH ($p < 0.001$), DV ($p=0.021$) and MCV ($p=0.043$) and significantly higher values of MPD ($p=0.023$) compared to HC. In the migraine group, we did not find significant correlations between pupillometric parameters and demographic, clinical features, HIT-6 and MIDAS. The pupil changes were not correlated with the interval since the last migraine attack.

Discussion and Conclusion: The results suggest subtle sympathetic and parasympathetic pupil dysfunction in the interictal phase of migraine. Automated pupillometry may play a role as a reliable and non-invasive tool to evaluate patients with migraine and may also provide insights into the pathophysiology of migraine.
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## MIGRAINE AND ARTHRITIS: ASSOCIATING MONOCLONAL CGRP AND INTERLEUKIN-17A ANTIBODIES


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Background: Preventive treatment of migraine with CGRP-mAbs is a valid option in polypharmacy because they degrade into amino acids, thus they do not interact with other drugs by bypassing hepatic and renal elimination steps. There are no clinical studies about their association with biologics for arthritis. Secukinumab is a highly selective IL-17A antagonist and it is the first non-TNF alpha inhibitor agent licensed for the treatment of psoriasis, psoriatic arthritis, and axial spondyloarthritis, in which IL-17A has been implicated in the pathogenesis [1].

Case Presentation: We report the case of a 56 years old woman with chronic migraine, migraine with visual aura, and MOH. During the anamnestic interview, she reported a clinical history of axial spondyloarthritis, bipolar disorder, arterial hypertension (under control), fibromyalgia, hypercholesterolemia, restless legs syndrome, mitral valve prolapse, and previous surgery. She had recently started taking secukinumab. She received a beta-blocker, a calcium channel blocker, a diuretic, an atypical antipsychotic, a dual serotonin and norepinephrine reuptake inhibitor, a hypolipidemic agent, a dopamine agonist, benzodiazepines and an anti-seizure drug (for bipolar disorder and migraine prophylaxis). At the time of her first evaluation, she had been taking combination analgesics daily for a month (MIDAS 220). It would have been difficult adding a prophylactic medication for migraine to avoid interactions with her complex polypharmacy. We opted for CGRP-mAbs (fremanezumab), even though there were no studies describing their interaction with secukinumab. After 1 month the patient reported the same frequency of headaches but a better efficacy of the acute medication (Eletriptan, taken daily). After 2 months, she reported a lower attack frequency. At the first trimester evaluation, she reported a MIDAS of 65, which remained constant at the six months follow-up. A month after the suspension of the first cycle she reported the worsening of her headache (MIDAS 100). She started a second cycle of

fremanezumab, associated with a low dose of pregabalin. Notably, she reported no migraine with aura after she started taking fremanezumab.

Discussion/Conclusion: CGRP-mAbs could be a good option for complex patients. The contributions of CGRP to human arthritis pain are incompletely defined. Targeting CGRP or its receptors within joint tissues might prevent persistent inflammation and relieve arthritis pain [2]. It's been recently shown in rats that IL-17 crosses the blood-brain barrier to trigger neuroinflammation, suggesting that it might be a novel target in the treatment of migraine [3].

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## VISUAL WORKING MEMORY AND VISUAL SPATIAL PERCEPTION IN MIGRAINE PATIENTS WITHOUT AURA

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Objective: To investigate visual spatial abilities and visual working memory in patients with migraine during the interictal phase.

Materials and Methods: A total of 15 migraineurs and 15 well-matched healthy controls. Visual spatial abilities were assessed using (VOSP). This test investigates both space perception and object identification. A Change Detection test was presented to each patient to test visual working memory. Clinical features and neuropsychological measures were calculated for patients and HC. Differences between the two groups were evaluated using Mann Whitney and Chi- Square ($\chi 2$ test).

Results: VOSP: In this ongoing test, no significant differences between groups were observed for the object recognition task. However, a significant difference between migraine patients and healthy controls was seen in the sub-task: number location (p=0.0082) and cube analysis (p=0.0080). In Both Tasks HC obtained more correct answers than migraine patients. In addition, at the Change Detection test significant differences were found between the two groups. HC achieved a rate of sure responses greater than migraineurs (p= 0.0238), whereas migraine patients obtained more uncertainty responses (p= 0.0041).

Discussion: New biomarkers are needed in migraine for both early diagnosis and monitoring of therapeutic intervention. Data reported here suggest that an accurate investigation of high-level visual functions in migraine patients may offer potential biomarkers of disease evolution and response to treatments and an opportunity to provide new insights into the understanding of important clinical and behavioral aspects of migraine.

## THE OTHER SIDE OF THE COIN: AN AGGRESSIVE FORM OF IGG4-RELATED DISEASE PRESENTING WITH ACUTE BILATERAL SUNCT-LIKE HEADACHE-CRISIS

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Introduction: IgG4-related disease (IgG4-RD) is an insidious immune-mediated disorder characterized by tissue-invasion of IgG4-producing plasmacells causing inflammatory infiltrates, tissue fibrosis and therefore organs-enlargment [1]. Central nervous system (CNS) can be rarely affected and hypertophic pachymeningitis (HP) is one of the most recognized entity. As a general concept, IgG4-RD is not associated with acute, inflammatory clinical presentation.

Methods: A case of an aggressive form of IgG4-RD is described.

Results: A 43-years-old man came at our attention in 08/2021 because of right-orbital headache-attacks associated with omolateral neurovegetative trigeminal-activation and, initially, lateral rectus muscle transient paresis. Brain-magnetic resonance imaging (MRI) showed modest thickening of right-sided cavernous region, prepontine cistern and alongside of right-uditive duct, without pathological contrast enhancement (c.e.). Interpreted as Tolosa-Hunt syndrome, he was treated with high dose intravenous steroid with initial complete benefit. Nevertheless, after steroid-therapy weaning, the symptoms acutely relapsed with bilateral, violent, steroid-resistant periorbital pain-attacks associated with intense neurovegetative trigeminal activation, sometimes lasting just few seconds and resembling those of Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival-injection and Tearing (SUNCT) syndrome. Brain-MRI lesions, stable and non-enhancing at a first control, evolved within one month in extension, thickness and c.e., erosion of the underlying bone and hypophysis-involvement. Liquoral IgG4-levels resulted elevated and therefore IgG4-RD was diagnosed. He was successfully treated with rituximab. One-year follow-up showed clinical-remission and radiological stability.

Conclusions: A case of aggressive IgG4-RD presenting with bilateral SUNCT-like symptoms is described. Taking into account a possible acute, highly inflammatory clinical presentation of these rare patients is warranted.

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## EVIDENCE OF HIGHLY SENSITIZED CENTRAL NEURONAL CIRCUITS IN MEDICATION OVERUSE HEADACHE: A STUDY OF THALAMOCORTICAL ACTIVATION AND LATERAL CORTICAL INHIBITION

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Objective: The objective of this study was to determine whether cortical hyperexcitability in chronic migraine with medication overuse headache (CM-MOH) is related to increased thalamocortical drive or aberrant cortical inhibitory mechanisms.

Materials and Methods: Somatosensory evoked potentials (SSEPs) were performed by electrically stimulating the median nerve (M), the ulnar nerve (U), and both nerves simultaneously (MU) in 27 CM-MOH patients and for comparison in 23 healthy volunteers (HVs). We

calculated the degree of cortical lateral inhibition using the formula [100–(MU/(M+U) *100)], and the level of thalamocortical activation by analyzing the high-frequency oscillations (HFOs) embedded in parietal N20 median SSEP.

Results: Compared to HV, CM-MOH patients showed higher lateral inhibition (CM-MOH 52.2% ± 15.4 vs HV 40.4% ± 13.3; p= 0.005), which positively correlated with monthly headache days, and greater amplitude of pre-synaptic HFOs (p= 0.010) but normal post-synaptic HFOs (p= 0.122).

Conclusion: Our findings suggest that central neuronal circuits are highly sensitized in CM-MOH patients, at both thalamocortical and cortical levels. These observed changes may arise from a combination of dysfunctional central pain control mechanisms, hypersensitivity, and hyperresponsiveness directly linked to the chronic use of acute migraine drugs.

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## HOW PCS SCORE CAN INFLUENCE CLINICAL RESPONSE TO MONOCLONAL ANTIBODIES AGAINST CGRP: A SINGLE CENTER THREE YEARS REAL-LIFE EXPERIENCE


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Objectives: Catastrophic thought, defined as “an exaggerated negative mental set brought to bear during actual or anticipated painful experience” [1], plays a crucial role in pain chronification, especially in migraine patients. We aimed to evaluate how pain catastrophizing, measured using the Italian version of the “Pain Catastrophizing Scale (PCS)”, could influence clinical response to anti CGRP monoclonal antibodies (Erenumab, Galcanezumab, and Fremanezumab) in patient with chronic migraine with or without abuse. We are furthermore interested in evaluating a possible relationship between tendency to ruminate (measured by Rumination subscale) and response to therapy [2].

Materials/Methods: We collected sociodemographic and clinical data from 20 consecutive patients attending at our headache clinic from July 2021 since now. Patients are diagnosed as chronic migraine with or without MOH, according to ICDH III criteria. All patients in the court were randomly assigned between Galcanezumab (120 mg), Erenumab (140 mg) and Fremanezumab (125 mg), respecting AIFA and EAN guidelines. PCS was measured at the beginning of therapy (T0) and repeated at three (T1) and six months (T2). Clinical response was measured by the HIT-6 “Headache Impact Test-6” scale and the MIDAS “Migraine Disability Assessment Test” scoring. Comorbid depression was assessed by BDI II “Back Inventory II” scale. All patients were treated by a psychologist. We utilized the Spearman’s test to analyze PCS and Rumination correlation with the other variables included. Statical analysis was performed using Python 3. Here are reported T0 data.

Results: The study included 20 patients (3 men and 17 women) with or without medication overuse. Migraine impact was moderate (HIT-6≥56) except for three cases. Disability is severe in the whole sample except for one patient (MIDAS 12). We also observe mild to severe level of depression (BI II ≥ 10). PCS and rumination are mildly correlated with HIT6 (0.65 and 0.58, respectively) but lowly with BACKII (0.49 and 0.39, respectively). While for the leftover variables (i.e., Sex, Age, and MIDAS) no correlation was found.

Discussion: In our court, composed by patients with chronic migraine, PCS and Rumination seem not to be correlated to depression, measured by BACK II scale. Surprisingly, PCS is not related to MIDAS scoring as sex.

Conclusions: In this real-life setting, rumination can predict clinical response to monoclonal anti CGRP Ab, regardless of depression burden.

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## LATE-ONSET MIGRAINE MIMICKING SECONDARY HEADACHES: TWO CASES SUCCESSFULLY TREATED WITH ONABOTULINUMTOXINA


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Objectives: Migraine is one of the most common neurological disorders and its typical onset is in young adult age. [1] Among the elderly population, its prevalence varies from 3 to 8%. [2] Headache onset in older age requires an accurate diagnostic process to exclude secondary forms and a careful management considering age and comorbidities often present in this subgroup of population. Goal of this report is to describe two patients with late onset migraine mimicking secondary headaches and to evaluate the effect of OnabotulinumtoxinA (BT-A) on their condition.

Materials: We describe two female patients with chronic migraine (CM) ab initio with onset over 50 years old. Because of atypical features and late onset, further investigations were performed to exclude secondary forms. Patient 1 had almost exclusively nocturnal attacks; patient 2 often experienced a vertiginous syndrome associated with headache. Also, many attacks lacked typical migraine features such as nausea/vomiting and phonophobia/photophobia. They both underwent repeated injections with BT-A after first-line prophylaxis failure, especially for difficulties in tolerability.

Methods: Patients were treated with BT-A following the PREEMPT protocol3 with additional specific "follow-the-pain" sites every three months for at least one year. We collected sociodemographic data and prospectively gathered clinical data at baseline and at every scheduled treatment. Outcomes measures included days of migraine and number

of acute medications before the treatment (t0) and after three (t1), six (t2), twelve months (t3) and HIT-6 and MIDAS scores at t0 and t3.

Results: Days of headache/month decreased in both patients (patient 1: t0=20; t1=6; t2=3; t3=2; patient 2: t0=25; t1=18; t2=8; t3=5), just as acute medications intake (patient 1: t0=10; t1=5; t2=3; t3=2; patient 2: t0=25; t1=18; t2=7; t3=2). MIDAS score lowered after one year of treatment (patient 1: t0=55; t3=15; patient 2: t0=53; t3=11), as well as HIT-6 score (patient 1: t0=63; t3=52; patient 2: t0=62; t3=50).
Discussion: Our results show that BT-A was an effective prophylaxis, as it reduced number of headache days, medications intake, MIDAS and HIT-6 scores, improving the quality of life. The excellent response to BT-A in these patients suggests that, despite atypical features, a migraine physiopathological mechanism probably underlies their headache.

Conclusions: BT-A might be a valid prophylaxis option for elderly patients suffering from late onset CM mimicking secondary headaches, not only for its effectiveness but also for its high tolerability profile and lack of interactions with other drugs frequently used in this subgroup of population.

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## MIGRAINE DURATION AND RESPONSE TO MONOCLONAL ANTIBODIES TARGETING CALCITONIN GENE-RELATED PEPTIDE (ANTI-CGRP MABS) IN PATIENTS WITH CHRONIC MIGRAINE (CM): REAL-LIFE DATA

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Monoclonal antibodies targeting calcitonin gene-related peptide (anti-CGRP mAbs) represent an effective therapeutic option in patients with chronic migraine (CM). However, it is unclear whether an early treatment with CGRP-mAbs can revert the mechanisms of CM more easily than late treatment, thus improving clinical outcomes. This real-world study aimed to evaluate whether the duration of migraine – and particularly of CM - influence the effectiveness of anti-CGRP mAbs. We included consecutive patients with CM treated with anti-CGRP mAbs in two third level Italian headache centers between 2019 and May 2023. We included in the analysis only patients with CM completing at least one year of treatment. We classified patients into "responders" - if reporting a ≥50% decrease in MMDs from baseline to Month 6 of treatment - and "non-responders" - if they not achieved a ≥ 50% reduction in MMDs. We compared the median duration of migraine from onset and the diagnosis of CM in responders with non-responders. We also tested the non-parametric correlation between the absolute decrease in MMDs from baseline to Month 6 of treatment and the duration of migraine or CM. We enrolled 375 patients (82% females, median age 49, IQR 38-57 years), with 31 years (IQR 21-40 years) of migraine duration and 12 years (IQR 6-22 years) of CM duration. At Month 6, 194 patients (52%) were responders and 181 (48%) non-responders; responders and non-responders had similar disease duration (30.0 years, IQR 21.0-40.5 vs 31.0, IQR 21.75-40; p=0.698) and CM duration (12.0 years, IQR 6-24 vs 11.0, IQR 6-20; p=0.256). We found no difference in MMD reduction from baseline in responders compared with non-responders. No correlation was found between the decrease in MMDs from baseline (rho=0.009, p= 0.874) and migraine duration (rho=0.069, p=0.252). Our data suggest that patients with CM achieve a significant clinical response to anti-CGRP mAbs independently from CM duration. This result is in contrast with the higher effectiveness of onabotulinumtoxinA in patients with shorter CM duration compared with those with long disease history [1]. According to our data from a multicenter real-world study, mAbs CGRP could be an effective therapeutic option for patients with CM even after a long disease history.
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## PERCEIVED EASE-OF-USABILITY AND LOCAL TOLERABILITY USING CGRP MONOCLONAL ANTIBODIES AUTOINJECTORS VERSUS SYRINGE: AN ONLINE QUESTIONNAIRE-BASED STUDY IN PATIENTS WITH MIGRAINE

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Aims: Monoclonal antibodies acting on the CGRP pathway (CGRP-mAbs) are characterized by subcutaneous administration via autoinjector pens or prefilled syringes. Unfortunately, significant local tolerability concerns about injection site pain may degrade patient comfort, increase the fear and stress of dose administration and negatively impact patient adherence. The aim of the present cross-sectional study was to assess the experience of patients with migraine using either CGRP-mAbs prefilled syringes or autoinjector pens, regarding local tolerability and ease of usability. Materials: In the present cross-sectional study, an electronic questionnaire was created using "Google questionnaires" and sent to all patients treated with CGRP-mAbs referring to the Headache Centre of the University of Campania "Luigi Vanvitelli".

Methods: The self-administered questionnaire was sent to 405 patients to collect: i) demographic and clinical parameters such as age, headache diagnosis, disease duration, frequency of attacks, ongoing preventive CGRP-mAbs treatment and interictal cutaneous allodynia; ii) data related to CGRP-mAbs administration as ISP (injection site pain, with numerical rating scale), site of injection (shoulder, leg, periumbilical area), local reactions at administration site, simplicity of administration and administration modality (self-administered or not); iii) data related to putative previous onabotulinumtoxin-A administration as ISP.

Results: After 10 days, 283 (69.87%) patients filled-in the electronic form. No significant differences were found among groups in data related to ease-of-usability and local tolerability of CGRP-mAbs regarding simplicity and modality of administration, ISP and other reactions at the sites of administration. Nevertheless, we identified young women with chronic migraine as the phenotype more prone to experience ISP during the CGRP-mAbs treatment. Among 96 patients who previously received at least 3 OnabotulinumtoxinA administrations, injections site pain was significantly higher with Onabotulinumtoxin-A compared to CGRP-mAbs ($6 \pm 4$ vs $4 \pm 5$; $p<0.001$).

Discussion: Devices used for CGRP-mAbs administration (autoinjector and prefilled syringes) are each characterized by several strengths and downsides, balancing each other so that no differences in easy-of-usability and local tolerability can be observed. The cranial localization of the administration as well as the higher number of injections could explain the difference in terms of ISP with Onabotulinumtoxin-A.

Conclusion: These findings may also arise economic and ecological implications, considering the lower impact on costs and environmental pollution of prefilled syringes compared to more expensive and polluting plastic autoinjector pens. Furthermore, since ISP represents a reason for discontinuation of Onabotulinumtoxin-A therapy, this data should be considered by the authorities regulating the modalities of access to therapy with CGRP-mAbs.

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## COMPARATIVE EFFICACY, QUALITY OF LIFE, AND SAFETY/TOLERABILITY OF ATOGEPANT AND RIMEGEPANT IN MIGRAINE PREVENTION: A MATCHING-ADJUSTED INDIRECT COMPARISON


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Objectives: Evaluate relative efficacy, quality of life, safety, tolerability of atogepant compared with rimegepant for prevention of episodic migraine (EM) using a matching-adjusted indirect comparison (MAIC) analysis.

Materials: Data were pooled from two phase 3 atogepant trials (PROGRESS and ADVANCE) and one phase 2/3 rimegepant trial (BHV3000-305). Participants receiving atogepant 60 mg once daily (QD) and rimegepant orally disintegrating tablet 75 mg once every other day (QOD) were included. Patients receiving placebo were also included.

Method: To make adjusted comparison between pooled atogepant and rimegepant trial populations, anchored MAIC was conducted utilizing patient level data from atogepant studies. Efficacy assessment of interest was change in MMDs, assessed for atogepant across weeks 1-12 relative to rimegepant across weeks 1-12. In scenario analysis, change in MMDs for atogepant across weeks 9-12 was compared relative to rimegepant across weeks 9-12. Change from baseline in Migraine-Specific Quality of Life Questionnaire v2.1 (MSQ v2.1) Role Function−Restrictive (RFR) domain score was assessed at week 12, safety/tolerability outcomes were evaluated across the 12 weeks.

Results: 252 patients were included in pooled atogepant 60 mg QD group, 348 patients in rimegepant 75 mg QOD group. Across weeks 1-12, atogepant 60 mg QD demonstrated statistically significant greater reduction in mean MMDs vs rimegepant 75 mg QOD (mean difference [MD] [95% CI]: −1.65 [−2.49, −0.81]; P<0.001). In scenario analysis, atogepant 60 mg QD demonstrated statistically significant greater reduction in mean MMDs across weeks 9-12 (MD [95% CI]: −1.5 [−2.55, −0.43]; P<0.01) vs rimegepant 75 mg QOD, confirming findings of base case. Atogepant 60 mg QD demonstrated significantly higher MSQ v2.1 RFR domain score (MD [95% CI]: 7.36 [1.88, 12.82]; P<0.01) vs rimegepant 75 mg QOD. While patients treated with atogepant 60 mg QD had similar odds of experiencing a treatment-emergent adverse event (OR [95% CI]: 0.91 [0.56, 1.45]; P=0.7366) and numerically higher odds of discontinuing treatment due to any reason (OR [95% CI]: 1.43 [0.69, 3.06]; P=0.3284) vs rimegepant 75 mg QOD, neither difference was statistically significant.

Discussion: Atogepant 60 mg QD group had significantly larger reductions in MMDs across weeks 1-12 and weeks 9-12, significantly greater improvement in the RFR domain score of MSQ v2.1, no statistical difference in treatment-emergent adverse events or all-cause discontinuation compared with rimegepant 75 mg QOD group.

Conclusions: Atogepant 60 mg QD demonstrated significant improvements in efficacy and quality of life endpoints compared with rimegepant 75 mg QOD, and similar safety/tolerability profile.

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## SPONTANEOUS INTRACRANIAL HYPOTENSION ASSOCIATED WITH LUMBOSACRAL DURAL ECTASIA


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Objective: To describe the syndrome of orthostatic headache, alterations in hearing, and nausea associated with spontaneous intracranial hypotension (SIH) and lumbosacral dural ectasia and propose potential pathogenetic mechanisms.

Background: SIH is typically characterized by orthostatic headaches, low CSF pressure, and distinct abnormalities on MRI. Other symptoms can include diplopia, neck stiffness, alterations in hearing and nausea, and rarely, numbness and coma.

Materials and Methods: Among 460 patients referred to one of us (E.F.) over a 28-year period for evaluation of orthostatic headache (OH) and suspected SIH, we identified one patient with an absence of direct or indirect signs of CSF leak detectable on head and spinal MRI. We reviewed her medical record.

Results: A 20-year-old woman, a competitive volleyball player, standing at 180 cm tall and weighing 60 kg, with ligament laxity, experienced anterior and vertex headaches rated at 7/10 on the Numeric Rating Scale (NRS). These headaches were associated with nausea and bilateral muffled voice during a workout. The headaches and auditory disturbances disappeared after a few minutes in a horizontal position but reappeared after about 5 minutes of standing up. The symptoms resolved after approximately 12 hours of bed rest. Over a period of 2

months, the patient had five similar episodes with intervals ranging from 5 to 20 days and short durations of symptoms, ranging from 6 hours to 5 days. All episodes resolved with conservative treatment (strict bed rest ranging from about 12 hours to 5 days and overhydration). Physical examination showed ligament laxity, while neurological examination was normal. Brain MRI with gadolinium was normal. Spine MRI and MRI myelography showed only a large lumbosacral dural ectasia. After 31 months of follow-up, the patient remained asymptomatic and continued to play competitive volleyball.

Conclusions: In the described case, we speculate that the congenital dural ectasia resulted in a disequilibrium between the content (unchanged CSF volume) and the increased container's volume (the dural space). It has been postulated that the orthostatic headaches seen in SIH result from an altered distribution of craniospinal elasticity. The spinal loss of CSF leads to spinal dural sac collapse and increased compliance of the spinal CSF space. The same mechanism may be involved in our patient's case.

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## EFFECTIVENESS OF GALCANEZUMAB VS. TRADITIONAL ORAL MIGRAINE PREVENTIVE MEDICATIONS (TOMP): INTERIM 3-MONTH DATA FROM REAL-WORLD TRIUMPH STUDY


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Objectives: The primary objective of TRIUMPH study is to evaluate effectiveness of galcanezumab, a calcitonin gene-related peptide (CGRP) monoclonal antibody, and traditional oral migraine preventive (TOMP) medications. We present the TRIUMPH [Italy] results, focusing on the 3-month timepoint.

Materials and Methods: TRIUMPH is an ongoing, prospective, international, observational study of adult patients with migraine who switched to or initiated a new preventive medication. The TRIUMPH interim data cut included all patients with baseline and available 3-month data (from Feb-2020 to Aug-2022), first patient enrolment in TRIUMPH [Italy] was Jul-2021 and continued to Oct-2022. Patients received CGRP antagonists including galcanezumab (at approved local dose/regimen), TOMP medication (beta blockers, anticonvulsants, tricyclic antidepressants, calcium channel blockers or angiotensin II receptor antagonists), botulinum toxin or other migraine preventives. In the effectiveness analysis set, patients had ≥4 monthly migraine days (MMDs) in the ≤30 days preceding baseline, started index preventive treatment ≤56 days after prescribed, and completed baseline patient-reported outcomes before, or ≤3 days after, starting treatment. According to the primary objective, treatment effectiveness was assessed as a reduction from baseline in MMDs at 3-months (response) of at least 30% in chronic and 50% in episodic migraine. The difference in proportion of responders between treatments was assessed using a weighted Chi-squared test (alpha 5%). Weights were derived from a least absolute shrinkage and selection operator (LASSO) model fit of propensity scores using 65 baseline covariates.

Results: Of 2573 patients in the TRIUMPH longitudinal phase, 37.0% (n=953) and 46.2% (n=1189) received galcanezumab and TOMP, respectively. For TRIUMPH [Italy] (n=195), 61.0% (n=119) and 25.1% (n=49) received galcanezumab and TOMP. Most patients were female (83-86%) and diagnosed with chronic migraine (TRIUMPH: galcanezumab=72.0%, TOMP=60.1%; TRIUMPH [Italy]: galcanezumab=70.6%; TOMP=34.7%). At baseline, mean(SD) MMDs for each cohort were: TRIUMPH: galcanezumab=14.4(7.5), TOMP=11.4(6.4); TRIUMPH [Italy]: galcanezumab=17.0(6.8), TOMP=13.3(6.8). Topiramate and amitriptyline were the most common TOMP. At 3-months, treatment effectiveness was greater in patients receiving galcanezumab than TOMP in TRIUMPH (weighted response rate 45.8% vs 34.1%; p<0.0001) and TRIUMPH [Italy] (69.2% vs. 39.7%; p=0.0012). Mean(SD) MMDs were: TRIUMPH galcanezumab=8.2(7.8), TOMP=7.3(5.8); TRIUMPH [Italy]: galcanezumab=8.5(8.0)[n=108], TOMP=8.8(6.7)[n=36]. Change from baseline in the mean number of MMDs with acute medication use were: TRIUMPH: galcanezumab=-4.98, TOMP=-3.47; TRIUMPH [Italy]: galcanezumab=-8.62, TOMP=-5.02.

Discussion and Conclusions: Global TRIUMPH and TRIUMPH [Italy] results show a significantly better galcanezumab effectiveness at 3-month in comparison with TOMP.

## TRANSITIONAL CARE FOR STROKE SURVIVORS FROM HOSPITAL TO HOME AND THEIR CAREGIVERS' CONTRIBUTION: A SYSTEMATIC REVIEW


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Introduction: Stroke represents one of the first causes of disability and mortality worldwide and the increased number of strokes will lead to expanded stroke-related health costs. After a stroke, survivors experience functional and cognitive disabilities such as depression, anxiety, fatigue, and difficulty communicating and impact negatively on physical, phycological, and social abilities in survivors' and caregivers' health, especially during discharge from hospital to home. Returning home after hospitalization can be chaotic and associated with many challenges.

Aim: To describe transitional care strategies from hospital to home in stroke survivors and their caregivers. In stroke survivors for improving, physical functions, quality of life, self-efficacy and social inclusion, and reducing hospital readmission and post-discharge adverse events, as well as reducing caregiver burden.

Methods: A systematic review was conducted on October 2022 on Pubmed, CINAHL, Scopus, and Web of Sciences. A PRISMA Flow Diagram was used to report the selection process. Randomized controlled trials (RCTs), and quantitative and qualitative studies, were extracted using the standardized data extraction tool from the Joanna Briggs Institute (JBI).

Results: The literature search yielded 699 records. After reading the full text, 30 articles were selected: twelve RCTs, two RCT designs, nine qualitative studies, two texts and opinions, two mixed method studies, one cross-sectional study, one pragmatic priority setting, and one retrospective study. The RCTs included the intervention as an educational intervention, coaching activities, home visits and telephone follow-up. These interventions started during hospitalization and continued at home after discharge and improved the quality of life, self-efficacy, and physical function in stroke survivors. The theme issue that emerged

in the other studies was the experience of stroke survivors and their caregivers regarding unmet needs and social integration.

Discussion and conclusions: This systematic review provides support for intervention programs during the transitional period from hospital discharge to home for improved stroke survivors' physical functioning, quality of life, self-efficacy, and caregiver burden. In addition, it has benefits in caregiver burden where health systems transfer the responsibility. Information about survivor or caregiver needs, abilities, and support, once they are transitioned home from the acute setting, rehabilitation facility, or skilled nursing facility, is important to evaluate.

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## DIFFERENT EFFECTS OF PROPHYLAXIS THERAPIES ON SLEEP QUALITY: AN ITALIAN MULTICENTER STUDY

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Objectives: Sleep alterations are closely linked to migraine, especially when a headache lasts several years. Pharmacological prophylaxis has a relevant impact on migraine frequency and associated symptoms. Also, monoclonal antibodies have an excellent effect on associated symptoms, such as sleep alterations, but conclusive data are unavailable. This study aimed to compare a population of migraine patients treated by pharmacological prophylaxis therapies with a group treated by monoclonal antibodies to evaluate the different impacts on sleep quality.

Methods: this was a multicenter study (Neurological Clinic, Marche Polytechnic University, Ancona; Department of Biomedicine, Neuroscience and Advanced Diagnostic, University of Palermo; Unit of Headache and Neurosonology, Campus Bio-Medico di Roma University, Roma;). We enrolled in the three Headache Specialistic Centers all the patients with a migraine diagnosis (with or without aura) and a migraine frequency of more than four attacks monthly. Each patient at enrolment (T0) was assigned to a pharmacological prophylaxis therapy (beta-blockers, calcium antagonists, antiepileptics, and antidepressants) or to monoclonal antibodies, according to international guidelines. We submitted each patient to general and neurological examinations and to different scales, including the Pittsburgh test, a scale to evaluate sleep quality specifically. After three months (T3) of therapy, we re-evaluated the patients and submitted them to the same battery. We excluded all the patients that had not regularly assumed prophylaxis therapies or subjects assuming sleep-inducing drugs.

Results: We enrolled 264 patients (168 treated with pharmacological therapies and 96 treated with Monoclonal antibodies). Pittsburgh score decreased significantly between T0 and T3 (mean difference 1,841 points; $p<0,0001$), and the use of monoclonal antibodies was associated with a greater decrease in Pittsburgh score (mean difference 1,491; $p=0,010$) in respect to pharmacological prophylaxis. Moreover, we observed a significant difference in the number of crises in three months at T0 between the monoclonal antibodies group and the pharmacological drugs group ($p<0,0001$), with a difference that remained significant also at T3 ($p<0,0001$).

Conclusions: Monoclonal Antibodies have updated the management of migraine with a well-documented, stable efficacy. Our data showed a probable good effect on sleep quality based on different etiopathologic and psychological aspects. Improving different features of migraine could contribute to an improved quality of life and better treatment compliance.

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## IMPACT OF MONOCLONAL ANTIBODIES AGAINST CALCITONIN GENE-RELATED PEPTIDE ON PAIN SYSTEM: A LASER EVOKED POTENTIALS STUDY

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Introduction: Anti-calcitonin gene-related peptide (anti-CGRP) monoclonal antibodies have opened a new scenario in the preventive treatment of migraine.

Objective: The aim of the study was to assess, using laser evoked potentials (LEPs), the impact on pain-processing pathways of a preventive treatment with Anti-CGRP monoclonal antibodies in migraine.

Methods: We studied 11 patients (10 women, mean age: $35,6 \pm 12,4$ years) affected by migraine, before and after 3-6 months of prophylactic scheme (Galcanezumab 120 mg monthly, with a starting dose of 240 mg). All subjects received stimulation over the right-hand dorsum and the right perioral region. Two scalp electrodes placed along the midline in the frontal (Fz) and in the vertex (Cz) regions and one electrode in the left temporal region (T3). The reference electrode was placed at the nose and the ground on the forehead (Fpz). Three consecutive repetitions were obtained for each stimulation site. The interstimulus interval varied randomly between 8 and 12 s. Repetitions were separated by a 5-minutes time interval. The stimulation sites were changed after 10-min intervals. Absolute values of N1, N2 and P2 latencies and amplitudes were compared before and after treatment. For the analysis of LEP amplitude habituation, the LEP amplitudes in the second and third repetition of each stimulation site were expressed as percentages of the amplitudes of the corresponding LEP components recorded in the first sequence, which were assumed as 100%.

Results: Data reported in diaries showed, after treatment when compared to baseline, a significant reduction of the mean number of monthly headache days ($p<0.0001$), monthly drug intake of acute medication ($p<0.0001$), and MIDAS score ($p=0.0019$). No significant differences were found, between pre and post treatment, for the VAS pain rating score, thresholds, LEP latencies and absolute amplitude of N1 potential and N2-P2 complex. A statistically significant modification (normalization) of the amplitude habituation of both N1 ($p=0.001$ after hand stimulation; $p=0.0052$ after face stimulation) and N2-P2 ($p=0.0019$ after hand stimulation; $p<0.0066$ after face stimulation).

Discussion and Conclusions: Our main finding is that patients with migraine showed a restore of habituation to repetitive stimuli after a prophylactic treatment with Galcanezumab. Several hypotheses can explain the normalization of the habituation phenomenon, including the re-modulation of central sensitization. The evidence of increased GABA levels in anterior cingulate cortex, associated with a decrease in migraine frequency, intensity and disability obtained by CGRP mAbs therapy, suggests a possible role of these central structure and neurotransmission.

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## USE OF GALCANEZUMAB FOR MIGRAINE PREVENTION IN A PATIENT ON CONCOMITANT NIVOLUMAB FOR MELANOMA SKIN CANCER: A CASE REPORT


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Objectives: The use of monoclonal antibodies (mAbs) has renewed the treatment landscape of many diseases. MAbs targeting the calcitonin-gene related peptide (CGRP) are currently used for migraine prevention. In real-life practice, treating migraine patients with comorbidities is challenging. To date, real-life experience of concomitant use of anti-CGRP mAbs and other mAbs with a different therapeutic indication in multimorbid patients is missing.

Materials: We describe the case of a 56-year-old female migraine patient treated with galcanezumab, a mAb blocking the CGRP, on concomitant treatment with nivolumab, a mAb targeting the anti-programmed death-1 (PD-1), because of melanoma skin cancer.

Clinical case: The patient came to our Headache Center in July 2021 because of a chronic migraine resistant to oral preventives; she had a history of melanoma skin cancer on the right leg surgically treated in 2016. Galcanezumab was initiated for her migraine. The patient had 30 monthly migraine days of severe intensity with daily assumption of analgesics before treatment with galcanezumab. After three months of treatment, a mean of 10 monthly migraine days of mild intensity was reported with a reduced related disability. After six months, the same result was observed. In February 2022, after the surgical remove of a locally recurrent melanoma, treatment with nivolumab was introduced. Galcanezumab was continued and monthly follow-up phone calls were scheduled since nivolumab was introduced. The clinical benefit of galcanezumab continued after introduction of nivolumab. No adverse event was reported.

Discussion: We describe a case of concomitant use of galcanezumab for migraine prevention and nivolumab for cancer prevention in a patient with migraine and a history of melanoma skin cancer. This is the first case-report of concomitant anti-CGRP mAb and another mAb with a different target in a multimorbid patient. No drug-drug interaction was observed, nor in terms of lack of effectiveness of galcanezumab, neither in terms of adverse events.

Conclusion: Galcanezumab proved to be effective and safe for migraine prevention when used in a patient with concomitant nivolumab. A wider real-life experience of use of anti-GCRP mAbs in multimorbid patients on concomitant treatment with other mAbs should be provided in order to be confident in treating these patients.

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# MOTONEURON DISEASES

## COGNITIVE IMPAIRMENT AND BULBAR FEATURES IN AMYOTROPHIC LATERAL SCLEROSIS: A RETROSPECTIVE STUDY


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Objectives: To clarify the role of bulbar involvement (BI) as a risk factor for cognitive impairment (CI) in non-demented amyotrophic lateral sclerosis (ALS) patients.

Materials: Data on N=347 patients were retrospectively collected. Cognition was assessed via the Edinburgh Cognitive and Behavioural ALS Screen (ECAS). Patients were free of 1) frontotemporal dementia, 2) ALS-unrelated brain disorders, 3) severe general-medical conditions and 4) uncorrected hearing/vision deficits. On the basis of clinical records and ALS Functional Rating Scale-Revised (ALSFRS-R) scores, BI was characterized as follows: 1) BI at onset – from medical history ; 2) BI at testing (an ALSFRS-R-Bulbar score $\leq$11); 3) dysarthria (a score $\leq$3 on item 1 of the ALSFRS-R); 4) severity of BI (the total score on the ALSFRS-R-Bulbar); and 5) progression rate of BI (computed as 12-ALSFRS-R-Bulbar/disease duration in months).

Methods: Logistic regressions were run to predict a below- vs. above-cutoff performance on each ECAS subscale based on BI-related features while accounting for sex, disease duration, severity and progression rate of respiratory and spinal involvement, disease stage and ECAS response modality.

Results: No predictors yielded significance on ECAS-Language/-Fluency/-Memory or -Visuospatial subscales (ps$\geq$0.118), albeit BI at

testing predicted a higher probability of an abnormal performance on the ECAS-Executive Functioning (OR=4.33, CI 95% [1.6, 11.93]). The raw relative risk of an impaired performance on such a subscale in patients with vs. without BI at testing was 2.62 (CI 95% [1.64, 4.19]). No other BI-related features affected ECAS performances.

Discussion: This study contributed to the clarification of the role of BI as a risk factor for CI in non-demented ALS patients by simultaneously encompassing BI-related predictors and motor-functional covariates and by addressing an ALS-specific measure of cognition (i.e., the ECAS) [1]. This reports suggests that, net of overall motor-functional status, BI itself, and neither its presence at onset, severity, progression rate or phenotype (i.e., the occurrence of dysarthria), increases the probability of executive deficits in non-demented ALS patients – by, nevertheless, not representing a risk factor for cognitive dysfunctions within other domains.

Conclusions: The occurrence of BI itself, but neither its specific features nor its presence at onset, selectively represents a risk factor for executive impairment in ALS patients – even when executive functions are assessed with motor disability-compensating tests and when covarying for other disease-related features.

Reference:

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## NEUROPSYCHOLOGICAL FEATURES AND ACTIVITIES OF DAILY LIVING IN AMYOTROPHIC LATERAL SCLEROSIS

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Objectives: To determine whether, net of motor confounders, neuropsychological features affect functional independence (FI) in activities of daily living (ADLs) in non-demented amyotrophic lateral sclerosis (ALS) patients.

Materials: N=88 ALS patients without frontotemporal dementia were assessed for FI (Katz ADL and Lawton-Brody IADL scales), cognition (Edinburgh Cognitive and Behavioural ALS Screen, ECAS) and behaviour (Beaumont Behavioural Inventory and Dimensional Apathy Scale). Patients were free of 1) ALS-unrelated neurological/psychiatric disorders, 2) severe/unstable general-medical conditions and 3) uncorrected sensory deficits. The two ADL scores were summed up to obtain an overall Functional Independence Index (FII) – thus ranging 0-14 –, whose reciprocal (computed as 14-FII, i.e. the Functional Dependence Index, FDI) was herewith addressed as the outcome.

Methods: By means of Negative Binomial models, the effect of cognitive and behavioural measures on the FDI was assessed net of demographics, anxiety and depression levels (as measured by the State- and Trait-Anxiety Inventory Form-Y and the Beck Depression Inventory, respectively), disease duration and motor confounders – i.e., ALS Functional Rating Scale-Revised (ALSFRS-R) scores, progression rate and both King's and Milano-Torino stages.

Results: Besides ALSFRS-R scores, the Language subscale of the ECAS was the only extra-motor predictor of the FDI (b=-.11, z=-3.32, p<.001; OR=.90, CI 95% [.84, .96]). When re-running the same model by substituting ECAS-Language scores with a below- vs. above-cutoff ECAS-Language performance, patients performing defectively (21.34%) were more functionally dependent (M=2.84; SE=.96) when compared to those performing normally (M=1.14; SE=.39). At αadjusted=.017, the FDI correlated with Naming (rs(88)=-.29; p=.009) and Comprehension tasks (rs(88)=-.30; p=.007), whilst not with Spelling scores (rs(88)=-.23; p=.043).

Discussion: This study suggests that, besides disease severity – as assessed by the ALSFRS-R –, language functioning – as assessed by the ECAS-Language – represents the only extra-motor factor affecting FI in ADLs in this population. To account for this, it can be hypothesized that language impairment (LI) might have undermined patients' communicative skills, thus in turn reducing their FI. This would also be supported by the fact that naming and comprehension abilities herewith proved to be selectively associated with FI – both these functions being ubiquitously engaged within everyday-life scenarios. Notably, this study did not replicate previous evidence pointing towards behavioural, rather than cognitive, dysfunctions impacting on FI in ALS [1].

Conclusions: FI in ADLs is dependent on both disease severity and LI in non-demented ALS patients, thus highlighting the ecological relevance of language changes in this population.

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## PREGNANCY EXPERIENCE IN WOMEN WITH SPINAL MUSCULAR ATROPHY: AN OVERVIEW IN THE COHORT OF THE UNIVERSITY OF NAPLES "FEDERICO II"

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Background and Aim: Female SMA patients reach fertile age with a different clinical picture. Many patients with SMA Type III are ambulatory during pregnancy, while the totality of women with Type II phenotype are wheelchair-bound. Little data is available about the possible effects of pregnancy on SMA course. In this study, we analyzed outcomes in the different stages of the pregnancy, with a special focus on maternal and fetal complications, mode of delivery, anesthesiological risk and respiratory function.

Results: Our cohort is compound by 10 SMA female (7 SMA III and 2 SMA II). The number of pregnancies was 9 (six term-pregnancy, three abortion). No one had medical assisted procreation. All have done genetic counseling, one of which was pre-conception. Two SMA II patients had two pregnancies each, all of which resulted in pre-term labor. Two SMA III patients had one pregnancy each, resulted in full-term labor. All pregnancies resulted in cesarian delivery performed under epidural anesthesia, except one under general anesthesia. Two patients referred motor symptoms worsening after delivery and chronic back pain during pregnancy. One had pneumonia after delivery. In three cases there were birth complications, but newborn outcomes were all healthy. Only two patients breastfed.

Conclusions: Our experience testify that a successful pregnancy is possible with SMA. Anyway, particularly the sitter patients experienced pregnancy or birth complications. A correct approach should include a standardized multidisciplinary team, with an obstetrician, neurologist, neonatologist, genetist, anesthesiologist, pneumologist and trained nurses, Our results focus on the need to consider motherhood experience in the management of SMA female patients and in the next future we will include the currently disease modifying therapies in this taking charge.

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## CORTICO-SPINAL TDCS IN AMYOTROPHIC LATERAL SCLEROSIS: A RANDOMIZED, DOUBLE-BLIND, SHAM-CONTROLLED TRIAL FOLLOWED BY AN OPEN-LABEL PHASE

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Objective: To investigate whether anodal bilateral motor cortex and cathodal spinal transcranial direct current stimulation (tDCS) could mitigate symptoms in amyotrophic lateral sclerosis (ALS) patients by modulating intracortical connectivity in the short and long-term via a randomized, double-blind, sham-controlled trial, followed by an open-label phase.

Methods: Thirty-one participants were randomized into two groups for the initial controlled phase. At baseline (T0), Group 1 received placebo stimulation (sham tDCS), while Group 2 received cortico-spinal stimulation (real tDCS) for five days/week for two weeks (T1), with an 8-week (T2) follow-up (randomized, double-blind, sham-controlled phase). At the 24-week follow-up (T3), all participants (Groups 1 and 2) received a second treatment of anodal bilateral motor cortex and cathodal spinal stimulation (real tDCS) for five days/week for two weeks (T4). Follow-up evaluations were performed at 32-weeks (T5) and 48-weeks (T6) (open-label phase). At each time point, clinical assessment, blood sampling, and intracortical connectivity measures using transcranial magnetic stimulation (TMS) were evaluated. Additionally, we evaluated survival rates.

Results: Compared to sham stimulation, cortico-spinal tDCS significantly improved global strength, caregiver burden, and quality of life scores, which correlated with the restoration of intracortical connectivity measures. Serum neurofilament light levels decreased among patients who underwent real tDCS but not in those receiving sham tDCS. The number of completed 2-week tDCS treatments significantly influenced patient survival.

Conclusions: Cortico-spinal tDCS may represent a promising therapeutic and rehabilitative approach for patients with ALS. Further larger-scale studies are necessary to evaluate whether tDCS could potentially impact patient survival.

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## RARE FUS MUTATION IN AN ALS-FTD PATIENT: CASE REPORT DESCRIPTION AND GENOTYPE-PHENOTYPE CORRELATION

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Background: Since 2009, over 50 different FUS mutations have been discovered to be linked to ALS and were thought to cause a stereotyped clinical phenotype characterized by early onset, aggressive course, and pure motor clinical presentation. However, some different presentations were reported. Recently, Grassano et al. analyzed data from literature and from an Italian cohort of genetically confirmed FUS-ALS cases, identifying 3 phenotype clusters arising from different specific FUS variants. These mutations were in the nuclear localization signal (NLS) domain, encoded by exon 14 and 15, at the C-terminal end of the gene; a genotype-phenotype correlation was not found for non-NLS FUS variants [1]. Nonetheless, among literature, some pathogenetic non-NLS FUS variants were reported, with various clinical presentation.

Objective: We present the case of a 62-year-old patient affected by FTL-ALS, in which a non-NLS FUS pathogenic variant was found. Case presentation: He presented with a marked speech disorder, started one year before and progressively worsening, characterized by speech-slowness, difficulties in words articulation and rhinolalia. Frequent choking in swallowing liquids were also present. Neurological examination showed severe spastic dysarthria, lingual hyposthenia, lingual fasciculations, and brisk jaw reflex. Mild spastic hypertonia of upper limbs, hypotrophy and hyposthenia of interosseous muscles were also present; there were spontaneous fasciculations in both forearms and symmetric hyperreflexia of upper and lower limbs. Needle electromyography (EMG) showed a marked denervation activity in every muscular district. Cognitive evaluation showed an impairment in non-ALS-specific ECAS domains and an FTD-compatible profile. The disease presented an aggressive course, and survival was 42 months since onset and 28 months since diagnosis. The search for genetic mutations was performed by molecular analysis of C9orf72 and by NGS of main ALS-related genes. A FUS missense mutation was found in exon 6 (c.760A>G variant), determining a methionine to valine substitution at codon 254 (p.Met254Val), which was probably pathogenetic according to ACMG criteria.

Discussion: Among literature, there is only one reported case of this mutation, in a patient affected by FTD and without signs of ALS [2]; only few other mutations were reported in the nearby region in exon 6 [3]. This region is highly evolutionarily conserved among species.

Conclusions: This case points out the importance of mutations in exon 6 in causing ALS. Further studies could be useful to better

understand the pathogenic mechanism giving this pathology and the prognostic value of each mutation.
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## RETINA ATROPHY IN AMYOTROPHIC LATERAL SCLEROSIS AND KENNEDY'S DISEASE. A LONGITUDINAL STUDY

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Background: To what extent retinal atrophy in neurodegenerative diseases reflects the severity and/or the chronicity of brain pathology or rather is a local independent phenomenon remains to be clarified. Moreover, the clinical (diagnostic and prognostic) value of retinal atrophy in these diseases needs to be further investigated.

Aim of the study: To add light on the pathological significance and on the possible clinical value of retinal atrophy in patients with amyotrophic lateral sclerosis (ALS) and Kennedy's disease (KD, bulbo-spinal muscular atrophy).

Methods: Thirty-five ALS, thirty-seven KD, and forty-nine age-matched healthy controls (HC) were included in a one-year longitudinal study. Spectrum-domain optical coherence tomography (OCT) was performed at study entry (T0) and after 12 months (T1). Possible correlations between retinal thicknesses and disease duration and functional rating scale (FRS) were investigated in both groups of patients.

Results: Compared to HC, peripapillary retinal nerve fiber layer (pRNFL) was significantly thinner in both ALS (p=0.034) and KD (p=0.003). pRNFL was also thinner in KD compared to ALS, but the difference did not reach the significance. In KD, pRNFL atrophy significantly correlated with both disease severity (r=0.296, p=0.035) and disease duration (r = -0.308, p=0.013) while no significant correlation was demonstrated in ALS (disease severity: r=0.147, p=0.238; disease duration: r=- 0.093, p=0.459). During the 1-year-follow-up, pRNFL thickness remained stable in KD while significantly decreased in ALS (p=0.043).

Conclusions: Our study provides further evidence of retinal atrophy in both ALS and KD and suggests that a primary local neurodegenerative phenomenon takes place in retina in motoneuron diseases. Our data seems to indicate that the analysis of pRNFL thickness may have a clinical significance in KD, but this aspect needs further investigation.
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## A LONGITUDINAL EVALUATION OF EARLY SLEEP AND RESPIRATORY IMPAIRMENT IN ALS PATIENTS

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Objective: To evaluate early impairment of sleep and breath in patients affected by amyotrophic lateral sclerosis (ALS) in order to do early treatments, for longer survival and a better quality of life (QoL).

Background: ALS is a neurodegenerative disease characterized by motor neuron death. 30% present a bulbar onset, while 70% a spinal one. Extra-motor systems involved in ALS include circuits regulating sleep; the early identification of sleep impairment and his better definition could improve patient's quality of life (QoL). One of the most important prognostic factors in ALS is respiratory impairment. Its early recognition and an early starting of non-invasive ventilation (NIV) allow prolongation of survival.

Methods: Between August 2021 and December 2022 we enrolled 45 ALS patients and 45 healthy controls (HC). At baseline and at month six, patients underwent neurological examination, polysomnography (PSG), arterial blood gases (ABG), spirometry and filled sleep and respiratory questionnaire (RLSRS, STOP-BANG, ISI, ESS, PSQI, PIRS, MEQ, STAI, BDI). SPSS software was used for data analysis.

Results: At baseline, ALS patients without respiratory symptoms showed an increase of the AHI-index and of the ODI-index compared to HC (respectively, p=0.001 and p=0.04). Contrarily, spirometry and ABG were not so altered. Longitudinally we observed a significant worsening of PSG parameters ($p<0.05$). Patients who started nocturnal-NIV (15 out of 45) showed a significant improvement of PSG parameters. At baseline we also observed an excess of periodic limb movement in ALS vs HC (p=0.01). Direct correlation between progression rate of disease and both AHI and ODI (r=0.546 and r=0.442 $p<0.05$).

Discussion: Classical spirometry and ABG parameters are not good markers of early respiratory impairment in ALS and are not good markers to evaluate respiratory muscle progression of the disease. Between them only pH and HCO3- seem to be associated with an early respiratory impairment. PSG data (in particular AHI and SpO2< 90%) are important in identifying muscle respiratory impairment when not clinically manifest. AHI and SpO2< 90% seem to be good biomarkers to evaluate the respiratory progression of disease in ALS. Sleep macro-structure and micro-structure are altered in ALS patients compared to HC, in particular an increase of deep sleep (with concomitant reduction of REM sleep) and an increase of arousal.

Conclusion: This preliminary study showed the presence of respiratory and sleep impairments in ALS patients since the beginning of the disease. Their identification is fundamental for early treatment and for the improvement of QoL.
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## AUTONOMIC CARDIOVASCULAR IMPAIRMENT IN ADULT PATIENTS AFFECTED BY SPINAL MUSCULAR ATROPHY: TOWARDS THE UNDERSTANDING OF MULTISYSTEM INVOLVEMENT IN SMA

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Objectives: In this single center observational study, we aimed to evaluate whether adult spinal muscular atrophy (SMA) patients present a cardiovascular autonomic dysfunction.

Materials and Methods: Two type-2 and 14 type-3 adult SMA patients followed up at the C. Besta Neurological Institute underwent an extensive cardiovascular autonomic assessments (CATs) which included 10 min head-up tilt after 10 min supine rest, Valsalva manoeuvre (VM), deep breathing, sustained handgrip, cold face test, mental stress, and completed the COMPASS-31 autonomic questionnaire. Heart rate variability (HRV), baroreceptor sensitivity, sympatho-vagal balance, were continuously evaluated during the CATs. Results were compared with aged and sex matched controls and normative data.

Results: Adult SMA patients presented a higher COMPASS-31 score compared to controls ($p<0,0001$), reflecting the presence of symptoms of dysautomomia. Cardiovascular reflexes indices were significantly more affected in SMA population compared with healthy subject, with a peculiar pattern characterized by increased bradycardic drive during deep breathing ($p<0.00002$), increased variability of blood pressure during rest and head up tilt test ($p<0.0001$). Moreover, we found an adrenergic hypofunction during VM ($p<0.0001$). Finally, a relative increased of HR at rest was found in 14 of 16 patients (87.5%).

Discussion: Systemic pathology is gaining prominence in SMA after the advent of new disease-phenotypes due to survival motor neuron protein (SMN)-rescue therapies [1]. Previous reports of a defective autonomic nervous system (ANS) in preclinical models of SMA [2] and severely-affected patients [3] suggested an involvement of the ANS in the disease, which remains to be elucidated. Detecting autonomic nervous system alterations becomes more important since new therapeutic strategies will improve functional abilities and increase stress on the cardiovascular system. It might be also relevant to take these evidences into account for optimal clinical success of the therapeutic approaches.

Conclusions: Our data indicate the presence of autonomic cardiovascular dysfunction in adult SMA patients, probably related to impaired inhibitory drive on sympathetic outflow and sympato-vagal unbalance, contributing to properly define SMA phenotypic expression.

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## MANAGEMENT OF LONG-TERM TREATMENT IN PATIENTS WITH ANTI-HMGCR IMMUNE-MEDIATED MYOPATHY

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Objectives: This study aimed to report the long-term immunotherapy results in patients with immune-mediated necrotizing myopathy (IMNM).

Material: A retrospective study was conducted involving 12 patients with an IMNM diagnosis in the period 2013-2022. Patients were selected based on clinical presentation, muscle biopsy and/or serological testing.

Methods: Medical records were systematically reviewed, extracting age at diagnosis, gender distribution, clinical presentation, statin exposure, laboratory results (creatine kinase levels and autoantibody profiles), magnetic resonance imaging (MRI), muscle biopsy findings and treatment approaches.

Results: We collected 12 patients with anti-HMGCR related myopathy (autoantibodies range 63-343 UA/ml), 7 were males, age at onset ranged from 17 to 79 years. 83% presented a progressive proximal muscle weakness particularly in the pelvic girdle. Three patients were paucisymptomatic but had elevated serum creatine kinase (CK) values. CK levels ranged 1000-28.000 IU/L. Ten patients had a history of statin exposure (mainly atorvastatin); the two youngest patients had no previous statin exposure. Cardiopulmonary involvement was excluded, dysphagia was reported in 25% of patients, mild dyspnoea by one female patient only; two male patients had a neoplastic history. Muscle biopsies (7 cases) showed a necrotic pattern with minimal inflammation signs. Steroid therapy was administered to all patients; three cases needed to add azathioprine. Intravenous immunoglobulin (IVIg) treatment was initiated in all patients, with a good recovery both in clinical aspects and CK levels. Five patients discontinued IVIg treatment, only one patient successfully, while four cases had to restart it due to increased CK levels and/or symptoms deterioration.

Discussion: Anti-HMGCR myopathy is a form of IMNM characterized by muscle weakness, elevated CK levels, necrotic pattern in muscle biopsy; statin usage is frequent [1,2]. The onset may occur acutely or subacutely with a progressive muscle weakness. Treatment strategies for IMNMs are based on immunomodulant/immunosuppressive therapy but are not well-established and rely on clinical experience [3]. Our findings confirm these known clinical and serological features. Moreover, in our cohort, the discontinuation of IVIG therapy (even in patients who achieved a successful remission) led to worsening in CK values and/or muscular symptoms, while resumption of IVIG therapy often resulted in a rapid amelioration.

Conclusion: Anti-HMGCR myopathy is a subtype of necrotizing myopathy whose pathophysiological substrate relies on a likely persistent dysimmune process; thus patients may require repeated cycles of treatment to manage their condition effectively, with strict clinical and serological follow-up.

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## BRAIN "NEUROVASCULAR COUPLING" IN AMYOTROPHIC LATERAL SCLEROSIS: CORRELATIONS WITH COGNITIVE IMPAIRMENT AND DISEASE PROGRESSION

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Advanced magnetic resonance imaging (MRI) techniques have been previously used to detect structural and functional abnormalities of the brain of patients with Amyotrophic Lateral Sclerosis (ALS). In particular, patients with ALS may show decreased spontaneous brain activity on resting-state functional MRI (RS-fMRI), for example in the Default Mode Network (DMN). Moreover, relatively few studies have addressed the role of neuroimaging in predicting the prognosis of ALS. Functional/metabolic alterations of the brain in ALS may be evaluated investigating the "neurovascular coupling" (NVC), which measures the interplay existing between local cerebral perfusion and neural activity within a given brain region or network. We aim at exploring the potential NVC alterations across different RS-fMRI networks via the above spatial combination of "cerebral blood flow" (CBF) and amplitude of low frequency fluctuations (ALFF) maps, respectively derived from arterial spin labeling (ASL) and blood oxygen level dependent (BOLD) RS-fMRI measurements, in a sample of ALS patients compared to healthy controls (HC). Additionally, we compared the NVC data at baseline in subsets of patients with different disease progression. Fifty-one right-handed ALS patients (31 males), and twenty-five right-handed healthy control subjects (HCs) (10 males) were enrolled. ALS patients were screened by clinical and neuropsychological (Italian version of the Edinburgh Cognitive and Behavioural ALS Screen, ECAS) scales. Furthermore, ALS patients were classified a posteriori as very fast, fast, and slow progressors (VFPs, FPs, and SPs), monitoring disease progression over 12 months according to change in the disability score (ΔALSFRS-R). MRI images were acquired on a 3 Tesla scanner. No patient was affected by dementia, and 17 patients had cognitive impairment (ALSci) according to Strong Criteria (2017). Among 7 RSNs, a statistically significant reduction of NVC was found in the DMN in the ALS patients compared to the HC. We found significant correlations between the NVC in the DMN and the executive function, memory, and visuospatial ability ECAS subscores, and ALS-non-specific subscale. We identified significant differences in NVC at baseline in the DMN between VFPs and SPs groups. Our findings suggest that significant changes in NVC occur outside the motor areas in correlation with changes in cognitive performances in ALS patients. So NVC measures might represent a valuable tool for exploring the early signature of cognitive/extra-motor impairment in ALS, thus allowing us to better characterize the complex phenotype of these patients. Moreover, NVC alterations in DMN could play a role in the detection of patients presenting faster clinical progression.

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## USE OF BRAIN 2-[18F]FDG-PET TO DISCRIMINATE ALS AND ALS-MIMICS

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Aims: Some studies showed the capability of brain 2-[18F]FDG-PET to discriminate ALS patients and healthy controls [1,2]. Nevertheless, in clinical practice neurologists face the issue of distinguishing ALS from disorders mimicking ALS. A previous study reported that the combination of brain and spinal cord 2-[18F]FDG-PET achieved a 81.5% accuracy in discriminating ALS and ALS-mimics, while the accuracy was 65.4% for brain metabolism alone [3]. Our study evaluated the capability of brain 2-[18F]FDG-PET as a single marker to discriminate ALS and ALS-mimics.

Methods: We considered eligible ALS patients who underwent brain 2-[18F]FDG-PET at diagnosis at the ALS Centre of Turin between 2009 and 2019, and a group of subjects with ALS-mimics (including cervical spondylogenic myelopathy, multifocal motor neuropathy, myasthenia gravis, etc). Since further analyses considered each voxel as a single feature, by using Automated Anatomical Labeling Atlas only the whole brain volume has been retained from entire PET scans reducing the amount of candidate voxels to 226954. Intensity normalization was performed at individual level averaging each voxel for the mean value of the whole brain. The dataset included 663 ALS and 40 ALS-mimics. We randomly collected 40 ALS from the whole group to calculate Laplacian scores. Subsequently, features were extracted from ALS and ALS-mimics. Finally, the dataset (40 ALS and 40 ALS-mimics) was split in a training set (80%) and a test set (20%). A Support Vector Machine (SVM) approach was used as classifier. The procedure was randomly repeated 10 times.

Results: SVM showed 85% specificity and 81% sensitivity on the test set, with an error rate of 17%. The classification was based on three cerebellar clusters, situated in left anterior lobe, right uvula and right culmen.

Conclusions: Our data support the possible role of brain 2-[18F] FDG-PET as a single diagnostic marker to discriminate ALS and ALS-mimics.

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## INTERPLAY BETWEEN COGNITIVE AND MOTOR PHENOTYPES IN AMYOTROPHIC LATERAL SCLEROSIS PHENOTYPES

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Objectives: Amyotrophic lateral sclerosis (ALS) is an heterogeneous disease in terms of both motor and cognitive manifestations. While some studies have suggested that the degree of upper motor neuron involvement might be the main driver of the severity of cognitive/behavioral changes in ALS, other works have rather observed a strong link between the site of disease onset, namely bulbar onset, and the occurrence of these extra-motor symptoms. In this study we therefore aimed at examining profiles of cognitive/behavioral impairment and their association with disease severity across diverse ALS motor phenotypes.

Materials: 101 ALS patients were classified as classic (N = 43), bulbar onset (N = 20), predominant-upper motor neuron (PUMN; N = 17), and predominant-lower motor neuron (PLMN; N = 21) phenotypes. Cognition was assessed using the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) and disease severity with the ALS Functional Rating Scale-Revised (ALSFRS-R). According to the revised consensus criteria patients were classified as pure motor ALS, ALS with isolated cognitive impairment (ALSci), ALS with isolated behavioral impairment (ALSbi), ALS with combined cognitive and behavioral impairment (ALScbi) and ALS with frontotemporal dementia (ALS-FTD).

Methods: Negative Binomial regressions were applied to test the effect of motor phenotypes on the ECAS-total and its sub-scores, and Pearson correlation analyses were used to examine the association between ECAS total and ALSFRS-R scores.

Results: Below cut-off ECAS-total scores were detected across all the diverse phenotypes, namely in 40.00% of bulbar onset, 18.60% of classic, 19.04% of PLMN, and 11.76% of PUMN patients. Bulbar onset patients performed worse than classic ALS (p=0.02) and PLMN patients (p=0.03) on the ECAS visuospatial domain. No other significant differences were observed between groups across the investigated domains. Worse ASLFRS-R scores correlated with poorer ECAS-total scores only in classic ALS patients (R=0.36; p=0.01).

Discussion and Conclusions: Cognitive impairment occurs across all the ALS phenotypes but is associated with greater disease severity only in classic disease forms. Notably, while the occurrence of deficits in ALS specific functions is common to the diverse phenotypes, bulbar onset patients exhibit more severe impairment in ALS non specific functions, suggesting a state of more generalized and advanced cognitive impairment in this clinical phenotype.

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## GENOTYPE-PHENOTYPE CORRELATION IN A POPULATION OF FUS-RELATED AMYOTROPHIC LATERAL SCLEROSIS PATIENTS: THE IMPORTANCE OF A MULTIDISCIPLINAR APPROACHE

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Introduction: Mutations in fused in sarcoma (FUS) are among the most common genetic causes of amyotrophic lateral sclerosis (ALS) and often cause aggressive early-onset forms (juvenile-ALS, J-ALS) or late-onset ALS with slow progression usually associated with frontotemporal dementia (FTD).

Methods: We identified and analyzed 14 FUS known mutations ALS patients from a single-center cohort, of 1182 patients genetically tested for the four major genes mutated in ALS in the last ten years.

Results: Three patients presented a juvenile onset of ALS: in this group all patients had a spinal onset, one patient a familiar history, a median age of onset of 16.31 years [9.38-29.90], a median diagnostic delay of 5 months [4.60-28.37]; one patient is still alive after 54 months from the onset, one was died after 24 months and one after 8 years, 1 [33.33%] underwent enteral nutrition by gastrostomy, 3 [100%] underwent non-invasive ventilation, and 2 [66.67%] underwent invasive ventilation. Symptoms were preceded by learning disability or mild mental retardation in all the three patients. Eleven patients presented adult onset of ALS: in this group median age onset was 51.24 years [43.66-68.05], median diagnostic delay was 21.27 months [9.10-35.47], familial ALS was found in 3 subjects[27.27%].The onset was on bulbar site on 5 patients [45.45%] , spinal site on 6[54.55%] ; 6 patients [54.55%] underwent enteral nutrition by gastrostomy, 4[36.36%]underwent invasive ventilation. Median survival was 89.27 months [15.30-97.60] (reduced at 57.50 in the subgroup of 7 patients who refused invasive ventilation). We found 11 different known mutations in our cohort; p.R521C was the most frequent, express in 3 individuals. Two patients presented a second mutation in other genes ALS-related (one in TDP43, one in C-9orf-72). On the J-ALS group we found three different mutations (two missense and one deletion).

Discussion and Conclusions: The analysis of our FUS mutated ALS population shows a high genotipic heterogeneity without a particular mutations more common than other. These are above all missense mutation, but we evidence also a delection in a j-ALS patient. Although all j-ALS patients were all characterized by aggressive history and by a mental retardation (many years before motor symptoms appear), also in this group we found different involvement and progression.

## CLINICAL AND GENETIC FEATURES OF CCNF GENE IN AN ITALIAN ALS COHORT: A SINGLE CENTER STUDY

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Background and Objectives: Genetic variants in the gene CCNF, encoding cyclin F, a component of an E3 ubiquitin-protein ligase complex involved in centrosomal duplication, gene transcription and DNA synthesis, stability and repair, are associated to amyotrophic lateral sclerosis (ALS) in familial (fALS) and sporadic (sALS) cases and/or to frontotemporal dementia (FTD). Objectives of this study were to determine the contribution of CCNF gene in a large monocentric cohort of Italian ALS patients, to assess the CCNF-associated clinical features and to look for genotype-phenotype correlation and penetrance of the mutations.

Materials and Methods: We applied next generation sequencing technologies on 847 unrelated Italian ALS patients referred to our

Center from November 2018 to May 2023 and we filtered results in CCNF gene.

Results: In total, 12 different rare variants, all in a heterozygous state, were identified in 14 index cases (1 fALS and 13 sALS) with a cumulative mutational frequency of 1.6%. 10 CCNF variants have never been described. The most prevalent variant was the novel p.Phe197Leu, found in three patients. The clinical presentation was heterogeneous, with a classic phenotype observed in 9 patients, UMN-D phenotype in 4 patients and flail arm in 1 patient. Clinical evaluation for cognitive impairment using the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) test was performed in 11 patients, demonstrating that 7 patients (64%) had variable degree of frontal dysfunction.

Discussion: In our cohort, we observed CCNF variants in 1.6% of patients (14/847), a percentage similar to that found in other series. Clinical presentation was heterogeneous but, as previously reported, CCNF variants are significantly associated to cognitive impairment.

Conclusions: Our study expands the CCNF genetic variant spectrum identified in a large cohort of Italian ALS patients. As previously reported, CCNF variants were common, especially in SALS patients. Further studies are needed to assess genotype-phenotype associations of CCNF variants.

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## SERUM TROPONIN T AND CREATININ KINASE MB IN AMYOTROPHIC LATERAL SCLEROSIS: A CASE-CONTROL STUDY


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Objectives: To analyze the differences in serum troponin T (cTnT) levels between patients with amyotrophic lateral sclerosis compared to other conditions and to analyze the role of serum troponin T and CK-MB as possible biomarkers of diagnosis and progression in patients with ALS.

Patients: We included patients with a probable, possible, probable laboratory-supported, or definite diagnosis of ALS according to El Escorial and Awaji criteria. We excluded patients with a history of cardiac disease that may lead to an increase in blood troponin T or CK-MB. As a control group, we recruited patients with diagnosed myopathies and axonal neuropathies.

Methods: We performed a case-control analysis comparing cTnT levels in ALS patients (n=48) and controls affected with other neuromuscular diseases (n=27), followed-up at the Unit of Neurology, Spedali Civili (Brescia, Italy), and the NeMO-Brescia Clinical Center for Neuromuscular Diseases (Brescia, Italy) between June 2022 and January 2023. Demographic and clinical variables were expressed as medians (first and third quartiles) or frequencies. The Mann–Whitney U test was used to test differences between two groups. To evaluate the diagnostic performance, we calculated the area under the curve (AUC).

Results: Serum cTnT was elevated in 94.3% of ALS patients (normal value: 14 pg/mL). We observed statistically significant higher levels of cTnT among ALS patients compared to controls (median value 37 vs. 14, p= 0.001). The optimal cut-off of cTnT to distinguish ALS from controls was set at 16 pg/mL with a sensitivity of 92% and a specificity of 68%. The AUC value was 0.82. In the ALS patient group (n=26), we also tested CK-MB levels, which showed no statistically significant difference from controls (median value 6.25 vs. 4.30/L, p= 0.53). Serum cTnT in the ALS cohort showed a strong direct correlation with ALS progression rate (r = 0,76) and patients weight (0,83), while a strong inverse correlation was evident with disease duration (r = -0,73).

Discussion: Serum cTnT and CK-MB are chronically elevated in ALS compared to other neuromuscular diseases. TroponinT's direct correlation with ALS progression rate and inverse correlation with disease duration could suggest a possible role for this molecule as a biomarker, especially for prediction of disease evolution.

Conclusion: Serum cTnT elevation in ALS may reflect lower motor neuron degeneration and re-expression of isoforms of TnT in skeletal muscle during remodeling of the motor unit, suggesting that its determination could be helpful in the diagnostic process and follow-up of ALS. Larger studies with a wider number of patients and longer follow-up are mandatory to confirm our preliminary findings.

## DEPICTING THE EYE MOVEMENT ABNORMALITIES IN AMYOTROPHIC LATERAL SCLEROSIS


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Objectives: To compare the fixation and saccadic eye movements between Amyotrophic Lateral Sclerosis (ALS) patients and Healthy Controls (HCs), and to investigate how the ocular data are related to clinical impairment in ALS patients.

Materials: Optometric instrumentation and an advanced screen-based eye tracker capturing gaze at 600Hz were used to perform the tests.

Methods: Subjects with definite, probable and probable laboratory supported ALS were enrolled, together with 21 age and sex-matched HCs. Each subject underwent a set of clinical, optometric and eye tracking assessments which includes calibration, fixation, saccades, horizontal and vertical anti-saccades, and delayed saccades. For each task, in addition to the inter group comparison and the correlation with clinical features, patients' performances were also considered on single patient level (values outside the mean ± 1.645 times standard deviation of normal controls were considered abnormal).

Results: 40 consecutive ALS patients were recruited (median age 59.32yrs], M/F ratio of 2.08). No significant differences emerged in the calibration between ALS and HC groups. Considering the fixation task, 14% of patients were out of normal range. Moreover, a significantly shorter time of fixation was detected in ALS patients if compared to HCs. In the horizontal and vertical saccades test, both peak velocity and average amplitude were significantly lower in ALS patients compared to HCs, with 20% of patients out of normal range

in each task. Finally, 40% and 20% of patients were out of normal range in the horizontal anti-saccades and in the delayed saccades test, respectively and ALS patients reported a significantly higher error rate in both tasks compared to HCs. Analysing the clinical variables, patients with the worse functional impairment documented by ALS Functional Rating Scale–revised reported a significantly higher error rate in horizontal and vertical anti-saccades, and delayed saccades. A faster disease progression was related to a significantly higher horizontal anti-saccades error rate. Finally, a worse functional impairment was significantly related to less accurate eye movements in fixation task.

Discussion: The comparison between ALS and HCs confirmed the involvement of the visual system in ALS; moreover, the worse the functional impairment is and the faster the disease course is, the more specific oculomotor abnormalities can be detected within the ALS cohort.

Conclusion: This study supports the evidence of oculomotor impairment in ALS. How and why the ocular impairment is related to ALS progression is under investigation, together with the influence of cognitive impairment on eye tracking tests.

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## COGNITIVE AND NEUROPSYCHOLOGICAL CORRELATION WITH BRAIN METABOLISM IN C9ORF72 AMYOTROPHIC LATERAL SCLEROSIS PATIENTS


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Background: Hexanucleotide repeat expansion (GGGGCC) in the first intron of the C9ORF72 gene accounts for a significant proportion of autosomal dominant amyotrophic lateral sclerosis (ALS)-frontotemporal dementia (FTD) spectrum disorders. In ALS, mutations in the C9ORF72 gene are present in 40% of familial and 5–10% of sporadic forms. Although not always clinically distinguishable from sporadic forms, ALS patients' carriers of the C9Orf72 mutation (C9+) more commonly have an earlier disease onset, a bulbar phenotype, and a high frequency of severe cognitive impairment. In our preliminary report, we compared the 18F-FDG-PET imaging findings in a group of genetic patients, observing an extensive motor and prefrontal hypometabolism in fast progressors, compared to a more limited hypometabolism in patients showing the same mutation but grouped as slow progressors, and several correlations between hypometabolism brain pattern and score in neuropsychological tests. This study aimed to confirm and expand the neuropsychological findings in a larger C9+ group.

Methods: We included ten C9+ patients who underwent a complete neuropsychological evaluation and an 18F-FDG-PET scan at baseline. Patients were recruited at ALS Tertiary Centre in Novara, Italy. We obtained hypometabolism maps at a single-subject level following a validated voxel-based Statistical Parametric Mapping procedure. The corresponding 18F-FDG-PET regional hypometabolism was extracted by anatomo-functional ROIs: prefrontal, temporoparietal, occipital, rolandic cortex, and supplementary cortical and subcortical regions. Patients, classified based on Strong criteria, were divided into ALS-normal (ALS-no, n=2), ALS-behavior (ALS-bi,n=2), and ALS-cognitive (ALS-ci, n=6). The ROIs' hypometabolism was compared with scores in neuropsychological tests. Also, a mean hypometabolism map was derived in each cognitive group to underline brain metabolism differences between ALS-no, ALS-bi and ALS-ci.

Results: We observed several correlations between hypometabolism and anatomo-functional ROIs, such as: prefrontal areas and phonological fluency test (PFT) (r=-0.86, p=0.03), Frontal Assessment Battery (FAB) (r=-0.87, p=0.002) and Clock Drawing test (CDT) (r=-0.79, p=0.01); temporoparietal area and Short Story Test (0.73, p=0.04), CDT (r=-0.80, p=0.001), and FAB (r=-0.88, p=0.002); insula and Raven's Progressive Matrices (r=-0.70, p=0.03), PFT (r=-0.80, p=0.008), and FAB (r=-0.88, p=0.02). Focusing on the hypometabolism maps, the ALS-no have hypometabolism confined in motor regions; the ALS-bi group showed prominent hypometabolism in temporoparietal and limbic areas, and the ALS-ci group showed extended hypometabolism in motor and prefrontal regions.

Discussion: The brain metabolism showed specific correlations with neuropsychological impairment in C9+ patients, confirming our preliminary results, and different hypometabolism maps based on the cognitive group. The results support the role of 18F-FDG-PET in revealing patterns of neuronal dysfunction, aiding the diagnostic workup in ALS.

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## ROLE OF TDP-43 IN THE DIAGNOSIS AND PHENOTYPIC CHARACTERIZATION OF AMYOTROPHIC LATERAL SCLEROSIS: COMPARISON BETWEEN CSF AND PLASMA DATA


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Background: The diagnostic work-up for Amyotrophic Lateral Sclerosis (ALS) diagnosis is complex and often associated with diagnostic delay. Scientific research focused on the neurodegeneration biomarkers that can anticipate the diagnosis and phenotypically characterize patients is necessary. Among these, TDP-43, which accumulates in the neuronal cytoplasm in most ALS patients, is one of the most promising. This study aimed to compare the data obtained from the cerebrospinal fluid

(CSF) and blood TDP-43 dosage and to correlate the results obtained from the assays with clinical and laboratory data.

Methods: 14 patients were recruited, and CSF and serum TDP-43 were determined by the ELISA method. Clinical-phenotypic and functional data (ALSFRS-R, BMI, FVC%), blood chemistry, and genetic data were also collected.

Results: A strong negative correlation (r=-0.70; p=0.03) was observed between CSF and serum levels. There was also a significant positive correlation (r=0.67; p=0.03) between CSF and Creatine phosphokinase (CPK) and a negative correlation (r=-0.90; p=<0.01) between serum TDP-43 and CPK values. Patients with the bulbar phenotype appear to show lower levels of CSF TDP-43 compared to spinals (p=0.04); moreover, there was a positive correlation between CSF TDP-43 and the bulbar subscore of the ALSFRS-R (r=0.67; p=0.03). Correlating with the genetic data, the patient carries the lowest absolute CSF TDP-43 concentration within the cohort characterizes a SOD1 mutation.

Conclusions: Data from this study support the utility of TDP-43 as a biomarker in ALS, both at CSF and plasma levels, also showing significant correlation with clinical and genetic data.

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## UPPER MOTOR NEURON INVOLVEMENT IN ALS: A CORRELATION BETWEEN NEUROPHYSIOLOGICAL AND METABOLIC BRAIN PATTERN


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Background: In Amyotrophic Lateral Sclerosis (ALS) diagnostic work-up, the involvement of lower motor neurons (LMNs) is easily demonstrated by electromyography; on the contrary, finding markers of upper motor neuron (UMN) suffering is harder. Transcranial magnetic stimulation (TMS)-induced motor-evoked potentials (MEPs) are one of the proposed markers of (sub)clinical UMN damage.

Aim: Our study aimed to verify a possible correlation between the metabolism brain pattern and the MEPs findings for highlighting the UMN damage.

Methods: A total of 20 ALS patients who underwent FDG-PET and TMS-MEPs at diagnosis were retrospectively enrolled in the study. Patients were enrolled between 2018 and 2022 at the ALS Tertiary Center, Novara, Italy. For each patient, we collected clinical-phenotypical variables (focusing on the UMN signs). We measured the motor latency, amplitude, and central motor conduction time (CMCT) for TMS-MEPs from the upper and lower limbs. For FDG-PET, following a validated voxel-based Statistical Parametric Mapping procedure, we obtained hypometabolism maps at the single-subject level, correlating the regional hypometabolism with clinical and neurophysiological values.

Results: Of enrolled patients, the mean age was 57.2±12.63 years (30% bulbar and 70% spinal onset). 14/20 patients (70%) had abnormal MEPs in at least one limb: 8/20 (40%) had unreliable MEPs, and 12/20 (60%) had delayed CMCT. Regarding the lower limbs, we observed a direct correlation between lower limbs CMCT and precentral, frontal superior, and supplementary motor areas (r=0.65, p=0.05; r=0.76, p=0.02; r=0.72, p=0.03). For the upper limbs, the correlation is limited with the supplementary motor area (r=0.78, p=0.02).

Discussion: Our data suggest an essential single and additive role of TMS-MEPs and FDG-PET in highlighting the UMN suffering in ALS patients at diagnosis.

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## A CASE OF SPASTIC PARAPLEGIA CAUSED BY ERLIN2 NOVEL VARIANT, WITH PROGRESSIVE EVOLUTION IN AMYOTROPHIC LATERAL SCLEROSIS


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Objective: ERLIN2 mutation is known to cause SPG18, a group of recessive or dominant hereditary spastic paraplegia, characterized by lower-extremity weakness and spasticity, due to upper motor neurons degeneration. Only a few reports have shown that patients with spastic paraplegia due to mutations in ERLIN2, can evolve to rapid progressive ALS.

Methods and Results: We described a case of a 64 year-old woman, with diagnosis of spastic paraparesis associated with a novel variant c.406G>A, p.Val 136IIe in the ERLIN2 gene. She developed progressive weakness and spasticity to lower limbs during the fifth decade of life. The same genetic variant was described in other three members of her family (her sister, son and nephew), also affected by lower-extremity weakness and spasticity. After 5 years from symptoms onset, the patient developed rapid bulbar involvement with dysphagia, dysarthria, associated with weakness and atrophy of upper limbs. Electromyographic data showed lower motor neuron involvement, in spinal and bulbar regions. This clinical evolution allowed the diagnosis of clinically defined ALS according to the Awaji criteria.

Discussion: Our case supports the results of previous few reports, showing that spastic paraplegia caused by ERLIN2 variants, can convert to ALS in time. These findings support the hypothesis that ERLIN2 mutations can present with a wide spectrum of motoneuron clinical disorders, including HSP and ALS.

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## TRANSCRIPTOME SIGNATURE IN AMIOTROPHIC LATERAL SCLEROSIS (ALS) PHENOTYPES

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Introduction and Objectives: Unmeet needs for ALS patients includes both the identification of criteria for clinical stratification, and the discovery of reproducible biomarkers. We aim to identify a transcriptome signature in homogenous MND sub-groups obtained using specific phenotype classification.

Materials and Methods: We have stratified n=48 newly-diagnosed sporadic ALS patients by Chiò et al [1] criteria, and enrolled n=19 age-matched healthy controls. We have isolated PBMCs, performed RNA sequencing, and compared the transcriptome profiles for all the subjects compared to healthy controls.

Results: We have collected the following phenotypes: n=12 classic, n=10 bulbar, n=7 flail arm, n=10 flail leg, n=9 pyramidal. We have observed a different gene expression between patients and controls ($p<0.05$), particularly for the flail leg subgroup. Moreover, bulbar phenotype has been characterized by a great number of altered genes ($p>0.05$). Finally, we have noticed a single gene altered in all the phenotypes (Y-RNA, a component of the Ro60 ribonucleoprotein involved in cellular response to interferon-alpha and in regulation of gene expression) while the other genes seem to be phenotype-specific, and many of them are involved in inflammatory pathways.

Discussion and Conclusions: The identification of phenotype-specific pathogenic mechanisms could be pivotal for the study of progression biomarkers. Future development of this work will regard the longitudinal evaluation of transcriptomic patterns.

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## DIAGNOSTIC CUES IN MULTIFOCAL MOTOR NEUROPATHY

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Objectives: Our objective was to describe clinical and neurophysiological follow up course and nerve ultrasound picture of our patients with Multifocal motor neuropathy (MMN), in order to describe correlations within clinical, neurophysiological and US pictures. Is a rare acquired immune mediated neuropathy with progressive motor multifocal neuropathy without sensory involvement. MRI and nerve US are emerging as useful tools in the diagnostic process. In particular, nerve and cervical root US has showed multifocal peripheral nerve or single fascicle enlargement in both clinically and electrophysiologically affected and unaffected segments, as well as normal nerve appearance in definite conduction block sites. Nerve US can be altered also in other immune-mediated neuropathies such as CIDP, but MMN presents an highed intra-nerve variability.

Materials and Methods: Four patients with multifocal motor neuropathy treated in our Neurophysiology Unit were recruited. Clinical (MRC sum scale, single MRC value for all involved muscles) and neurophysiological data were retrospectively collected and follow up evaluation was performed. Nerve US of median, ulnar, peroneal, tibial nerves was performed and cross sectional area was measured in all abnormal sites and in definite/probable nerve conduction block sites.

Results: Four patients were evaluated: 4 males, mean age 56 (range 45-69), mean disease duration 9 years (range 5-13 years). Chronic and frequent IVIg provided in 3 patients partial efficacy with initial improvement followed by progressive axonal damage over the years. In fact, these patients (3/4) depend on periodic infusions. One patient, the one with shorted disease duration, showed a slight initial clinical and neurophysiological improvement followed by stabilization. Nerve US showed in all patients multifocal nerve enlargements in both affected and unaffected nerve segments. Table 1 summarizes patients' information while nerve ultrasound cross sectional area values are reported in table 2 and 3 respectively for lower and upper limbs.

Discussion: Follow up examination showed clinical and neurophysiological stability in some patients, while others showed a axonal damage progression despite therapy. In our case series, nerve US showed results consistent with pre-existing literature. This finding is not highly specific as it is also observed in other immune mediated neuropathies. Although nerve conduction studies remains the gold standard for its high specificity, nerve US could help increase diagnostic sensibility in showing a multifocal damage and aiding differential diagnosis.

Conclusions: We can hypothesize that the observed variability may be related not only to the different pathogenesis but to the stage and type of nerve damage and to the duration of the disease.

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## A SINGLE-CENTER LONGITUDINAL AND RRETROSPECTIVE STUDY OF DYSPHAGIA IN 113 PATIENTS WITH MYOTONIC DYSTROPHY TYPE 1 (DM1)

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Objectives: Pneumonia is the main cause of death in DM1 and aspiration may play an important role. Yet dysphagia is a seldom complaint, it is poorly studied in the initial stages of disease, it has a high impact on patients quality of life and information on progression is scanty in this disease. Our aim is to describe swallowing function and nutritional status of patients with DM1 at baseline and over time.

Materials: Adult patients with a DM1 genetically determined diagnosis admitted to the Nemo Clinical Center in Milan from 2013 to 2021 were included.

Methods: Dysphagia was assessed using validated questionnaires and fiberoptic endoscopic evaluation (FEES) and correlated to demographic features, nutritional status and disability.

Results: 113 adult patients with DM1 were evaluated. At baseline FEES showed that out of 113 patients (mean age: 49 years [42.50 – 57.50], mean disease duration: 16.76 years [9.56 – 23.72]; mean MIRS: 4 [3 – 4]) 27 (24%) had a normal swallowing function (Dysphagia Outcome Severity Scale (DOSS): 6-7), 81 (72%) had mild-moderate impairment (DOSS: 3-5) and 5 (4.5%) had severe impairment (DOSS: 1-2). Follow-up data available in 65 patients showed progression to a mild-moderate swallowing impairment in 8 of 16 with normal swallowing function at baseline, while only 3 of 45 (6%) with mild-moderate swallowing impairment at baseline showed progression to severe impairment.

Discussion: Dysphagia had a high prevalence in our cohort and most of our patients showed mild-moderate swallowing impairment, but with scarce awareness and possible unexpected complications. The progression from mild-moderate to severe dysphagia appeared to be slow, which was in line with the general slowly progressive course of this disease. Nevertheless, the progression from normal function to mild-moderate impairment in 50% of our patients in less than 3 years is a factor that can not be underestimated.

Conclusion: Our study brings out the crucial role of dysphagia in DM1 clinical phenotype. In addition, the progression from normal swallowing to mild-moderate dysphagia strongly suggests that regular and systematic swallowing assessments are highly recommended in this population.

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## VIROME, INFLAMMATION, AND METABOLISM SIGNATURES FOR THE STRATIFICATION OF AMYOTROPHIC LATERAL SCLEROSIS PATIENTS

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Amyotrophic Lateral Sclerosis (ALS) is a relentless disease, characterized by wide genetic and clinical heterogeneity which reflects its biological complexity and not fully understood pathomechanisms. Currently, the identification of significant biological indicators of the disease state and progression represents an urgent unmet need. Although ALS is typically classified as a disease involving motor neurons, increasing evidence show the contribution of different systemic players to the disease pathogenesis, including metabolism, immunity and microbiome. Microbiome is crucial for immune system functioning and it has been recognized as a critical regulator of brain physiology, therefore influencing the host susceptibility to neurodegenerative diseases, including ALS. In detail, the gut microbiota exerts its effects on the central nervous system (CNS), through a bidirectional interaction, the gut-brain axis, influencing neuronal health via production of neuroactive metabolites such as the short chain fatty acids (SCFA) and toxins and through the modulation of immune system, e.g. T cells' activity and their differentiation. In addition, the viral components of the microbiome, termed as "virome", may have a relevant role in maintaining the immune system health as well. The most prevalent element of the human virome is the torque teno virus (TTV). There is mounting evidence that TTV viremia levels are closely correlated with host immunity and it has been proposed as a biomarker for assessing the immune system's functionality. Since the microbiome composition is considered a major source of inter-individual variation in immunity, susceptibility to diseases and clinical heterogeneity, we analyzed a panel of microbiome- and inflammatory-related components as potential diagnostic and prognostic biomarkers in ALS. For the first time, we showed, through the serum level assessment of 14 cytokines, TTV viremia and 18 FFA (free fatty acids), that a set of these parameters may clearly distinguish ALS (n=100) from healthy controls (n=34). Moreover, the combination of these factors allowed to match the patients based on biological profile bringing potential for biotyping. Infact, among the ALS patients' group, the examined biological variables lead to identify four clusters of patients with a distinct biological profile, although without correspondence with clinical features such as site of onset, sex, progression rate, phenotype or C9ORF72 expansion. In addition, we found an association between 2-ethylexanoic acid level and patients' survival that was different in males and females. Our work adds new evidence to the involvement of microbiome, metabolism and immunity in ALS, offering new parameters for clinical disease phenotyping.

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## GOLD COAST CRITERIA IN ALS PATIENTS: A CLINICAL PRACTICE SINGLE-CENTER EXPERIENCE

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Objectives: Revised El Escorial (rEEC) and Awaji Criteria are currently used for diagnosing and categorizing Amyotrophic Lateral Sclerosis (ALS). However, they are complex, their sensitivity is still not optimal for research purposes, and present high inter-rater variability in clinical practice. To address these points, in 2019, a new set of diagnostic criteria was proposed, namely the Gold Coast Criteria (GCC), characterized by a dichotomous diagnostic categorization, i.e., ALS or not ALS. Their reliability compared to the previous ones is debated. The aim of our study was to evaluate the sensitivity, specificity, and clinical usefulness of GCC in a practical clinical setting.

Materials: We evaluated retrospectively 131 patients diagnosed with ALS and 104 control subjects with no diagnosis of ALS at the Unit of Neurology, ASST Spedali Civili (Brescia, Italy), and NeMO-Brescia Clinical Center for Neuromuscular Disease (Brescia, Italy) between October 2003 and May 2023.

Methods: A complete clinical assessment, electrophysiological tests, neuroradiological investigations, and CSF analysis were obtained for each subject. rEEC, Awaji, and GCC at the first and last evaluations were applied.

Results: The mean age at onset was 63 and 60 years for ALS and the control group, respectively. For the ALS group, the difference between the first evaluation and the last follow-up visit was about 16 months. The mean ASLFRS-R at onset and at last evaluation was 41.78 and 27 points, respectively. The sensitivity of GCC (93.1%; 96.1%) was greater than rEEC (71.7%; 87%) and Awaji criteria (77.8%; 89.3%) both at the first visit and last follow-up. The GCC specificity (28.8%) is lower than that of the other two criteria (rEEC 45.2%; Awaji criteria 43.2%).

Discussion: Our study suggests that GCC has a greater sensitivity compared to rEEC and Awaji criteria in our population. rEEC has been found to have the highest specificity, but it might delay the diagnosis. Even if GCC's positive predictive value (62.2%) is nearly the same as previous criteria (rEEC 62.2%; Awaji criteria 63.3%), GCC has shown a negative predictive value significantly higher (77%) than rEEC (56%) and Awaji criteria (60.8%). Proving a substantially lower risk of false negative diagnoses compared to previous ones, the novel criteria could help to not delay the correct diagnosis and refer patients early to the correct treatment.

Conclusions: The reduced specificity of GCC is less likely to impact patient recruitment in clinical trials, therefore, its use might allow an earlier diagnosis of ALS and a faster enrolment.

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## DRUG USE PATTERNS IN MYASTHENIA GRAVIS: A REAL-WORLD OBSERVATIONAL STUDY IN ITALY - THE CAESAR STUDY

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Objectives: In the context of a comparative study of efficacy and safety of drugs used in rare neuromuscular and neurodegenerative diseases (CAESAR - call AIFA_FV_2012-13-14) we assessed the use patterns of drugs indicated for Myasthenia gravis (MG).

Materials: For each region, the following administrative healthcare data sources were considered: healthcare assistance, hospital discharge records, emergency department visits, disease specific co-payment exemptions, drug claims for reimbursed drugs for outpatient use, mortality information system.

Methods: A retrospective cohort study was conducted based on administrative healthcare data. For a cohort of MG patients, prevalent and incident use of pyridostigmine (Py) and other indicated drugs in the first year after case identification was evaluated. Prevalent combined use of major therapies (azathioprine (Az), prednisone (Pr), vitamin d (Vd)) stratifying by Py use was assessed, and a comparison between therapies at MG identification date and during the first year of follow-up was performed.

Results: We included 1,114 MG patients in 2013-2019. In the first year of follow-up, we observed prevalent and incident use of Py in 60% and 3.5% of patients, respectively, 57.1% and 4.4% for Pr, 24.7% and 3.3% for Az, and 42.5% and 8.2% for Vd. Among 668 Py prevalent users, 19.9% also used Az, Pr and Vd, while 13.2% none of these. Among 446 non-Py users, 2.9% used Az, Pr and Vd, while 58.3% none of these. An increase of combined therapies was evident only in incident Py users.

Discussion: Most MG patients use Py, often in combination with one or more drugs among Az, Pr, and Vd. Corticosteroid therapy is more frequent in new users of Py. Most non-Py users are not treated with either of these drugs. Our real-world analysis showed that the management of MG patients in clinical practice generally follows guidelines. Unexpectedly, we found a relevant number of patients who were not receiving treatment. Despite available treatment options, the impact of the disease remains high for many MG patients.

Conclusion: Our results suggest that, for some MG patients, there may be a need for treatments that combine a rapid onset of benefit with long-term and consistent disease control. These issues may be addressed by the new treatments currently being developed. To date, more studies are needed to address the heterogeneity, quality, and generalisability of the existing data, and to evaluate patterns of use, efficacy and safety of new or emerging therapies for MG.

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## CARDIAC ORGANOIDS AS AN IN VITRO PARADIGM FOR MYOTONIC DYSTROPHY TYPE 1: AN INNOVATIVE APPROACH TO DISEASE MODELING

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Aims: Myotonic Dystrophy type 1 (DM1) is a multisystemic disease caused by a triplet expansion of the 5' untranslated region of DMPK gene. Its pathophysiology is still debated, although it is thought that RNA toxicity plays a pivotal role in sequestering splicing factors of a multitude of genes involved in muscle contraction, cardiac conduction and central nervous system functions [1]. In recent years organoids, tissue cultures derived from induced pluripotent stem cell (iPSCs), have been able to recapitulate organ development, structure, and physiology [2]. Our aim is to generate cardiac organoids as in vitro model of DM1 to better explore disease mechanisms and as a preclinical model for testing candidate drugs.

Materials: Four induced pluripotent stem cells lines from National Institute for Neurological Disease and Stroke (NINDS) repository of four different caucasian patients (NH50153, NH50156, NH50159, NH50256) affected with myotonic dystrophy, harboring different expansion triplet numbers (CTG range: 150 – 1170). We used iPSCs of unaffected subject as control.

Methods: IPSCs were thawed and progressively transitioned them in Essential 8 medium (Thermofisher). Once the cells were ready, cardiac differentiation wee induced via transforming growth factors. Cardiac differentiation was completed in a week by sequential exposure of inhibitor of glycogen synthase kinase 3 CHIR99021 (Miltenyi Biotec), Activin A and Bone Morphogenetic Protein [3].

Results: Beating organoids of subject NH50153, NH50156 & NH50159 appeared approximately at day 7 of the differentiation protocol. We were unable to expand iPSCs of subject NH50256 (harboring 1170 CTG mutation) as they died during passages. We are performing sequential morphological analyses as well as immunohistochemistry and gene expression analyses to characterize the role of DMPK expression in organoids throughout maturation period.

Discussion: New approaches are required in order to address the limitations of current cellular and animal models. From the best of our knowledge, this is the first attempt to generate cardiac organoids from DM1 patients. We demonstrated that obtaining cardiac organoids of DM1 is feasible and allows to perform multi-dimensional and serial analyses on models directly generated from patient's genotype. This is especially important in DM1 since somatic instability plays a pivotal role in disease progression. By allowing to visualize dynamic processes happening throughout time, organoids may pave the way for more accurate disease modeling, drug screening, and personalized therapeutic approaches.

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## SOD1-ALS FEATURES AND PREDICTORS OF DISEASE PROGRESSION AND SURVIVAL FROM TWO ITALIAN POPULATION-BASED REGISTRIES

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Background: Uncovering distinct features and trajectories of amyotrophic lateral sclerosis (ALS) associated with SOD1 mutations (SOD1-ALS) can help with patients' counseling and stratification for trials, and timing of interventions. Our study aims to identify distinctive clinical features of SOD1-ALS focusing on genotype-phenotype correlation and on factors that may affect disease progression.

Methods: This is a retrospective observational study of a SOD1-ALS cohort from two Italian registers of Emilia Romagna and Piedmont and Valle d'Aosta regions.

Results: Among 2204 genotyped ALS patients, 2.5% carried SOD1 mutations, with a M:F ratio of 0.83. SOD1-ALS patients were younger and reported more frequently a family history of ALS or FTD. SOD1-ALS had a longer survival if compared to patients without ALS associated gene mutation, but a high variability was found across mutations and a mean survival shorter than one year was found for L39V, G42S, G73S, D91N mutations. Among SOD1-ALS, multivariate analysis showed that, besides well-known clinical prognostic factors such as late age at onset and high progression rate at diagnosis, mutations localized in exon 2 or in highly conserved gene positions, predicted a worse survival. On the contrary, among comorbidities, cancer history was independently associated to better survival.

Discussion: The prevalence of SOD1 mutations in our population was consistent with previous reports in European datasets [1]. In the context of an overall slower disease, SOD1-ALS presents a certain heterogeneity linked to the high genetic diversity dictated by the multiplicity of possible mutations sites, and to some clinical prognostic factors, among which cancer history. Recognizing the modulators of SOD1-ALS phenotypic heterogeneity may be useful for improving response to forthcoming therapies.

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## ATYPICAL HIRAYAMA SYNDROME CASES WITH PROXIMAL UPPER LIMB ONSET

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Aims: To provide an insight into atypical manifestation of Hirayama disease (HD), describing two cases with insidious proximal upper limb involvement at onset.

Background: HD is a flexion-induced myelopathy, characterized by the juvenile onset of unilateral or asymmetric weakness and amyotrophy of the hand and ulnar forearm, predominantly affecting C8–T1 and most common in males in Asia [1].

Methods: Dynamic flexion magnetic resonance imaging (dfMRI) is the imaging modality of choice to diagnose HD [2]. The pathology is enhanced by flexion of the cervical spine, revealing forward migration of dura with enlargement of posterior epidural space. Herein, we present two cases of Hirayama disease with a juvenile insidious onset, atypical proximal upper limb weakness and hypotrophy with a proximal-distal progression.

Results: Case 1. A 41-year-old man reported a focal weakness and wasting of the proximal left arm, starting before the age of 18. The symptoms remained stable until the age of 38 years, when there was a progressive worsening with subsequent slow involvement of the contralateral proximal upper limb. DfMRI revealed a segmentary detachment between the posterior dural sac and the subjacent lamina at the C3-C5 level. The “snake-eye appearance” was enhanced by cervical flexion. Repeated electromyography revealed a progressive neuronopathic impairment. Case 2. A 15-year-old boy presented an insidious and progressive right proximal arm weakness for one year. After 8 months from onset, weakness spread to distal right arm muscles, and proximal hypotrophy appeared. Neurological and neurophysiological examinations highlighted right arm lower motorneurons impairment. DfMRI showed a myelopathic process in the right lateral paramedian midline between C4-C6, associated with detachment of the posterior cervical dural sac.

Discussion: The reported cases fulfil the recent Huashan diagnostic criteria for HD [1]. The prominent shifting of dural sac in C3-5 and C4-C6 segment, respectively, detected by dfMRI, may explain the unusual distribution of the disease, with the atypical involvement of the proximal upper limb at onset [3]. Case 1 experienced repeated disease relapse with an interval of stable stage. Both neurophysiological and imaging findings indicate irreversible lesions, a poor prognosis with progression of the disease, and a possible need for surgical intervention.

Conclusions: HD should be suspected in young patients presenting with slowly progressive weakness and wasting restricted to one limb at onset. While most cases involve the lower cervical myotomes, proximal upper limb involvement has been seen rarely. Nerve conduction studies and dfMRI are fundamental tools to lead to a correct diagnosis also to exclude other similar entities.

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## COLCHICINE TREATMENT IN AMYOTROPHIC LATERAL SCLEROSIS: SAFETY PROFILE, BIOLOGICAL AND CLINICAL EFFECTS IN A PHASE 2 MULTICENTER, RANDOMIZED, CONTROLLED, DOUBLE-BLIND CLINICAL TRIAL (CO-ALS)

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Background: In preclinical studies the anti-inflammatory drug colchicine enhanced the expression of autophagy factors like HSPB8, the master regulator Transcription Factor EB (TFEB), the adaptor protein SQSTM1/p62 and the Microtubule- associated protein 1A/1B-light chain 3 (LC3). The concomitant induction of these proteins counteracted TDP-43 accumulation, a hallmark of ALS. Colchicine has never been tested on ALS patients.

Material and Methods: In this multicenter, randomized, double-blind trial, probable or definite ALS patients with symptoms onset within 18 months, were randomly assigned in a 1:1:1 ratio to receive colchicine 0·01 mg/kg/day, 0·005 mg/kg/day or placebo for 30 weeks. The primary outcome was the number of patients exhibiting a decrease fewer than 4 points in the ALS Functional Rating Scale-Revised (ALSFRS-R) total score from baseline to treatment end. Secondary outcomes included changes from baseline of stress granule and autophagy responses, TDP-43 and neurofilament accumulation, extracellular vesicles secretion, comparing colchicine and placebo arms. Clinical outcome measures of disease progression, survival, safety and quality of life were also collected.

Findings: Fifty-four persons were randomly assigned to colchicine or placebo. In intention-to-treat analysis, 33·3% of patients treated with colchicine 0·005 mg/kg/day versus 13·3% with placebo had a decline fewer than 4 points at ALSFRS-R in 30 weeks (95%CI 0·39 to 40·42, p=0·416). During and after treatment ALSFRS-R monthly decline slowed down only in patients treated with colchicine 0·005 mg/kg/day compared to those who received the placebo (mean difference 0·53, 95%CI: 0·07 to 0·99, during treatment; mean difference 0·46, 95% CI: 0·07 to 0·84, after treatment). Reported adverse events (AEs) were 14 (42·8% of which were severe) for placebo arm, and 34 for the colchicine arms (35·3% of which were severe). Events occurring at a greater frequency in the colchicine group were mainly gastrointestinal disorders. Based on safety, clinical and biological effects, colchicine 0·005 mg/kg/day resulted the best dosage in this study.

Discussion: For the decline in ALSFRS-R fewer than 4 points a difference of only 20% was found in the low-dose group with respect to placebo, leading to missing the primary outcome. In patients treated with colchicine 0·005 mg/kg/d, there was a trend towards a slower ALSFRS-R monthly decline during and after treatment, but we cannot

exclude heterogeneity in disease progression. Colchicine treatment was well-tolerated and provided reassuring preliminary safety findings in ALS patients.

Conclusion: Colchicine treatment was safe, but further trials are necessary to evaluate efficacy of this commercial drug in ALS.

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## THE OUTPATIENT CLINIC: A NEW PERSPECTIVE TO TAKE CARE OF PEOPLE AFFECTED BY NEUROMUSCULAR DISEASE

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Aim: The aim of the study is to verify whether the early outpatient care of social-welfare needs supports the patient and the clinician in the early definition of the treatment plan. We are implementing the early outpatient care model in the adult population of patients affected by neuromuscular diseases that typically occurs when an individual is usually fully engaged in working activities and is in the most active life phase with relevant social and familiar impact. In the NeMO Clinical Center there is a specialized nurse, called Nurse Coach, dedicated to take care of patients and family and who has acquired specialized skills to manage clinical and nursing aspects and to facilitate the access at home nursing cares and to socio-economics aids. During a first-time visit to the site, a newly diagnosed patient with neuromuscular disease, is not only seen by a neurologist but the initial visit includes a nurse coach and a psychologist. This allows to target the intervention early in the disease process.

Materials and Methods: Retrospective qualitative analysis of needs, aids and homecare service detected by Nurse Coach in the outpatient clinic of the NeMO Center from January 2022 to April 2023.

Results: The Nurse coach has launched a care plan in 60 patients (mainly affected by amyotrophic lateral sclerosis and myotonic dystrophy) and their caregivers (average time of this initial evaluation = 60 minutes per patient). Information on the bureaucracy of disability rights and economical aids which are the most important needs in the first stage of the disease were collected as well as the request for educational aspects to manage symptoms.

Discussion: Together with the diagnosis the family context and the economic status must be taken into consideration as soon as possible; they can affect the disease course and the possible therapeutic adherence. The nurse coach must therefore have defined skills and competences that go beyond the predetermined practical "nurse skills" to find the best solution with the families.

Conclusion: The care of patient with a neuromuscular disease and his or her family could be improved with an early multidisciplinary approach, including also social and economic aspects.

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## GIVING BREATH TO MOTOR NEURONS: NON-INVASIVE MECHANICAL VENTILATION SLOWS DISEASE PROGRESSION IN AMYOTROPHIC LATERAL SCLEROSIS

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Background and Objectives: Non-invasive mechanical ventilation (NIMV) improves Amyotrophic Lateral Sclerosis (ALS) quality of life and survival. However, data about its effect on disease progression are still lacking. Here, we test whether NIMV use changed the rate of functional decline among ALS patients.

Methods: In this retrospective observational study, we included 465 ALS patients followed up at the ALS Center in Turin, Italy, who underwent NIMV during the disease course. The primary outcome was the change in functional decline after NIMV initiation when adjusting for covariates. Functional decline was based on the non-respiratory items of the ALS Functional Rating Score – Revised (ALSFRS-R).

Results: A slower progression of functional decline followed NIMV initiation (mean improvement 0.13, 95%CI 0.11 to 0.16, $p<0.001$) regardless of sex, age at diagnosis, and disease duration before NIMV initiation. Indeed, the disease stage at NIMV initiation (early or advanced) did not influence the results. Respiratory support exerts its slowing effect mainly on the progression of spinal motor function.

Conclusions: We proved that NIMV influences the rate of motor progression in ALS. This result was not a consequence of the ALSFRS-R floor effect. The functional decline slowed after starting NIMV independently of the site of disease onset. Our results reinforce the importance of not delaying NIMV initiation in all ALS patients. NIMV-induced slowing of disease progression should also be accounted for when evaluating clinical trial outcomes.

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## COGNITIVE DETERMINANTS OF SOCIAL COGNITION IN AMYOTROPHIC LATERAL SCLEROSIS: A CROSS-SECTIONAL STUDY

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Objectives: Deficits in all Social Cognition subdomains have been reported in Amyotrophic Lateral Sclerosis [1] and have been included in 2017 Strong revised criteria [2]. However, cognitive determinants of SC subdomains are largely unknown. The aim of the present study was to investigate the functional correlation between SC abilities, specifically Facial Emotion Recognition (FER) and Theory of Mind (ToM), with the other fundamental cognitive domains.

Materials: We enrolled 102 consecutive patients attending the Turin ALS Center between February 2019 and December 2022. All patients underwent a neuropsychological battery assessing fundamental cognitive domains, included SC. FER was assessed by the Ekman 60-Faces test (EK-60F), ToM was assessed by the Reading the Mind in the Eyes Test-36 faces full version, and the Story-Based Empathy Task (SET).

Method: A multiple linear regression model was conducted to correlate SC tests corrected scores as independent variables, with 8 neuropsychological tests chosen as independent variable, representative of each cognitive domain assessed. Specifically, as independent variable we included Letter Fluency test, Category Fluency Test, Trail Making Test B-A, Digit Span Backward, Wisconsin Card Sorting Test (WCST), Frontal Assessment Battery, Rey Auditory Verbal Learning Test-Delayed Recall, Rey Osterrieth Complex Figure Test-Immediate and Delayed Recall.

Result: EK-60 F test showed an overall significant correlation with the other cognitive tests (R2 adj 0.286, p 0.037), without any specific correlation. RMET-36 showed an overall moderate significant correlation (R2 adj 0.382, p 0.002), and a significant specific correlation with Wisconsin Card Sorting Test (WCST) (p 0.032). SET-GS showed an overall weak significant correlation (R2 adj 0.250, p 0.033), and also a specific significant correlation with WCST (p 0.034). SET-IA did not show an overall weak significant correlation with the other cognitive tests. SET-EA showed an overall moderate significant correlation (R2 adj 0.262, p 0.027), and a significant specific correlation with WCST (p 0.003) and TMT B-A (0.044).

Discussion: our study shows that SC subdomains have a different pattern of correlation with the other cognitive domains. Specifically, while FER does not show any specific correlation, ToM shows a specific correlation with executive functions, in line with previous results [3].

Conclusions: The relationship of ToM with other cognitive domains, especially with Executive Functions, should be further explored as it is relevant in clinical conditions with frontal involvement, where a dysexecutive syndrome may be associated with ToM deficits and/or behavioural symptoms, as we observe in ALS patients.

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## EARLY ADMINISTRATION OF RITUXIMAB IMPROVES CLINICAL OUTCOME REGARDLESS OF MYASTHENIA GRAVIS SUBTYPE: A SINGLE CENTER COHORT STUDY

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Background: Rituximab (RTX) is a chimeric monoclonal anti-CD20 antibody that had shown good effectiveness and safety in generalized Myasthenia Gravis (gMG) patients and that is currently recommended as a therapeutic option in MuSK-MG in recent consensus guidelines update. Yet, evidence indicating its most appropriate use is still scarce.

Aim and Methods: We retrospectively evaluated a cohort of gMG patients treated with RTX as an add-on therapy consecutively seen at the MG Clinic of Azienda Ospedaliero-Universitaria Pisana in order to investigate clinical predictors of better outcome after RTX infusion.

Results: Of the 36 patients included, 27 were women (75%) and antibodies against muscle specific tyrosine kinase (MuSK) were present in 18 patients (50%); mean (SD) age at treatment start was 48 (17) years. Mean (SD) MGFA composite score before RTX administration was 12,3 (8,3) and 3,5 (5,7) at last follow-up. 5 patients achieved complete stable remission and discontinued steroid therapy. We did not observe significant differences in clinical outcome and steroid sparing effect between the two MG subtypes, indeed patients who received RTX within 12 months of disease onset had a greater improvement in MGFA composite score in both groups ($p< 0.001$).

Conclusions: In our cohort of gMG patients early administration of RTX (e.g. within 12 months of disease onset) obtained better outcomes in terms of clinical improvement irrespectively of antibody status, suggesting a greater benefit of RTX earlier in the disease course also in new-onset generalized MuSK-MG. Larger prospective studies are warranted to provide further evidence.

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## GENDER DIFFERENCES IN CLINICAL OUTCOMES IN MUSK-MG PATIENTS

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Background and Aim: Evidence on gender differences in Myasthenia Gravis (MG) patients showed an increased disease severity in females, especially on patient-reported outcome measures. However, studies are almost entirely based on anti-AChR positive MG patients and data is lacking regarding MuSK-MG ones. We therefore explore the potential differences in outcome measures and therapeutic approach with respect to gender in this specific subtype of MG.

Methods: We collected demographic and clinical data of 54 MuSK-MG patients out of the 202 consecutively admitted to the MG Clinic of the Azienda Ospedaliera-Universitaria Pisana with a median follow-up time of 2.3 ± 1.4 (median ± DS) years. The clinical diagnosis of MG was confirmed in all patients by a positive test for MuSK antibodies using radioimmunoassay. The Myasthenia Gravis Foundation of America (MGFA) clinical classification criteria, MG-Composite (MGC) score and the MG-Activities of Daily Living (MG-ADL) score were used to assign clinical state as outcome measures at baseline and follow-up visits, then analyzed for relationships with gender. Demographic features, comorbidities, antibodies titer and therapeutic data, including the type and dosage of standard medical therapies administered were also recorded at each evaluation and analyzed for gender influence.

Results: Our cohort comprehends 16 male patients (29.6%) and 38 (70.4%) female patients, with a median age of 49 ± 17 years. Duration of disease at first visit was di 2.6 ± 3.2 years (median ± DS) and the distribution of symptoms and clinical MGFA grade were predominantly IIb to V. There were no significant gender differences in baseline and follow-up scores, disease duration, age at disease onset, age, MGFA classification and antibodies titer. All patients improved over time when comparing baseline measures to follow-up, again without any significant gender difference. Notably, with respect to treatment, we did not observe a gender biased approach to the choice of steroid therapy and steroid-sparing agents.

Discussion and Conclusions: To date, this is the first study to investigate gender differences in clinical outcomes in MuSK-MG patients and we did not observe a gender influence on patient-reported and composite outcomes measures. Our results could reflect the distinct features of MuSK-MG. Indeed, the predominant bulbar involvement and the severity of the disease with a high tendency to frequent relapses and respiratory failure could impact on the quality-of-life scores irrespectively of gender. Further studies are needed to confirm these data and investigate how gender affects also the different immunological pathway of MuSK-MG.

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## COGNITIVE FUNCTIONING IN MYASTHENIA GRAVIS: A COHORT STUDY IN A THIRD-LEVEL ITALIAN CENTER

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Background: Currently there are conflicting results about the neuropsychological profiles of people with Myasthenia Gravis (MG) [1-3] while screening measures of global cognitive functioning in this population are scarcely available.

Objectives: This study aims to investigate the prevalence of individuals with MG with significant differences in performance on neuropsychological tests, compared to the general population; we will investigate the relationships between these performances and disease's clinical features, work productivity, activities of daily living, anxiety, depression, fatigue, disability, and quality of life.

Methods: 150 people with MG will be enrolled at Carlo Besta Neurological Institute in Milan. We will collect Information about socio-demographic and disease features (such as current drug therapy and antibody profile), neuropsychological tests (Brief Neuropsychological Examination-3 and Global Examination of Mental State), disability (MG-Disability), quality of life (MG-Quality of Life), work productivity (WPAI-GH), independence in daily life (MG-Activities of Daily Living), anxiety, depression (Hospital Anxiety and Depression Scale), and fatigue (Fatigue Severity Scale). Correlation analyses will be carried out between the neuropsychological performances and the other administered questionnaires. Analysis of variance models between groups of patients belonging to different clinical disease subtypes will also be implemented.

Discussion: The assessment of cognitive functioning and disease outcome's indicators such as well-being, disability, quality of life and work productivity in people with MG will allow to better understand the care, support and treatment needs of these patients, facilitating a multidimensional approach to identify tailored care pathways that will successfully respond to patient needs.

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## RESPIRATORY QUOTIENT AS INDEPENDENT PREDICTOR OF PROGNOSIS IN A LARGE COHORT OF AMYOTROPHIC LATERAL SCLEROSIS PATIENTS

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Objective: Since a lower Respiratory Quotient (RQ) in Amyotrophic Lateral Sclerosis (ALS) patients was associated with worse functional status, lower Lean Soft Tissue Mass, higher Fat Mass %, and longer disease duration [1], which in turn are factors associated with worse survival [2,3], the aim of the study was to evaluate the prognostic role of RQ as independent predictor of survival.

Material: The RQ is the ratio of the patient's carbon dioxide production (VCO2) to the oxygen consumption (VO2), and it is obtained by indirect calorimetry (IC), a noninvasive, reliable, and valuable tool in assessing energy expenditure.

Methods: ALS patients with RQ value available at first evaluation, were retrospectively recruited at the NEMO Center (Milan) between July 2008 and November 2017. Extensive demographic and clinical features were also collected.

Results: A total of 249 ALS patients (mean age: 62yrs ± 12, bulbar/spinal ratio: 0.46) were enrolled. The decrease in RQ resulted to be significantly related to a shorter tracheostomy-free survival (p=0.0130), and this relationship was confirmed independently from age at evaluation, disease duration, ALSFRS-R total score and disease progression rate as results of backward selection method of a set of candidate confounders. An RQ ≤ 0.78 emerged as best cut-off (Contal and O'Quigley outcome-oriented approach) in discriminating short- and long-term survival (HR: 1.50 [1.11–2.02], p=0.0084). Moreover, although any significant association emerged between RQ and body composition, patients with RQ ≤ 0.78 reported a significantly lower ALSFRS-R total and subscores, seated FVC% and FEV1% compared with patients with RQ > 0.78.

Discussion: RQ level could describe the functional and respiratory condition of ALS patients and seems to independently predict survival in ALS patients. However, a prospective study will be needed to understand the relationship between respiratory involvement and nutritional aspects in defining RQ changes.

Conclusion: RQ could be used as prognostic factor in ALS to categorize patients in short- and long- term survival classes, although there is a need to more deeply investigate the RQ proportion of variance explained by both respiratory involvement and nutritional status.

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## PHENOTYPIC HETEROGENEITY OF MONOGENIC AMYOTROPHIC LATERAL SCLEROSIS: THE CASE OF TARDBP MUTATION

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Background: Mutations in 43-kDa transactive response (TAR)-DNA-binding protein (TARDBP) are associated with 2-5% of familial ALS cases. TAR DNA-Binding Protein 43 (TDP-43) is an RNA/DNA binding protein involved in several cellular mechanisms (e.g., transcription, pre-mRNA processing, splicing). Many ALS-linked TARDBP mutations have been described in literature, but few phenotypic data of monogenic TARDBP-mutated ALS are available. This study aims to investigate the clinical genotype-phenotype heterogeneity of different mutations in TARDBP.

Material: We analyzed the clinical features of ALS patients carrying mutations in the TARDBP gene evaluated at the Tertiary ALS Center at the Maggiore della Carità University Hospital, Novara, Italy, from 2010 to 2020. Of 350 patients genotyped, 4 were carriers of TARDBP mutation.

Results: Patient 1: a 61-year-old man presented with a slowly progressive muscle weakness in the left leg first, then in the right for two years. Neurological examination showed spasticity in the lower limbs, diffuse hyperreflexia, and left Babinski's sign. No signs of lower motor neuron (MN), bulbar or cognitive impairment were evident. Genetic analysis revealed the presence of c.G1144A, p.A382T (NM_007375) missense variant in heterozygous status in exon 6 of the TARDBP gene. Patient 2: at the age of 55 a woman presented with 10 months history of progressive lower limb weakness. Neurological examination showed fasciculations with diffuse hyperreflexia. Electromyography and Motor Evoked Potentials also confirmed the involvement of both upper and lower MNs. Genetic analysis revealed the p.M539V (NM_007375) mutation in exon 6 of the TARDBP gene. Patient 3: a 66-year-old man showed a 2-year history of rapidly worsening disease till respiratory failure occurred. He presented bulbar onset with dysphonia and dysarthria. Neurological examination showed upper and lower limb hyperreflexia and spasticity. No EMG signs of lower MN involvement were observed. Genetic analysis revealed the p.G294V (NM_007375) mutation in exon 6 of the TARDBP gene. Patient 4: a 72-year-old man presented with a slow progressive history of dysarthria and dysphagia. Symptoms then proceeded with mild lower limb weakness and spasticity. No EMG signs of lower MN involvement were detected, neither sign of cognitive impairment at the neuropsychological tests. Genetic analysis revealed the p.N390S (NM_007375) mutation in exon 6 of the TARDBP gene.

Discussion: Our clinical data and those in the literature support and confirm the hypothesis that TARDBP pathogenic variants have considerable geno-phenotypic heterogeneity within the ALS spectrum, both in terms of clinical presentation at onset, prevalent phenotype, cognitive impairment, and disease progression and duration.

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## A NOVEL KIF5A MUTATION LINKED TO HEREDITARY SPASTIC PARAPLEGIA AND ASSOCIATED WITH GLUTEAL CLONUS

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Objectives: Hereditary spastic paraplegia (HSP) includes a heterogeneous group of genetic diseases, mainly characterized by degeneration of upper motor-neurons. HSP 10 is a rare form of autosomal dominant HSP caused by mutations within the Kinesin Family member 5A (KIF5A) gene. We report the case report of a patient with HSP 10.

Materials: A 57-year-old male was referred to our department due to progressive limb weakness and gait unsteadiness. Neurological examination showed diffuse upper motor-neuron signs, with iperreflexia and bilateral Babinski sign. Bilateral pes cavus was also present. A stereotyped rhythmic muscular contraction of gluteal muscles was triggered by sudden gluteal stretch by the examining physician, consistent with muscle clonus. Patient reported presence of slight motor impairment since childhood with progressive worsening in the adult age. A similar motor impairment pattern was also reported in patient's son.

Methods: We describe a novel complicated HSP10 phenotype in two siblings with signs and symptoms of upper motor neuron degeneration, Charcot-Marie-Tooth (CMT)-like axonal neuropathy and associated with a newly described gluteal clonus. Clinical data, genetic tests and electrophysiological features of index case and family members are reported.

Results: A genetic sequencing disclosed a novel pathogenetic mutation in the KIF5A gene (c.776T>C, p.L259P) in both patients, and electrophysiological study confirmed features of CMT-like axonal neuropathy and gluteal clonus.

Discussion: We report on a novel mutation in KIF5A gene leading to a complex form of HSP, characterized by a HSP phenotype associated with CMT2 axonal neuropathy. This mutation occurs within the N-terminal protein motor domain confirming that missense mutations involving the N-terminal motor domain mainly leads to HSP and CMT2 phenotypes, while loss of function mutations involving the C-terminal of the protein are linked with an ALS-phenotype [1]. In KIF5A-associated ALS protein aggregates accumulation within neuronal bodies might spread through an anterograde transport leading to widespread (upper and lower) motor-neuron degeneration [1-3]. Additionally, we found that index patient displayed a gluteal clonus, possibly linked to the widespread degeneration involving long motor-neuron cortico-spinal fibers. We postulate that gluteal clonus might be a previously undescribed and underreported neurological sign of cortico-spinal dysfunction and could be looked up into cases where gastrocnemius muscle clonus is found.

Conclusions: We describe a novel pathogenetic mutation in KIF5A in two family members with a complicated HSP10 phenotype with features of upper motor-neurons degeneration and CMT-like axonal neuropathy. We also describe for the first time clinical and electrophysiological characteristics of gluteal clonus.

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## A CLUSTER OF ALS PATIENTS WITH ALA96GLY SOD1 MUTATION DETECTED IN A SARDINIAN VILLAGE


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Objectives: To describe clinical features of a cluster of amyotrophic lateral sclerosis (ALS) patients with Ala96Gly variant in SOD1 gene.

Cases Description: Along 2021 and 2022, three unrelated patients originally from a small village in Oristano province (Sardinia) were diagnosed with spinal-onset ALS. The first neurological examination revealed in patient 1 (female, 67 years-old) bilateral weakness and hypotrophy of lower limbs and walking instability, in patients 2 (male, 54 years-old) and 3 (male, 51 years-old) asymmetric hypotrophy and weakness of distal upper limbs muscles. All patients had hypoactive deep tendon reflexes and no bulbar functions involvement. No cognitive impairment was detected. During the follow-up period, a slow progression of limbs motor impairment was observed, without involvement of speech and swallowing. Patient 3 was diagnosed with nocturne respiratory insufficiency two years after disease onset and started non-invasive ventilation cycles. Genetic analysis for major genes responsible for ALS in Sardinia was proposed.

Results: Sequencing of coding regions of SOD1 gene identified a missense variant c.287C>G in heterozygosis in exon 4, previously described in two Sardinian patients originally from the same village. Retrospective research of our database identified other four deceased and three alive ALS patients native of the same small area and genetic analysis tested positive for the same mutation. All retrospective patients had shown a very slow progression and a long survival duration (up to 30 years), a predominance of lower motor neuron signs, late involvement of respiratory and bulbar functions and no cognitive impairment.

Discussion: With the advent of targeted gene therapies, the importance of genetic testing in ALS is increasing. Mutations in SOD1 gene have been found in 13-20% of familial ALS cases and in 1-2% of sporadic cases and up to 200 different mutations had been described to date. We describe a cluster of ALS patients with a SOD1 mutation, so far identified in a small Sardinian area only. A predominant spinal lower motor neuron involvement and a very slow progressive course are common features of this variant. Counseling for targeted gene therapy is ongoing.

Conclusion: We described a SOD1 mutation linked to slowly-progressive spinal ALS and we underline the importance of offering genetic testing to all patients early after diagnosis.

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## "CROSSING" PHENOTYPE OF JUVENILE LOWER MND CASE ASSOCIATED WITH RARE SYNE-1 VARIANTS

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Introduction: Juvenile amyotrophic lateral sclerosis (JALS) is a group of MNDs, with a genetic cause in 40% of cases. Most commonly mutated genes are FUS and SOD1 associated to typical presentation and variable time course, SETX and ALS2 [1], associated to UMN phenotype and slow disease progression. We describe a patient who carried novel compound heterozygous pathogenic variants of SYNE-1 (spectrin repeat containing nuclear envelope protein-1), presenting a very atypical phenotype and slow progression.

Case Report: A 27-years-old male born to non-consanguineous marriage, with negative family history, came to our attention six years ago suffering from weakness in right upper limb (rUL). Neurological examinations showed clinical signs of LMN involvement (fasciculations, hyposthenia, amyotrophy and hypo-areflexia) restricted to rUL and, more lightly, to lLL (proximal and distal districts). He also presented fine postural tremor reported since he was eleven. Any UMN signs, nor cognitive, cerebellar, bulbar and respiratory impairment were detected. Electromiography confirmed signs of LMN damage in clinically affected limbs. Motor Evoked Potentials were normal, despite DTI sequences of brain MRI showed slight reduction of Fraction Anisotropy in pyramidal tracts. Left femoral muscle biopsy, performed because of CK value > 1000 U/ml, showed neurogenic pattern. Basal and flexion cervical MRI and CSF standard examination were negative as well as the extensive research for occult cancer. SOD1-FUS-TARDBP43-C9ORF72-VCP-SMN1/NAIP-AR-ATTR genetic analysis were negative. Next Generation Sequencing revealed c.22720G>T (p.(Ala7574Ser)) variant inherited from healthy father and c.6574C>T (p.(Leu2192Ile)) variant inherited from healthy mother in exon 126 of SYNE-1 gene. Only in the last two years mild LMN involvement of other limbs was observed with sparing of bulbar, respiratory, cerebellar functions.

Discussion: Overall data led us to a diagnosis of atypical phenotype of JALS. Mutations in SYNE-1 are commonly known to cause autosomal-recessive pure cerebellar ataxia (SCA8). Some recent studies have revealed that SYNE-1 variants lead to heterogenous and multisystemic phenotypes, not necessarily pure cerebellar, such as MNDs, brainstem dysfunctions, cognitive impairment, intellectual disability, musculoskeletal abnormalities, respiratory distress with different combinations [2]. Only three Asiatic cases are described with pure JALS associated to SYNE 1 variants[1]. To our knowledge the current patient is the first reported in Caucasian ethnicity. SYNE-1 encodes for a structural protein involved in vesicular trafficking, expressed abundantly in cerebellum but in motor neurons and brainstem also. Aberrant vesicular trafficking is one of MND possible causes [3]. Our observation would confirm the pathogenetic role of SYNE-1 variants in MNDs.

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## RATE OF CHANGE IN UPPER AND LOWER MOTOR NEURON SIGNS PREDICTS SURVIVAL IN AMYOTROPHIC LATERAL SCLEROSIS

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Objectives: The role of upper (UMN) and lower motor neuron (LMN) involvement in amyotrophic lateral sclerosis (ALS) has been extensively studied in relation to clinical phenotype, neuropsychological involvement, and survival. Conversely, no study has explored whether the rate of change (RoC) of UMN and LMN signs from symptom onset to first clinical assessment could provide useful information related to ALS disease evolution. In this study, we investigated if RoC of UMN and LMN signs might be more informative than single quantification of UMN and LMN involvement in predicting survival.

Materials: An inpatient cohort of 1017 ALS patients, recruited at Istituto Auxologico Italiano, was retrospectively evaluated. Burden of UMN and LMN signs was assessed using the Penn Upper Motor Neuron Score (PUMNS) and Lower Motor Neuron Score (LMNS), respectively. The time interval between symptom onset and first evaluation was used to quantify the RoC of UMN and LMN scores. ENCALS survival model, survival, time from symptom onset to percutaneous endoscopic gastrostomy (PEG), and time to non-invasive ventilation (NIV) were used as outcomes.

Methods: Multinomial regression model was used to compare different measures of UMN and LMN signs among ENCALS groups. Cox regression was performed to estimate the effect of the above-mentioned variables on survival.

Results: ENCALS groups characterized by shorter survival were significantly associated with higher RoC of PUMNS and LMNS when compared to those with longer survival. Moreover, higher RoC of PUMNS and LMNS had a significant negative association with survival (RoC of PUMNS: HR= 1.33, 95% CI= [1.27-1.39], p< 0.001; RoC of LMNS: HR= 4.08, CI= [3.47-4.78], p <0.001) and were inversely associated with time to PEG (RoC of PUMNS: rho= -0.29, p= 0.010; ROC of LMNS: rho =- 0.55, p< 0.001) and time to NIV (RoC of PUMNS: rho= -0.36, p< 0.001; RoC of LMNS: rho= - 0.65, p< 0.001). Conversely, no significant associations of PUMNS or LMNS with the above-mentioned variables were observed.

Discussion: Findings from our work reveal that the RoC in UMN and LMN signs might represent a reliable clinical index to estimate disease evolution and survival in ALS patients. Indeed, these two measures provide distinct clinical information in addition to that derived from the burden of UMN and LMN signs at first evaluation.

Conclusion: By reflecting the progressing degeneration of the two distinct motor neuron subpopulations, RoC in UMN and LMN signs might offer dynamic parameters that could help clinicians to evaluate disease aggressiveness.

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## SPECIFIC MOLECULAR SIGNATURES OF BULBAR-ONSET AMYOTROPHIC LATERAL SCLEROSIS

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Aims: To investigate the molecular signature of bulbar onset ALS through integrated miRNA and proteome profiling.

Materials and Methods: We included 54 patients meeting the diagnostic criteria for ALS and 50 sex-age matched healthy controls (HC). We performed an integrated miRNA and proteome profiling in serum of a discovery cohort of 26 ALS patients and 28 HC. Serum samples were analyzed with untargeted TaqMan Human MicroRNA array cards containing 754 miRNAs. Validation of dysregulated miRNAs was performed in a second independent cohort of 28 ALS patients and 22 HC by real-time PCR using specific Taqman assays. We performed a proteomics analysis of extracellular vesicles obtained from the serum of 7 bulbar onset ALS patients, 7 spinal onset ALS patients, and 6 HC by means of a shotgun label-free platform based on the coupling of nano liquid chromatography and high-resolution tandem mass spectrometry.

Results: Discovery phase revealed four miRNAs (miR-885-5p, miR-150-5p, miR-483-5p, miR-342-3p) significantly down-regulated in bulbar onset compared to spinal onset ALS patients and HC. We did not find any differentially expressed miRNA in spinal onset ALS patients with bulbar impairment compared to spinal onset ALS patients without bulbar impairment (data not shown). These findings indicate a specific signature for bulbar onset ALS, rather than the impairment of bulbar muscles due to the progression of the disease. To validate the results of the discovery phase we analyzed the four dysregulated miRNAs in the serum of further 28 ALS patients and 22 HC by real-time PCR. A significant down-regulation of miR-150-5p and miR-483-5p in bulbar compared to spinal onset ALS patients and HC was identified, confirming the discovery phase results. Receiver Operating Characteristic curve analysis showed that serum miR-150-5p and miR483-3p could discriminate with high sensitivity and specificity the bulbar from the spinal onset ALS patients (miR-150-5p AUC=76% and miR-463-5p AUC=81%) and HC (miR-150-5p AUC=76% and miR-463-5p AUC=96%). Proteomic analysis identified three clusters of proteins indicating a distinct proteomic profile of bulbar onset ALS patients compared to spinal onset patients and HC. Integration analysis between miR-150-5p and miR-483-5p, and the selected differentially expressed proteins in bulbar onset ALS patients compared to spinal onset and HC, confirmed that distinct molecular signatures underly different biological processes.

Discussion: Our findings from integrated miRNA and proteome profiling revealed distinct molecular signatures of bulbar onset ALS.
Conclusions: We provided robust demonstration that bulbar onset ALS has a distinct molecular profile, paving the avenue for a new biology-driven classification of ALS.

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## COEXISTENCE OF AMYOTROPHIC LATERAL SCLEROSIS AND AUTOIMMUNE DISEASES: THREE CASES

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Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder involving upper and lower motor neurons. Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease characterized by chronic synovitis that may progress, leading to articular deformities and functional disability. Multiple sclerosis (MS) is a potentially disabling autoimmune disease of the central nervous system (CNS) characterized by inflammation, demyelination, gliosis, and neuronal loss. Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction caused by antibodies against acetylcholine receptors in the postsynaptic membrane. Although the exact etiopathogenesis of ALS is partially unknown, a dysfunction of the immune system is supposed to take part in ALS pathogenesis, and several reports and nationwide registry studies have often confirmed an higher association between ALS and autoimmune diseases. Here we describe three patients affected from autoimmune diseases who also developed ALS. First case: A woman suffering from RA since the age of 13, developed, at the age of 55, fasciculations, weakness of right upper limb and, a few months later, hyposthenia in right lower limb. Brain and spine MRI were normal, while an electromyogram showed neurogenic pattern with acute denervation in all tested muscles. The neurological examination showed right limbs hyposthenia and hypotrophy with homolateral brisk reflexes, consistent with ALS. Second case: A man suffering from MS developed, after several years of clinical stability, rapidly progressive head drop, diffuse muscular hypotrophy and fasciculations. The electromyogram showed neurogenic pattern with acute denervation in all tested muscles. Brain and spine MRI were unchanged, while a high camp brain MRI disclosed the new occurrence of a T2* hypointensity in primary motor cortex, consistent with upper motor neuron burden. Third case: A man affected from MG diagnosed in 2013 came to our attention, 7 years later, for the occurrence of cramps, fasciculations and weakness in the left lower limb. Clinical, radiological, and neurophysiological

assessment were consistent with ALS, and ruled out a possible MG-relapse. Interestingly, in all the three cases above-mentioned the genetic tests for ALS resulted negative. Several studies have reported an increased risk of developing ALS in patients with autoimmune diseases, since immune dysregulation and a pro-inflammatory milieu may act as triggering factors for motor neurons' degeneration in predisposed patients, easing the possibility of forward or backward spreading of damage. Case description of these cases may help in shedding light on ALS pathogenesis.

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## DATA ON SAFETY AND EFFICACY OF RISDIPLAM TREATMENT IN A SMALL APULIAN COHORT OF ADULT 5Q SPINAL MUSCULAR ATROPHY

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Introduction: Risdiplam is an oral small-molecule drug recently approved for the treatment of Spinal Muscular Atrophy (SMA). It increases the functional Survival Motor Neuron (SMN) protein by modifying pre-mRNA splicing of the SMN2 gene. The aim of the study was to investigate the safety and efficacy of Risdiplam in our adult cohort of SMA patients.

Materials and Methods: The inclusion criteria were clinical and molecular diagnosis of SMA2/SMA3, SMN2 copy numbers <4, availability of clinical data, and specific motor scale assessments [Hammersmith Functional Motor Scale Expanded (HFMSE), Revised Upper Limb Module (RULM), six-minute walking test (6MWT)] at treatment baseline, after six months (T6), and one year (T12). Responders were defined as individuals showing an improvement of at least 3 points on the HMFSE, at least 2 points on the RULM score, or at least 30m on the 6MWT from baseline.

Results: We included 18 patients (9 SMA2 and 9 SMA3), with median age 41 (IQR 36-47) years at the first administration (only 4 were walkers). 13 out of 18 patients reached 12 months follow-up. HFMSE significantly increased from T0 to T6 (p=0.027) and from T0 to T12 (p=0.046). The RULM did not improved from T0 to T6, but significant improvement was observed at T12 (median values: 15.5, IQR: 8-22 vs 19, IQR: 13-25, p=0.031). No changes in the 6MWT were detected at T6 or T12 in walking patients. At T6, 10 out of 18 patients (59%) were classified as responders, and at T12, 9 out of 13 patients (69%). Among all demographic and clinical variables, the number of SMN2 copies was independently associated with clinical improvement at T6 (p=0.023) and T12 (p=0.045). No severe adverse events were reported.

Discussion: The natural history of types 2 and 3 SMA involves disease progression and continued loss of function. In patients with prolonged disease duration, early improvements are not expected. In our cohort of adult SMA patients, Risdiplam showed efficacy in improving or stabilizing motor symptoms, as demonstrated by the positive changes in HFMSE and RULM, even in a relative short follow-up.

Conclusions: Our data highlight the safety and efficacy of Risdiplam even in the first year of treatment, regardless of age, gender, functional clinical status at baseline, and SMA type. Number of SMN2 copies influence positively clinical improvement.

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## 3D-STEM CELL SPINAL CORD MODEL TO STUDY THE THERAPEUTIC MECHANISMS OF RISDIPLAM-LIKE COMPOUND FOR SPINAL MUSCULAR ATROPHY

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Our study aimed at improving the treatment of Spinal Muscular Atrophy (SMA) by investigating the efficacy of a Risdiplam-like compound on 3-dimensional (3D) spinal cord model. SMA is a severe neurological disorder characterized by early onset and degeneration of lower motor neurons due to mutations in the SMN1 gene. To reproduce reliable human models, we generate and phenotypically characterize human spinal cord organoids from induced pluripotent stem cells (iPSCs) of SMA type 1subjects (n=3) and healthy controls (n=2). Our analysis revealed that SMA presents a pervasive cellular and molecular developmental alteration in multiple cell populations, including neural progenitors, beyond motor neurons. This was ascertained using bulk transcriptomics, single cells RNAseq, and multi-electrodes array analysis, along with immunophenotypic characterization. Treatment was started at different time points during the first 80 days of organoid development which parallels the first trimester post conception and was provided as daily therapy every two days. Our preliminary results demonstrated that 1) Risdiplam-like compound models ~ 15% of disease affected genes; 2) long-term in vitro treatment is well-tolerated; 3) ratio between full length SMN2 and Δ7 is robustly established; 4) pathological hallmarks are restored, all in all supporting the idea that SMA organoids represent a reliable model to explore drug kinetics and efficacy. Further, exploiting organoids, our study highlights the early-onset and pervasive developmental nature of SMA pathogenesis, which should be considered in therapeutic perspectives. Optimizing Risdiplam therapy for all SMA patients and developing combined therapeutic approaches is very useful and can be achieved by understanding the complex mechanisms of the drug's action. Our study contributes to the optimization of Risdiplam therapy and to the identification of complementary treatment targets for SMA patients.

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## ACOUSTIC VOICE ANALYSIS AS A USEFUL PROGNOSTIC TOOL TO DISCRIMINATE DIFFERENT ALS PHENOTYPES

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Objectives: To evaluate the role of acoustic voice parameters as prognostic biomarker in clinical phenotypes of Amyotrophic Lateral Sclerosis (ALS) disease.

Materials and methods: We recruited thirty-six ALS patients and twenty healthy controls (HCs). Exclusion criteria included severe dysarthria, cognitive dysfunctions, hearing impairments. ALS patients were categorized into prevalent upper (pUMN) or lower (pLMN) impairment based on the median value of the Penn Upper Motor Neuron Score and the site of onset. The assessed acoustic voice parameters were Triangular Vowel Space-Area (tVSA), Alternating Motion Rates (AMR), and Sequential Motion Rates (SMR). Dysphagia severity was evaluated using the ALSFRS-r bulbar subscore and the Dysphagia Outcome and Severity Scale (DOSS). We compared the acoustic voice parameters between ALS patients and HCs, pUMN and pLMN patients, and patients with different onset types: bulbar-onset (B-ALS), spinal-onset without bulbar symptoms (S-ALS), and spinal-onset with bulbar symptoms (generalized-S-ALS) during clinical evaluation. Additionally, correlations were performed between acoustic voice parameters and clinical scales.

Results: All ALS patients showed significantly lower values of tVSA, AMR, and SMR compared to HCs ($p<0.005$). The subgroup of ALS patients with pUMN had significantly lower values of tVSA, AMR, and SMR than pLMNs. Among the acoustic parameters, tVSA showed higher accuracy in discriminating between pUMN and pLMN patients (AUC: 0.83, CI: 0.707–0.965, $p<0.001$). No differences in tVSA were observed based on the site of onset. B-ALS patients had significantly lower values of AMR and SMR compared to generalized-S-ALS, while these latter had lower values compared to S-ALS without bulbar symptoms. Furthermore, AMR and SMR positively correlated with ALSFRS-r bulbar subscore (/pa/ rs= 0.554, p= 0.001; /ta/ rs= 0.467, p= 0.005; /ka/ rs= 0.479, p=0.004; /pataka/ rs=0.427, p=0.011) and DOSS (/pa/ rs= 0.620, $p<0.001$; /ta/ rs= 0.574, $p< 0.001$; /ka/ rs= 0.614, $p< 0.001$; /pataka/ rs=0.566, $p<0.001$).

Discussion: Our study demonstrated that acoustic voice analysis can be considered a sensitive biomarker to distinguish ALS patients from HCs, and among the ALS cohort, to differentiate those with spastic and flaccid dysarthria, particularly using tVSA. Lower values of AMR and SMR were associated with higher bulbar impairment, as observed in ALS patients with B-ALS and generalized-S-ALS or in ALS patients with lower ALSFRS-r bulbar score and lower DOSS.

Conclusions: Acoustic voice analysis may serve as a useful prognostic tool to differentiate between spastic and flaccid dysarthria and assess the degree of bulbar involvement in ALS.

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## FLEXIBILITY OF BRAIN DYNAMICS AS A PREDICTOR OF CLINICAL IMPAIRMENT IN AMYOTROPHIC LATERAL SCLEROSIS: A SOURCE RECONSTRUCTED MEG STUDY

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Background and Objectives: Amyotrophic Lateral Sclerosis (ALS) is a multisystem disorder characterized by neurodegeneration of the whole brain. Normally, the brain dynamically reconfigures over time by large-scale bursts of activations, called neuronal avalanches [1] and defined as events starting when at least one brain region deviates from its baseline activity, and ending when all areas are back to normal activity. Conversely, neurological diseases induce stereotyped brain dynamics which, in turn, are linked to clinical impairment. Based on recent evidence showing that functional brain networks become more connected as ALS progresses [2], we hypothesized that less flexibility in brain dynamics could predict symptoms severity.

Materials: The brain activity of 42 ALS patients and 42 healthy controls was recorded by magnetoencephalography (MEG) [3]. Magnetic resonance (MR) scans were also acquired, and MEG and MRI data were used to reconstruct time series related to the regions of interest. Then, we used source-reconstructed MEG signals to quantify brain flexibility through the functional repertoire. More specifically, an avalanche pattern is the set of all brain areas recruited during the avalanche, while the functional repertoire is the set of unique avalanche patterns.

Method: The activity of brain areas was reconstructed in the classical frequency bands, and the functional repertoire was estimated to quantify spatio-temporal fluctuations of brain activity. Finally, we used the size of the functional repertoire to build a k-fold cross-validated multilinear model to predict the clinical impairment.

Results: We found a reduced functional repertoire in ALS patients compared to healthy controls, resulting in more stereotyped brain dynamics. The size of the functional repertoire correlated with clinical scores in the ALS group in both delta and theta frequency bands. Furthermore, the functional repertoire predicted both clinical staging and symptoms severity when we used a k-fold cross-validated multilinear regression model.

Discussion: In our work, we demonstrated that the pathophysiological processes of ALS reduce brain flexibility and that the smaller size of the functional repertoire predicts both disease stage and symptoms severity, even after accounting for age, education, gender, disease duration, phenotype and ECAS. This approach could provide a non-invasive tool to quantify alterations in brain dynamics in ALS and, possibly, other neurodegenerative diseases.

Conclusions: In the context of personalized medicine, our approach could serve to adapt large-scale mechanistic models to individual patients. Furthermore, neuronal avalanches can be also observed using EEG, which might allow the application of our methodology on a broader scale.

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## A CASE OF LATE-ONSET NEMALINE MYOPATHY (SLONM) ASSOCIATED WITH MOTOR NEURON DISEASE: A CASUAL OR CAUSAL LINK?

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Introduction: Sporadic late-onset nemaline myopathy (SLONM) is a rare condition characterized by the presence of nemaline bodies in muscular biopsy. It can be inherited in an autosomal dominant/recessive manner and is caused by mutations in at least 12 genes, with the most common forms associated with genes encoding skeletal-muscle-α-actin (ACTA1) and nebulin (NEB). There have been occasional reports of an association between nemaline myopathy and motor neuron disease (MND), which could either be coincidental or indicate a relationship between these two conditions.

Case description: We present the case of a 52-year-old patient with a history of idiopathic juvenile arthritis since childhood. The patient had undergone left-hip prosthesis implantation, which resulted in partial relief of symptoms. Since January 2020, the patient has experienced progressive weakness in the lower limbs, which later extended to the upper limbs, accompanied by gradual respiratory fatigue. A muscular biopsy conducted in April 2022 revealed "central core primitive myopathy," and genetic testing showed a heterozygous variant of uncertain significance in the NEB gene, suggestive of Nemaline Myopathy type 2. The patient's symptoms progressively and rapidly worsened, leading to hospitalization in August 2022 due to acute restrictive respiratory failure. Nocturnal non-invasive ventilation was subsequently required. Electromyography revealed a chronic neurogenic pattern with acute denervation. Further evaluation and neurological examination revealed anserine gait, absence of bulbar signs, weak reflexes, weakness in left thigh flexion, bilateral dorsal feet flexion, spontaneous fasciculations in lower limbs. Brain MRI with Diffusion Tensor Imaging sequences showed depletion of the corticospinal tracts (CSTs), and Motor Evoked Potentials (MEPs) revealed subclinical damage of the upper motor neurons. Muscle MRI also indicated initial fibrous fatty muscle degeneration in both thighs. Based on these overlapping features, the patient was diagnosed with central core myopathy with a coexisting motor neuron disease.

Discussion: The clinical features, genetic tests, and muscular biopsy findings supported a diagnosis of SLONM. However, the rapid clinical deterioration and progressive respiratory fatigue raised concerns about the possibility of coincidental disorders. Electromyography indicated a potential overlap between end-stage disease myopathy MND. This was further supported by CST thinning on MRI and abnormal central motor conduction time, as evidenced by MEPs.

Conclusions: The relationship between skeletal muscle damage and MNDs remains unclear. It is uncertain whether there is an interplay between the conditions or if the observed association is coincidental. Further research is needed to explore the possible role of skeletal muscle degeneration in the etiopathogenesis of MND.

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## TRANSITION PROGRAM TO ADULT CARE FOR YOUNG PEOPLE WITH NEUROMUSCULAR DISEASES IN TUSCANY

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Aims: For patients with rare diseases, the transition phase from the pediatric care specialist center to the adult neurologist represents a complex and sensitive process involving patients in their late-childhood and adolescence age, caregivers, and health professionals, were disease-specific physical and cognitive needs, age-related changes and health system differences need careful integration and a gradual transformation. Unfortunately, in many cases this delicate moment remains subject to casualty or personal involvement and efforts of patients, families, associations, and healthcare professionals, facing the lack of a structured, dedicated, and progressive route. In present time, given the progress in therapeutic and global care of patients, life expectancy and quality of life have expanded, so that an abrupt change of direction or loss of patients once they reach young adulthood is no more acceptable.

Methods: In this framework we developed the project of a dedicated program for case management of "transition" patients with different form of neuromuscular diseases (NMD). The project involves the Neurology Unit AOUP, center for adult patients, and the Metabolic and Hereditary Diseases Unit of Meyer Hospital and Neurology and Rare Diseases Unit of IRCCS Stella Maris, both for pediatric patients. All the three are regional reference Centers for diagnosis and care of NMD. Based on the disease prevalence and number of patients followed at the Centers, we plan to include in a period of three years an estimated number of 60 NMD young patients.

Results: During the project development, the various health care professionals (neurologist, childhood neuropsychiatrist, cardiologist, pneumologist, physiotherapist, biologist, and others, to be tailored based on each case's specific needs) involved in global care of NMD patients will be identified and included in a multidisciplinary team. Patients will be evaluated firstly in the same time both by the childhood neurologist and the adult neurologist and in the pediatric Center. Subsequently, the following examinations will occur at the adult Center in Pisa.

Conclusion: Recording of diagnostic and functional parameters during this peculiar phase of our patients' life will provide a better knowledge on how to optimize global management but also on disease natural history.

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## NEW CELLULAR IMAGING-BASED BIOMARKERS FOR SPG4 SUBTYPE OF HEREDITARY SPASTIC PARAPLEGIA

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Aims: Microtubule defects are a common feature in several neurodegenerative disorders, including hereditary spastic paraplegia (HSP). The most frequent form of HSP is caused by mutations in the SPG4/SPAST gene, encoding the microtubule severing enzyme spastin. To date, there is no effective therapy available but spastin-enhancing therapeutic approaches are emerging [1,2] thus prognostic and predictive biomarkers are urgently required.

Materials and Methods: We have developed an automated, simple, fast and non-invasive cell imaging-based method to quantify microtubule cytoskeleton organization changes in lymphoblastoid cells (LCLs) and peripheral blood mononuclear cells (PBMCs).

Results: LCLs and PBMCs from individuals affected by SPG4-hereditary spastic paraplegia show a polarized microtubule cytoskeleton organization. In a pilot study on LCLs and PBMCs, our method discriminates SPG4-HSP from healthy donors and other HSP subtypes. In addition, it is shown that our method can detect the effects of spastin protein level changes [3].

Discussion and Conclusions: These results open the possibility to develop a test useful to recognize SPG4-hereditary spastic paraplegia subtype and evaluate the effects of spastin-enhancing drug in non-neuronal cells. We will extend these analyses to a large cohort of patients to perform clinical and molecular correlations to identify non-invasive diagnostic, prognostic and predictive biomarkers.

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## PROGNOSTIC USEFULNESS OF MOTOR UNIT NUMBER INDEX (MUNIX) IN PATIENTS NEWLY DIAGNOSED WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)

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Introduction: Amyotrophic lateral sclerosis (ALS) has a highly heterogeneous clinical course, and this diversity has been brought up as a possible cause for the failure of most clinical trials to date. Motor Unit Number Index (MUNIX) is a non-invasive EMG technique that can estimate the number and size of surviving motor units (MUs). Previous studies on ALS found correlations between MUNIX and several clinical measures, such as the ALSFRS-R (1), but its potential role as a predictor of disease progression rate (DPR) [obtained as "ΔALSFRS-R (48-observed score)/disease duration (months)"] has not been evaluated so far. We aimed to investigate MUNIX's ability to predict DPR at six months.

Methods: We enrolled 24 ALS patients followed-up at two Brescia University Centers with short disease duration (<24 months from symptoms' onset); they underwent MUNIX on 5 muscles (abductor pollicis brevis, abductor digiti minimi, first dorsal interosseus, tibialis anterior, trapezius). DPR was calculated six months after baseline. Multivariable linear and simple logistic regression analyses were used to assess MUNIX parameters as predictors of DPR at six-month follow-up.

Results: MUNIX was found to predict DPR at follow-up ($\beta$=-0.228, p=0.033), along with baseline DPR and ALSFRS-R values, while no other variable considered (gender, age, bulbar site of onset, use of riluzole) showed the same ability. Precisely, patients with lower MUNIX values at baseline displayed the greatest DPRs after six months. The result was replicated considering the dichotomic category "MUNIX-Low" (derived using the sample's median as cut-off) as the independent variable and the outcome "Fast progressors" (with DPR $\geq$ 1.1) as the dependent variable.

Discussion: The application of MUNIX to a relative "early ALS" cohort (disease duration: 13 months, median) makes our results applicable to the setting of clinical trials in which patients more likely to be eligible for disease-modifying pharmacological interventions are those newly diagnosed. Our study demonstrates that the presence of few surviving MUs in the first months after the onset of symptoms reflects a rapidly evolving process.

Conclusion: Our preliminary findings pave the way for the use of MUNIX examination as a prognostic tool in early ALS, enabling patients' stratification according to their rates of future decline.

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## ECULIZUMAB FOR IMMUNE CHECKPOINT INHIBITORS (ICIS)-RELATED MYASTHENIA GRAVIS

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Immune-check point inhibitors (ICIs) have been increasingly used in advanced or non-responsive tumors with promising results. Among them, Pembrolizumab is a humanized monoclonal immunoglobulin (Ig)G4 antibody directed against human cell surface receptor PD-1

(programmed cell death-1), an inhibitory signaling receptor expressed on the surface of activated T cells. Regardless of this breakthrough therapy, ICIs could cause immune-related adverse events (irAEs) or reactivate pre-existing autoimmune conditions, including Myasthenia Gravis (MG). Beyond classical therapies, complement inhibitors like Eculizumab represent a new frontier of treatment in MG, especially in patient with multiple comorbidities that cannot receive high dosage steroids and other immunosuppressive agents. Herein we report on a case of a 76-year-old male affected by generalized anti-AchR positive Myasthenia Gravis (MGFA IIb) successfully treated for 4 years with prednisone and azathioprine. He also received a diagnosis of metastatic colorectal cancer at the age of 74 unsuccessfully treated with surgery and first-line chemotherapy. For this reason, an ICI (Pembrolizumab) was started with remarkable tumor remission and azathioprine was discontinued. After the first two Pembrolizumab infusions, MG symptoms relapsed showing complete bilateral ptosis and ophthalmoplegia, fatigable dysarthria and swallowing impairment. IVIG (2 gr/kg) was started with mild clinical improvement. Therefore, a third line therapy with complement inhibitor (Eculizumab) was started. After three months therapy, MGADL and QMG improved from 15 to 9 and from 21 to 16 respectively. Neurologic irAEs related to use of ICIs are rare but often severe and can require discontinuation of ICIs. Immunomodulatory therapies, such us high dose steroids and immunosuppressants, as well as plasma exchange, are not allowed during ICIs treatment because can interfere with their efficacy. MG onset and relapse has been often described after ICIs treatment, also in association with myositis and/or myocarditis. Among MG treatments, Eculizumab is a new available drug and does not interfere with ICIs mechanism of action. Eculizumab resulted to be a good choice able to control MG symptoms without hindering Pembrolizumab action. So, are complement inhibitors suitable for ICIs-related Myasthenia Gravis?

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## COMPARATIVE ANALYSIS OF PLASMA MIRNA SIGNATURES IN AMYOTROPHIC LATERAL SCLEROSIS


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Background: Several studies highlight the miRNA's role in Amyotrophic Lateral Sclerosis (ALS) pathology by describing their deregulation in various biological fluids, such as plasma [1]. Furthermore, TARDBP promotes the biogenesis of miRNAs and is fundamentally involved in the pathogenesis of Amyotrophic Lateral Sclerosis (ALS). To detect potential non-invasive preclinical and clinical progression biomarkers in a TARDBP-ALS family, we assessed the expression levels of circulating microRNAs in affected patients and asymptomatic mutation carriers.

Materials and Methods: In this study, we applied qRT-PCR in 7 symptomatic patients (P), eight mutation carriers (C), and 13 healthy controls (HC) to investigate 15 tissue- and disease-specific circulating miRNAs. These are involved in targeting TARDBP or binding TDP-43 during their biogenesis/mature form [2] and are able to classify symptomatic, presymptomatic TARDBP-G376D carriers and healthy members belonging to a large ALS family [3].

Results: Five out of 15 miRNAs were significantly dysregulated between HC and P. Furthermore, 13 out of 15 miRNAs were significantly dysregulated in C; eight were deregulated exclusively in this group. We highlighted the potential of miR-132-5p, miR-132-3p, miR-124-3p, and miR-133a-3p expression levels in serum as biomarkers of preclinical progression for G376D-TARDBP-associated ALS.

Discussion: We identified miRNAs differentially expressed between clinical conditions suggesting that miRNA dysregulation may be used as an early prognostic biomarker for ALS. Interestingly, miR-574-3p, -133B, and -558-3P were identified as significantly overexpressed in C compared with HC, suggesting that the expression of this miRNA is associated with TARDBP mutation. Additionally, -124-3p was significantly deregulated in patients compared with C, which supports the correlation of miRNA-133b expression with the progression of TARDBP-associated disease.

Conclusion: This is the first study evaluating plasma miRNAs expression in a large TARDBP family of HC, C, and P samples. The results showed a specific miRNA differential expression in the symptomatic and asymptomatic mutation carriers compared to healthy controls, underlining a probable peripheral signature capable of stratifying the disease progression.

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## PHENOTYPIC SPECTRUM OF THREE UNRELATED SMA ITALIAN PATIENTS WITH A COMPOUND HETEROZYGOSITY FOR A DELETION AND RARE MISSENSE MUTATION IN SMN1 GENE


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Objective: Spinal muscular atrophy (SMA) is caused by mutation of the survival motor neuron (SMN) gene and in only the remaining 5% there is an intragenic mutation.

Materials: We analyzed the phenotypic spectrum of three unrelated SMA patients with missense mutation (exon 7 c.840C>T) in SMN1 which causes its conversion to SMN2.

Methods: For the genetic analysis we used (MLPA) and (NGS) while for the clinical evaluation the (HFMSE) and the (RULM).

Results: In our cohort twenty-four SMA patients we found three patients (2M/1F) with the deletion of exons 7 and 8 of SMN1 and a rare missense mutation (exon 7 c.840C>T). All patients had 2 copies of SMN2.

Discussion: One of two male patients with large deletion in NAIP gene, shows the most severe phenotype (SMA II) and at last neurological examination his score at HFMSE is 14 and RULM is 17. The other two patients were classified as SMA III, but their clinical severity was very different: the male's scores was 18 at the HFMSE and RULM was 24 while the female patient showed a milder phenotype and presents HFMSE score 60 and RULM 38.

Conclusions: The rare point mutation (exon 7 c.840C>T) occurs more frequently than described previously (< 3%) and there is the same phenotypic variability for patients presenting the homozygous deletion but male subjects are worse off than female ones. This could be explained by the deletion of the NAIP gene but the difference between the other male and the female remains substantially unexplained.

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## VAGUS NERVE HIGH RESOLUTION ULTRASONOGRAPHIC FEATURES IN DIFFERENTIATING PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS FROM INFLAMMATORY AND HEREDITARY NEUROPATHIES


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Background and aims: High Resolution Ultrasound (HRUS) represent an easy noninvasive tool for in vivo detection of peripheral nerve changes in several diseases. Our aim was to evaluate sonographic features of Vagus Nerve (VN) trunks in patients with Amyotrophic Lateral Sclerosis (pALS) in an attempt to assist discrimination between pALS from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and Charcot-Marie-Tooth disease (CMT).

Material and Methods: We scanned and measured the caliber (cross-sectional area, CSA) and perimeter of the VN in 10 consecutive pALS, in 10 pt. with CIDP and 4 pt. with CMT using HRUS imaging. Evaluation were performed by blinded raters using a Telemed Echo-wave II or an Esaote MyLabGamma device in conventional B-Mode with a 19 MHz probe.

Results: In both sides, the VN-CSA was larger in CMT and CIDP compared to pALS (7.3 and 6.4 mm2 respectively versus 4.4 mm2; p <0.001); the perimeter was also greater (9.7 and 8.9 mm versus 7.5; p <0.001). Moreover, these data provides evidence that nerve imaging are different in pALS from those with CMT and CIDP.

Discussion and Conclusion: Our findings provide evidence that VN's US CSA and perimeter in pALS differs from other neuropathies and has the potentials to differentiate between ALS and CMT or CIDP and may represent a robust diagnostic marker even in very small-sized samples. Moreover, HR HRUS represent a non-invasive easy imaging modality of screening and a possible interesting additional value with other instrumental method to disentangle the spectrum between more inflammatory or more degenerative disease variants.

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## INVESTIGATION OF UNPLEASANT SENSATION PERCEPTIONS AMONG PATIENTS AFFECTED BY AMYOTROPHIC LATERAL SCLEROSIS (ALS), DURING CLINICAL TRIALS PROCEDURES


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Introduction: ALS diagnosis is considered a traumatic life event for both the patient and their next-of-kin/carers, due to the lack of treatment for. Clinical Trials can offer pioneering treatment to reduce the impact of the disease and improve future treatments worldwide. Research protocols may involve routine diagnostic and/or therapeutic procedures which the patients may be already aware of and, therefore, expecting specific sensations. These could compromise participation or drop-out rate. Despite everything, participation in a clinical trial can guarantee continuity of care also thanks to the execution of these same procedures, through preferential access compared to other patients.

Aim: To investigate the perception of unpleasant sensations during procedures in clinical trials of ALS patients. Analysing what type of pain/discomfort frightens patients during diagnostic and/or therapeutic procedures in ALS clinical trial, including the different methods of administration of the study drug.

Methods: Descriptive phenomenological study and data will be analysed according to Sundler's method. Based on the experience of the researchers and the recommendations proposed by Sandelowski, a total of 20 interviews are estimated in order to reach the theoretical saturation per category of reference. Data collection will be carried out through in-depth semi-structured interviews recorded (13 open-ended questions after the execution of the procedures).

Expected Results: The identification of painful/unconformable procedures will help patients' retention in ALS clinical trials and improve patients' experience and mental health, while increasing adherence and reducing dropouts. Furthermore, this could enhance adherence to the clinical trial pathway, through the reduction of anxiety states generated by annoying/painful procedures. Provide data to implement

effective therapy and offer constant patients support throughout ALS specific and needed procedures. Evaluate if this support could influence adherence rate of ALS patients to conduct clinical trials as required.

Conclusion: This study could holistically evaluate the quality of care and the taking charge of patient problems by the nurses and medical team. Implementing strategies, multidisciplinary care, and assistance. This study could provide information for future studies to create an ALS Clinical Trials multiple-retention-factors adherence scale. Moreover, the study could help create and implement an ALS-specific pain scale accounting for its impact on daily activities, aiding an interdisciplinary approach of pain management. Identify the best pain management strategies and compliance techniques to address ALS, not merely in clinical trials. Provide the best individualised care for ALS patients improving their quality of life and mental state, as well as those of the caregivers.

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## FOOT DROP AS PRESENTING MOTOR SYMPTOM OF CERVICAL SPONDYLOTIC MYELOPATHY


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Background and aims: Cervical spondylotic myelopathy (CSM) is a neurologic condition developing insidiously when degenerative spinal alterations cause medullary compression. Typical manifestations include sthenic and sensory deficits from the level of compression downwards, as well as upper motor neuron signs. Lower limb muscle weakness is most frequently seen in proximal areas such as the iliopsoas muscle and the quadriceps, whereas more distal muscle weakness is less frequently reported in literature. Here we present a case of CSM with foot drop as presenting motor symptom.

Case report: A 74-year-old man presented with distal upper and lower limb paraesthesia and hypoesthesia, developed over the course of seven months, and left foot drop, present for two months, causing gait instability with left steppage. The neurological examination found diffuse mild muscle weakness, mostly scoring 4/5 at the MRC scale. It also demonstrated hyperreflexia at four limbs, Hoffmann sign, Babinski sign and Achilles clonus. Initially the case was suggestive for a deficiency-related neuropathy; the patient presented an inadequate diet and lost over 10 kilos in one year following a personal mourning. Blood tests found no significant deficiency of vitamin B12 or folic acid; a brain CT scan showed no major alterations. The nerve conduction study showed normal conduction of sensory and motor nerve trunks at four limbs, including left external popliteal sciatic nerve (EPSN). The electromyographic examination documented lack of voluntary muscle activation of the left anterior tibial muscle. The patient underwent a cervical MRI which showed retrolisthesis of the C4 vertebra on C5, resulting in stenosis of the spinal canal with compressive myelopathy at that level.

Results: We presented a case of insidious onset of upper and lower limbs paraesthesia and hypoesthesia, diffuse mild muscle hyposthenia and severe left foot dorsiflexion deficit. The symptomatology seemed suggestive for a deficiency-related neuropathy; left foot drop could also have been explained by EPSN compression due to the recent weight loss caused by malnutrition. The neurological examination showed signs of upper motor neuron suffering at four limbs, and neurophysiological examinations showed no signs of abnormal nerve conduction. Spine cervical MRI found compressive myelopathy at C4-C5 level, congruous with the patient's symptomatology.

Conclusions: CSM should be suspected in slowly progressive sensitive and motor disorders. While most reported cases involve proximal lower limb motor involvement, more distal lower limb involvement can be seen rarely. Nerve conduction studies and spinal MRI are fundamental tools to lead to a correct diagnosis.

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## HIGH-CONTENT SCREENING APPLIED TO MUSCLE PATHOLOGY


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Introduction: Through the use of a high throughput microplate imager for high-content analysis (HCA), it is possible to acquire, analyze, and manage fluorescence, brightfield and digital phase contrast images, providing information about nuclei acids, proteins, organelles, cell metabolism and structure. It is also possible to obtain discrimination of phenotypes not only in 2D cultures but also in 3D samples of tissues and cultures, providing a machine-learning based automated analysis of the desired features. To date, the HCA system has been mostly used in physiology, pharmacology, and infectious diseases studies, but there are few data in literature about its application on muscle pathology.

Materials and Methods: We selected five frozen muscle biopsies and five myoblasts cultures lines acquired for diagnostic purpose from patients referring to the Neurology Clinic of AOU Pisan. We studied nuclei number and position with DAPI, muscle fibers and myoblasts' structure and dimension with actin and components of the cell membrane, mitochondria with Mitotracker and autophagy with LC3B by using Operetta CLS.

Results: We are obtaining preliminary results about automated detection of cells number, dimension, nuclei number and position, autophagy, and mitochondrial function. The system correctly analyses regular slices from frozen muscle biopsy samples and cell cultures. Preliminary analyses on the parameters at study reflect the expected results in correlation with histopathology and genetic diagnosis.

Conclusion: Based on the acquired results, we will take advantage of the innovative high content screening system to analyze altered gene expression of the autophagy and mitochondria pathways in myoblasts obtained from muscle biopsies of patients with late onset Pompe disease and selected interfering RNAs (shRNAs and siRNAs) will be applied to identify druggable targets.

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## PLASMA GFAP INCREASE IN AMYOTROPHIC LATERAL SCLEROSIS REFLECTS A CONCOMITANT ALZHEIMER'S DISEASE PATHOLOGY

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Objective: Recent data show that plasma p-tau181 levels in amyotrophic lateral sclerosis (ALS) are independent from a concomitant Alzheimer's disease (AD) pathology, probably reflecting a peripheral axonal degeneration [1]. Glial fibrillary acid protein (GFAP) is an established biomarker of astrocitopathy and was found increased in AD patients. Here we aimed to study the plasmatic levels of GFAP in ALS patients and investigate their accuracy in discriminating ALS patients with an AD co-pathology.

Methods: We included 156 patients diagnosed with ALS [1] with both plasma and cerebrospinal fluid (CSF) samples available at diagnosis, and 48 age and sex-matched controls. Plasma GFAP and p-tau181 and plasma/CSF neurofilament light chain (NfL) levels were measured with the Single molecule array (Simoa) technology. CSF AD biomarkers were determined through automated chemiluminescent enzyme immunoassay. Patients were stratified according to the ATN classification [2] using in-house validated cutoffs. The CSF Aβ ratio was calculated as Aβ42/Aβ40 multiplied by ten.

Results: Plasma GFAP levels were significantly higher in ALS patients than controls ($p<0.001$). In ALS, plasma GFAP values correlated with age at sampling ($\beta=0.026$, $p<0.001$) and were higher in patients showing a concomitant frontotemporal dementia ($p=0.04$). Plasma GFAP was moderately associated with CSF Aβ ratio (rho=-0.34, $p<0.001$) and resulted associated with a poor prognosis (HR 2.46, $p<0.001$). Stratifying ALS patients according to their A and T status, we found 20 ALS patients (12.8%) showing a positive amyloid status (A+ profile), with 9 of them (5.8% of the whole ALS cohort) also having a CSF profile suggestive of a tau deposition (A+T+ profile). In the multiple-group comparison, plasma GFAP significantly differed among A+T+, A+T-, A-ALS patients and controls, with each A+ subgroup showing higher values than controls ($p<0.001$) and A- subjects ($p<0.001$ for A+T+, $p=0.02$ for A+T-). GFAP was slightly different between A-ALS patients and controls, with a trend of significance ($p=0.07$). Plasma GFAP showed the highest accuracy (AUC 0.932±0.027) among the examined plasma biomarkers in identifying ALS patients with a full-blown AD (A+T+) co-pathology ($p<0.001$ vs. p-tau181 and NfL). Interestingly, A+T+ ALS patients showed significantly lower cognitive performances, with lower total equivalent scores at Edinburgh Cognitive and Behavioural ALS Screen ($p=0.04$), at Mini Mental State Examination ($p=0.03$) and at visual memory tests ($p=0.01$).

Conclusions: ALS A+T+ patients may show a different cognitive profile; therefore, their identification might be useful in clinical practice. Plasma GFAP could serve as an accessible and high accurate biomarker of amyloid co-pathology in ALS.

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## SEASONALITY IN ALS MORTALITY: A TIME-SERIES ANALYSIS USING DIFFERENT METHODS

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Aim: Seasonal patterns in ALS mortality have been poorly studied[1]. However, identifying any periodicity would be beneficial in enhancing the surveillance of these patients. Here we analyzed the seasonality of ALS patients mortality using a large population-based cohort.

Methods: Data from the Piemonte and Valle d'Aosta ALS Register (PARALS) were used[2]. All patients who received the ALS diagnosis from 1995 to 2020 were considered. The average mortality during each Gregorian month and during each season were compared using a chi-square test. We also performed seasonal decomposition using moving averages to specifically detect periodical patterns[3].

Results: A total of 3417 patients were considered. The average number of deaths showed a seasonal variation, with lower frequencies during the late summer and early autumn months (July 8.95±3.51, 7.49%, deaths, August 9.13±2.72, 7.63%, September 8.38±3.20, 7.02%), increased thereafter and reaching a peak in December (11.25±3.64 deaths, 9.41%) and January (11.12±3.76)($p=0.06$). Accordingly, similar results were found when comparing seasons ($p = 0.07$). However, this trend was not consistent throughout the entire follow-up period. Accordingly, the seasonal decomposition did not reveal any seasonality when considering months or the canonical seasons.

Discussion. Our findings suggest that ALS mortality could be lower during the late summer months (July to September) and higher in December. However, these results are not consistent across all years and months, making it difficult to accurately predict such events.

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## ADVANCED CARE PLANNING FOR MECHANICAL INVASIVE VENTILATION IN AMYOTROPHIC LATERAL SCLEROSIS IN BERGAMO PROVINCE

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Objective: Given the often-predictable respiratory involvement in the course of motoneuron disease (MND), an early and accurate advanced care planning (ACP) for mechanical invasive ventilation is recommended. Despite this, data of the literature show low rates of ACP in MND patients. Aim of this study is to assess rate and relative results of ACP for mechanical invasive ventilation in our centre.

Materials: Medical records of MND patients attending the Papa Giovanni XXIII Hospital of Bergamo (Italy) were reviewed.

Methods: We performed a descriptive retrospective study collecting data of all the patients with a clinically and neurophysiologically established diagnosis of MND, attending our centre from the 1st of January 2019 to the 31st of December 2022. Demographic, clinical and ACP data were collected.

Results: Of 233 patients identified, 142 are male (60,94%) and 91 are female (39,06%). Patients with a diagnosis of Amyotrophic Lateral Sclerosis (ALS) were 179; 16 patients have an Upper Motoneuron Disease, 36 have a Lower Motoneuron Disease and 2 a Brown-Vialetto-Van Laere Syndrome diagnosis. Of the 233 patients 130 expressed ACP (55,79%), of whom 4 in an emergency setting, at the mean age of 67. Among 130 ACP expressed, 35 were favourable to the mechanical invasive ventilation, while 83 were against it. 12 patients were undecided All the whishes expressed in the ACP were respected except in one case. 40 patients died without ACP, of whom 15 in 2020.

Conclusions: Our rate of expressed ACP is higher than that generally reported in the literature in ALS patients. However a small number of patients died without ACP.

Discussion: The covid pandemic may have contributed to the missed ACP. Nevertheless a constant and multidisciplinary effort is mandatory to lead MND patients through the most difficult choices.

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## PHOSPHORYLATED TAU IN PLASMA AS BIOMARKER OF AMYOTROPHIC LATERAL SCLEROSIS

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Objectives: To measure plasma P-tau181 (pP-tau181), which has recently been proposed as ALS biomarker, in a cohort of deeply phenotyped patients with ALS, analyzing its relationships with clinical phenotype, neurophysiological, respiratory, and neuropsychological measures, as well as other biochemical parameters, including serum levels of NFL and GFAP.

Materials: Retrospective cohort of 29 (M = 17, F = 12) sporadic ALS (sALS) patients.

Methods: pP-tau181 was quantified using the new fully automated Lumipulse assay on the Fujirebio G600II instrument.

Results: pP-tau181 levels correlated positively with a clinical lower motor neuron (LMN) score (r = 0.3803; 95% CI, 0.004710 - 0.6619; p = 0.0418), and negatively, albeit not significantly, with a composite index of muscle strength (p = -0.3416; 95% CI, -0.6457 - 0.05589; p = 0.0811; N = 27), but not with Penn Upper Motor Neuron (UMN) Score (p > 0.05). Accordingly, pP-tau181 correlated with electromyographic indices of spinal active (r = 0.4507; 95% CI, 0.08965 - 0.7071; p = 0.0141) and chronic denervation (r = 0.3864; 95% CI, 0.01178 - 0.6659; p = 0.0384), as well as with the index of active denervation of the lumbosacral region (r = 0.4882; 95% CI, 0.1371 - 0.7303; p = 0.0072), but not with transcranial magnetic stimulation parameters of UMN dysfunction (p > 0.05 for all). pP-tau181 levels did not correlate with those in the CSF, serum NFL or GFAP, CSF/serum albumin ratio, or estimated glomerular filtration rate (p > 0.05 for all), but correlated with plasma creatine kinase levels (r = 0.4661; 95% CI, 0.1089 - 0.7167; p = 0.0108). Finally, while not being associated with neuropsychological phenotype, pP-tau181 correlated negatively with pH (r = -0.5632; 95% CI, -0.8553 - 0.0006245; p = 0.0479) and positively with partial pressure of CO2 (PaCO2; r = 0.7092; 95% CI, 0.2425 - 0.9093; p = 0.0084), HCO3- (r = 0.6667; 95% CI, 0.1651 - 0.8943; p = 0.0152) and base excess (r = 0.6611; 95% CI, 0.1555 - 0.8923; p = 0.0165; N = 13 for all) on arterial blood gas analysis.

Discussion: pP-tau181 has potential as ALS biomarker and could be associated with LMN impairment. Its raised levels might reflect pathophysiological processes (tau hyperphosphorylation and/or release) occurring in the axons of LMNs distantly from the CNS and the CSF. pP-tau181 could also be associated with respiratory dysfunction.

Conclusions: pP-tau181 might be a new biomarker of LMN and respiratory dysfunction in ALS.

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## NOVEL HOMOZYGOUS OPTN MUTATION PRESENTING AS PRIMARY LATERAL SCLEROSIS

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Aims: To describe the unusual genotypic profile of a patient diagnosed with primary lateral sclerosis (PLS).

Materials and methods: The proband underwent clinical, neurophysiological, neuroradiological and neuropsychological evaluation, and DNA collection for next generation sequencing testing.

Results: A 57-year-old man was admitted to the Motor Neuron Centre of our Institute reporting a 4 year history of subtle-onset clumsiness in his right hand with slowly progressive course. Our patient came from consanguineous parents, and his dead father had previously received a diagnosis of Parkinson's disease. The neurological examination showed mild weakness of right hand finger and wrist extensors, mild right arm spasticity, widespread increased deep tendon reflexes with extension of the reflexogenic area at upper limbs, bilateral ankle clonus, and mirror movements during voluntary upper limb activation. Motor and sensory NCS were normal, while needle EMG showed diffuse neurogenic changes in all limbs with no acute denervation potentials apart from left anterior tibialis. Motor evoked potentials revealed significant increase of central motor conduction time at the right extremities and increased cortical excitability. There was no clinical nor neurophysiological sign of bulbar muscle impairment. Cognitive and behavioral profile were normal. Brain MRI showed T2 weighted hyperintensity of the corticospinal tracts which was more evident on the left site, and SWI weighted images revealed hypointensity in the left precentral gyrus ("motor band sign"). The patient fulfilled the current consensus diagnostic criteria for definite PLS [1]. Genetic testing unraveled a novel homozygous single nucleotide deletion (c.523delG) in OPTN (optineurin) gene, which results in a premature stop codon. In silico pathogenicity prediction tools predicted it as likely disease-causing.

Discussion: OPTN gene mutations are an established, although rare, cause of amyotrophic lateral sclerosis (ALS), found both in heterozygosity and homozygosity. OPTN encodes for a protein known to be detectable as part of inclusion bodies in different neurodegenerative disorders including ALS, frontotemporal dementia and Parkinson's disease [2]. Here we describe the first case of PLS associated with a novel OPTN mutation that is predicted to be likely pathogenetic.

Conclusions: Our findings widens the genotypic-phenotypic correlation of ALS variants and suggest that OPTN mutations should be searched also in patients diagnosed with the PLS variant.

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## CLINICAL, NEUROPHYSIOLOGICAL, IMAGING FEATURES AND COMPARISON WITH AMYOTROPHIC LATERAL SCLEROSIS IN A MONOCENTRIC CASE SERIES OF HIRAYAMA DISEASE

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Objectives: Hirayama's disease (HD) is a rare juvenile neurological disorder characterised by weakness and amyotrophy of the distal part of upper limbs. The aim of this study is to better define this clinical entity and assess whether HD should be considered a motor neuron disease or a cervical myelopathy.

Methods: We conducted a retrospective analysis of demographic, clinical, neurophysiological and neuroimaging data. Furthermore, by comparing HD and ALS patients with distal upper limb onset and available median and ulnar nerve CMAP values of abductor pollicis brevis (APB) and abductor digiti minimi (ADM), we calculated APB/ADM and ADM/APB ratios and APB-ADM amplitude difference.

Results: 7 HD patients and 18 ALS patients referring to our Centre were included. Among HD patients 5 were males; mean age at onset was 16,86 years and mean progression time was 3,3 years (SD 4.1). All HD patients showed oblique amyotrophy, while no patients showed lower limb weakness. Cold paralysis was found in 5 out 5 patients and tremor in 5 out of 6. Sensitive impairment and local sweating alterations were reported by 3 and 1 of them, respectively. MRI revealed in all of the cases forward displacement of the posterior dural sac, epidural venous plexus congestion and spinal cord atrophy. HD cases presented younger age at onset ($p<0.001$), higher stature ($p=0.021$) and longer diagnostic delay ($p=0.042$) compared to ALS patients. Finally, we analysed 3 HD and 18 ALS CMAPs, finding a statistically significant difference concerning the APB amplitude (HD=6.603 and ALS=3.186; $p=0.029$), APB/ADM ratio (HD=1.704 and ALS=0.673; $p=0.034$), ADM/APB ratio (HD=0.703 and ALS=1.992; $p=0.034$) and the APB-ADM difference (HD=2.370 and ALS=-1.531; $p=0.005$).

Discussion: In our case series typical MRI patterns have been replicated. These findings suggest that HD could be considered a flection myelopathy, due to forward dislocation of spinal cord with anterior horns' compression and microcirculatory damage. In agreement with literature, all our patients showed sparing of brachioradialis muscles. In line with a trend reported by Singh and colleagues [1], we found that, compared to ALS, HD patients tend to present higher APB/ADM ratios. These neurophysiological findings resulted consistent with the clinical detection of more severe ulnar side muscles wasting ("reverse split hand syndrome").

Conclusion: In case of young patients presenting with distal upper limb weakness, neck-flexion MRI with gadolinium should be considered mandatory, whereas in atypical cases, clinical and neurophysiological features can help in different diagnosis between HD and upper limb-confined ALS.

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## A CASE OF RARE T138A SOD1 MUTATION IN A PATIENT AFFECTED BY AMYOTROPHIC LATERAL SCLEROSIS SHOWING A SLOW CLINICAL PROGRESSION

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Introduction: Amyotrophic lateral sclerosis (ALS) is currently classified as either familial or sporadic. Familial amyotrophic lateral sclerosis (FALS) constitutes 10–15% of cases. Mutations in more than forty genes have been reported to associate with ALS. The most frequent gene involved in FALS is SOD1 encoding the antioxidant enzyme Cu, Zn superoxide dismutase [1]. More than 150 different mutations have been described in SOD1 gene of ALS patients [2]. We report a very rare mutation of SOD1 gene (p. T138A) associated with slow clinical progression.

Case: A 52-years-old male, presented with a three-years history of progressive lower limb weakness and wasting. He had a family history for ALS, his mother and his uncle were affected, and died at 62 and 70-years-old respectively. Neurological examination showed difficult gait, possible without support for 100 meters, lower and distal upper limb weakness and wasting, diffuse fasciculations and positive left Babinski sign. Bulbar and cognitive functions were normal. Blood, cerebrovascular fluid examinations and motor evoked potential were unrevealing. Needle electromyography (EMG) showed widespread fasciculation, fibrillation, PSW potentials and signs of chronic partial denervation at four limbs. Nerve conduction study revealed a mild reduction of compound muscle action potential amplitude of bilateral peroneal nerve. Based on clinical and electrophysiological features, diagnosis of ALS was established and treatment with riluzole started. His Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score was 41/48. At present, six years after onset, the patient is 57 years old, and his disability has slowly progressed. His ALSFRS-R score is 37/48. No cognitive dysfunction or bulbar impairment are noticed. A genetic analysis was performed and the T138A mutation of SOD1 gene was found. Prediction of the pathogenetic role of a T138A mutation was performed using PolyPhen-2 tool and it is classified as "probably damaging".

Discussion: In literature are described only three patients, two of which in the same family, carrying the T138A mutation, all with a slowly progressive ALS phenotype without bulbar impairment [2,3]. Our report confirms the surely T138A mutation's pathogenicity and the ALS phenotype associated with this mutation. Our case has the same clinical phenotype of the others described in literature. It is characterized by slow progression with sparing of bulbar and cognitive function. This report could help to better understand the possible role of SOD1 mutation in ALS etiopathogenesis.

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## SURVIVAL ANALYSIS AND SAFETY PROFILE OF TAUROURSODEHOXYCHOLIC ACID IN ALS PATIENTS: A RETROSPECTIVE POPULATION-BASED COHORT STUDY IN ITALY

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Background: Oral tauroursodeoxycholic acid (TUDCA) is a drug currently tested in Amyotrophic Lateral Sclerosis (ALS). While results of phase 3 clinical trials are awaited [1,2], TUDCA is easily administered and reachable for ALS patients.

Objectives: To evaluate overall survival and safety profile in patients with ALS from Emilia Romagna Region (Italy) treated with TUDCA in a real-world setting.

Design and materials: Multicenter, propensity score–matched cohort study conducted between January 2015 and February 2022 in Emilia Romagna Region (ERR) where a population registry collects key clinical features from all specialized MND centers in the region. Since 2015 in ERR, TUDCA has been prescribed from the same specialized centers after approval from the regional rare diseases technical group. Of the 627 patients screened, 86 patients with ALS treated with TUDCA for at least three consecutive months were matched using propensity score analysis with 172 ALS patients receiving usual care. All patients were residents of Emilia Romagna Region and regularly followed till 1st February 2022.

Methods: Propensity score matching was based on age at onset, sex, phenotype, diagnostic latency, ALSFRS-R at first visit, disease progression rate at first visit, BMI at diagnosis. The exposure was oral TUDCA administration versus standard therapy. The primary study outcome was survival difference between TUDCA exposed and unexposed patients. Secondary outcomes were the rate of decline of ALSFRS-R from onset to last visit and frequency and time to support procedures.

Results: 86 patients assumed TUDCA; 64 were male (74.4%) and mean age was 58.2 years (SD 9.2). Median overall survival time was 49.6 months among TUDCA treated patients (95%CI, 41.7-93.5) and 36.2 months in controls (95%CI, 32.7-41.6), with a lower risk of death for higher dosage TUDCA-exposed patients (HR 0.56; 95% CI, 0.38−0.83; P=0.004). No differences were observed in terms of rate of ALSFRS-r decline or time to support procedures. TUDCA was well tolerated except for a minority of patients (n=7, 8.1%) who discontinued the drug.

Discussion and Conclusions: Real-world evidence studies may provide complementary information to randomized controlled trials, by observing treatment effects for a longer time and consider ALS patients at all stages of disease, without the restrictions of RCT criteria [3]. However, they are limited by their retrospective nature with missing or non-uniform information at irregular time points. This retrospective, propensity score-matched study showed that ALS patients treated with TUDCA may have a survival benefit. These findings need to be confirmed by additional prospective randomized studies.

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## MOVEMENT DISORDERS

### CLINIMETRIC PROPERTIES OF THE ITALIAN VERSION OF THE ALTERNATE VERBAL FLUENCY BATTERY (AVFB) IN PARKINSON'S DISEASE

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Objectives: To evaluate the psychometrics and diagnostics of the Alternate Verbal Fluency Battery (AVFB) [1] in an Italian cohort of non-demented Parkinson's disease (PD) patients, as well as to derive disease-specific cut-offs for it.

Materials: N=192 idiopathic PD patients without dementia or further psychiatric disorders were screened with the Montreal Cognitive Assessment (MoCA) and underwent the AVFB – which includes phonemic, semantic and alternate verbal fluency (VF) tests (PVF; SVF; AVF), as well as a Composite Shifting Index (CSI) reflecting the "cost" of shifting from a single- to a double-cued VF task. Patients were on medication when tested.

Methods: Construct validity and diagnostics were assessed for each AVFB measure against the MoCA. A demographically adjusted score below the inner tolerance limit of the current Italian normative dataset [2] was addressed as the positive state. Internal reliability and factorial validity were also tested.

Results: At αadjusted=.013, MoCA scores proved to be strongly associated with PVF (r(192)=.53; p<.001), SVF (r(192)=.51; p<.001) and AVF (r(192)=.54; p<.001) scores, whilst moderately with the CSI (r(192)=.34; p<.001). The AVFB was internally consistent (Cronbach's α=.77) and underpinned by a single component (67.65% of variance explained); however, an improvement in both internal reliability (Cronbach's α=.86) and fit to its factorial structure (79.44% of variance explained) was observed when dropping the CSI. Demographically adjusted scores [1] on PVF, SVF and AVF tests accurately identified patients with a below-inner tolerance limit MoCA score (5.2%), whilst this was not true for the CSI (PVF: AUC=.91; SVF: AUC=.85; AVF: AUC=.84; CSI: AUC=.58). Disease-specific cut-offs derived on PVF, SVF and AVF adjusted scores [1] (PVF: <29.537; SVF: <38.038; AVF: <25.191) yielded overall optimal diagnostics.

Discussion: This study provides Italian practitioners and researchers with evidence on the psychometric and diagnostics soundness of the AVFB, as to its PVF, SVF and AVF tests, in non-demented PD patients. Notably, these findings support the use of the AVF as a measure of set-shifting abilities that, at variance with other, widespread tests assessing such functions (e.g., the Trail-Making Test – Part B), is not confounded by upper-limb disabilities associated with PD.

Conclusions: In conclusion, PVF, SVF and AVF tests [1] are reliable, valid and diagnostically sound instruments to detect cognitive impairment in non-demented PD patients and are therefore recommended for use in clinical practice and research.

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### MOTOR AND NONMOTOR CORRELATES OF IRON DEPOSITION WITHIN THE BASAL GANGLIA AND THALAMUS IN EARLY DRUG-NAÏVE PARKINSON'S DISEASE PATIENTS

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Objective: Iron deposition using Quantitative Susceptibility Mapping (QSM) has been reported in several cortical and subcortical areas in patients with Parkinson's disease (PD), and a relationship with clinical outcomes has been proposed. We aimed at exploring the association between MRI-derived iron deposition content within the basal ganglia and thalamus, and several motor, nonmotor and neuropsychological features in a cohort of early drug-naïve PD patients.

Materials: 3T MRI images of 58 early drug-naïve PD patients (41 males, 17 females) were analyzed and compared.

Methods: QSM values were extracted from 22 subcortical deep gray matter nuclei and 16 thalamic subregions. Several PD-validated scales were performed as follows: disease severity and stage were assessed by Unified Parkinson's disease rating scale part III (UPDRS III) and modified Hoehn&Yahr (mH&Y), nonmotor symptoms severity were rated by the Nonmotor symptoms scale (NMSS), autonomic dysfunction were assessed by the Scale for Outcomes in Parkinson's disease for Autonomic symptoms (SCOPA-AUT), global cognitive functioning were assessed by the Montreal Cognitive Assessment (MoCA). Beck Depression Inventory (BDI-II), Parkinson Anxiety Scale (PAS) and Apathy Evaluation scale (AES) were also performed to determine the severity of behavioral symptoms. A partial correlation analysis

using Pearson correlation coefficient was run between MRI metrics and clinical data.

Results: Disease stage positively correlated with higher iron deposition within the bilateral dentate nuclei. UPDRS III scores positively correlated with higher iron deposition within the right substantia nigra pars compacta and left nucleus accumbens. AES scores positively correlated with higher iron deposition within the left externus globus pallidus and bilateral putamina. BDI-II scores positively correlated with higher iron deposition within the left internus globus pallidus, right red nucleus and right substantia nigra pars compacta. PAS scores positively correlated with higher iron deposition within the right substantia nigra pars compacta. SCOPA-AUT scores positively correlated with higher iron deposition within the left dentate nucleus. Higher iron content within different thalamic subregions correlated with higher burden of motor and nonmotor symptoms.

Discussion: We found that the presence of specific motor and nonmotor features is associated with increased iron deposition within different subcortical nuclei, even in the early stages of PD.

Conclusions: We hypothesize that these findings may reflect the presence of diffuse neuropathological changes, that may be associated with a more severe clinical picture at baseline and may potentially lead to more rapid worsening of motor, nonmotor and neuropsychological performances over time.

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## A NOVEL PATHOGENIC MUTATION ASSOCIATED WITH EPISODIC ATAXIA

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Objective: Episodic ataxia is a clinically and genetically heterogeneous group of disorders that are characterized by recurrent spells of truncal ataxia and incoordination lasting minutes to hours. We report a potential novel genetic mutation associated with the phenomenology of episodic ataxia.

Materials: A 43-years-old man referred to our outpatient clinic for the slowly progressive onset of recurrent spells of limb weakness and gait ataxia associated with postural instability and falls, with variable duration (minutes to hours), since the age of 40 years. Episodes were anticipated and associated with anxiety. No other triggers were identified. As disease progressed, paroxysmal episodes increased in duration and frequency along with panic attacks, impacting patients' quality of life. The fear of falling forced the patient to use a wheelchair. Familiar history was positive for myocardial infarction and unspecified numbness in the lower limbs in his father. Intercritical neurological examination showed slightly wide based gait, mild limb and gait ataxia, downbeating nystagmus, slow smooth pursuit movements, mild dysarthria, with evident worsening during the paroxysmal attacks.

Methods: Brain MRI without contrast, EEG, routine blood tests, neuropsychological assessment were acquired. Moreover, we performed genetic testing for the most frequent ataxia.

Results: Brain MRI showed mild cerebellar atrophy. EEG and blood tests were unremarkable. Neuropsychological assessment revealed neurodevelopment delay during childhood. Next generation sequencing revealed a novel c.641A>G heterozygous mutation within the KCND3 gene.

Discussion: KCND3 encodes the voltage-gated potassium ion channel subfamily D member 3, involved in the transient outward K+ current. Mutations in KCND3 are associated with spinocerebellar ataxia 19/22, which has been rarely reported to present as episodic ataxia.

Conclusions: We found a potential novel pathogenic mutation linked to episodic ataxia. This confirms previous findings and expands the spectrum of spinocerebellar ataxia 19/22-related disorders.

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## THE EFFECT OF CATHODAL TRANSCRANIAL DIRECT CURRENT STIMULATION IN THE TREATMENT OF LEVODOPA-INDUCED DYSKINESIAS IN PARKINSON'S DISEASE: A PRELIMINARY REPORT

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Introduction: In Parkinson's disease (PD), Levodopa is to date the most effective treatment for the management of motor symptoms. However, in a certain number of patients, prolonged treatment is associated with development of Levodopa-induced dyskinesias (LIDs). In the pathophysiology of LIDs, aberrant synaptic plasticity seems to play a key role at different levels of brain system, including the primary motor cortex (M1) [1]. Non-invasive brain stimulation (NIBS) may restore normal functioning and ameliorate clinical deficits reversing these brain plasticity abnormalities. Based on these assumptions, our study aims to demonstrate the possible effect of transcranial direct current stimulation (tDCS) in the treatment of LIDs.

Methods: We applied cathodal bilateral tDCS over M1 of PD patients with LIDs, selected according to similar age, disease duration, and levodopa equivalent daily dose (LEDD). Clinical assessment (MMSE; UPDRS I, II, III and IV; UDyRS) and neurophysiological evaluation (TMS potentiation-depotentiation paradigm) were performed before and after stimulation protocol at 3 days, 1 month and 3 months. To test depotentiation phenomenon, usually impaired in LIDs, we used a protocol already described in literature [2], in which LTP-like effect of a 20-s train of cTBS followed by 1-min contraction of the target muscle (cTBSc0) is reversed by a shorter (10-s) inhibitory form of cTBS (cTBS150). Primary endpoint was reduction in LIDs severity measured by UDyRS. Secondary endpoint was improvement in depotentiation degree measured by MEP amplitude changes.

Results: At the moment, we enrolled 8 dyskenitc PD patients (age: 63.7 ± 9.3; disease duration: 13.4 ± 8.4; LEDD: 861.9 ± 338.1). tDCS over bilateral M1 induced a reduction in LIDs of 32% at 3 days, 9% at 1 month, and 9.8% at 3 months compared with baseline. In addition, a significant change in depotentiation paradigm (p=0.01) was observed in post-tDCS recordings compared with baseline.

Conclusion: In conclusion, this preliminary report shows that, in PD patients with LIDs, cathodal bilateral tDCS over M1 induces a short-term improvement in LIDs severity associated with useful changes in synaptic plasticity.

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## INCIDENCE AND RISK FACTORS FOR THE DEVELOPMENT OF POSTURAL ABNORMALITIES IN PARKINSON'S DISEASE

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Objective: Postural abnormalities (PA) are debilitating motor symptoms associated with Parkinson's disease (PD). However, there is limited understanding of the incidence and risk factors for PA development in PD. We aimed to evaluate the incidence of PA in the first five years of PD and identify predictors for PA development using data from the Parkinson's Progression Markers Initiative (PPMI) cohort.

Materials and Methods: The PPMI cohort comprised drug-naïve PD patients within two years of diagnosis. Among participants, we included only PD patients for whom there was at least a 4-year follow-up. Data on demographic characteristics, PA, motor impairment (by means of the MDS-sponsored Unified Parkinson's Disease Rating Scale -UPDRS- part III), physical activity (by means of the Physical Activity Scale for the Elderly -PASE- questionnaire), autonomic symptoms (with the Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire -SCOPA-AUT-), and clinical phenotypes were collected. Statistical analyses included Kruskal-Wallis, Fisher exact test, and Cox regression.

Results: The analysis included 441 PD patients, of whom 10.9% had PA at baseline. Within the first five years, 23.7% of patients without PA at onset developed PA, all at the last follow-up. Comparing patients without PA, with PA at baseline, and who developed PA, we found significant differences for age ($p < 0.001$), MDS-UPDRS part III scores ($p < 0.001$), SCOPA-AUT ($p < 0.001$), PASE score ($p=0.025$), and PD phenotype ($p < 0.001$). Older age (Odds ratio [OR] per year: 1.03) and higher motor symptom severity (OR per point of MDS-UPDRS score: 1.009) were significant predictors of PA development in the multivariate analysis. Physical activity levels showed a trend towards significance as a protective factor for PA development at the univariate analysis.

Discussion: This longitudinal study provides insights into the incidence and predictors of PA in PD. Axial PA was present in a substantial proportion of PD patients within the first five years since diagnosis; on the contrary, severe axial PA remains an uncommon feature in early PD. Moreover, we found that different features can predict the onset of axial PA within 5 years since diagnosis, including a malignant phenotype, a higher burden of dysautonomic symptoms, a lower level of physical activity, an older age, and a higher severity of motor symptoms.

Conclusions: The findings highlight the importance of early monitoring and intervention in patients with older age and greater motor symptom severity at onset. The protective role of physical activity merits to be further investigated.

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## SUBTHALAMIC NUCLEUS - DEEP BRAIN STIMULATION WORSENS HYPOKINETIC DYSARTHRIA IN PARKINSON'S DISEASE

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Objectives: Patients with Parkinson's disease (PD) manifest a complex and multidimensional impairment of speech fluency known as hypokinetic dysarthria. Deep brain stimulation of the subthalamic nucleus (STN-DBS) can further worsen speech performances in PD patients with hypokinetic dysarthria [1,2]. We have previously demonstrated that artificial intelligence can automatically and objectively detect and classify speech abnormalities in PD, with high diagnostic accuracy [1]. In this study, we examined objectively and automatically the hypokinetic dysarthria in PD patients with STN-DBS, by using specific algorithms of artificial intelligence, with classification purposes [3].

Materials: We enrolled 108 controls and 101 patients (50 with STN-DBS and 51 under the best medical treatment). The voice was clinically evaluated using the Unified Parkinson's Disease Rating Scale part-III subitem for voice (UPDRS-III-v). All PD patients were assessed ON treatment with L-Dopa.

Methods: Voice samples of the sustained emission of a vowel were collected through a smartphone from controls and the overall cohort of PD patients. Then, audio tracks underwent specific procedures of machine-learning analysis through the support vector machine (SVM) classifier. ROC curves for comparisons between controls and PD patients with L-Dopa, controls and PD patients with STN-DBS and lastly, PD patients with L-Dopa and STN-DBS were provided to calculate diagnostic accuracies. The likelihood ratio (LR) was also calculated as an objective measure for clinical-instrumental correlations.

Results: Clinically, voice impairment was greater in STN-DBS patients than in those under oral treatment. Machine-learning discriminated voices recorded from STN-DBS patients and those under oral treatments, objectively and with high accuracy. We also found significant clinical-instrumental correlations since the greater LRs, the higher UPDRS-III-v scores.

Discussion: STN-DBS further deteriorates speech performances in patients with PD by current spreading in the phonological loop network.

Conclusions: Future strategies based on current steering and closed-loop devices would be useful to reduce the negative impact of STN-DBS on hypokinetic dysarthria in PD.

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## LONGITUDINAL CHANGES OF ENERGY EXPENDITURE, BODY COMPOSITION AND DIETARY HABITS IN PROGRESSIVE SUPRANUCLEAR PALSY PATIENTS

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Objective: Recent evidence suggest that neurodegenerative diseases are associated with a wide spectrum of metabolic changes. The aim of this study is to describe longitudinal changes in energy expenditure, body composition and dietary habits in patients with Progressive Supranuclear Palsy (PSP), a rare neurodegenerative disease characterized by rigid-akinetic parkinsonism, postural instability, oculomotion dysfunction and cognitive-behavioral changes.

Materials: A total of 15 PSP patients, referred to the Center for Neurodegenerative diseases (CEMAND) of the University of Salerno, were evaluated at baseline and after a median of 7 months (interquartile range IQR=5). We assessed anthropometric parameters (weight, body mass index, waist circumference), energy expenditure, body composition and dietary intake. Disease severity was assessed with the PSP rating scale (PSP-rs) and Movement Disorder Society-Unified Parkinson's Disease Rating Scale III (MDS-UPDRS III), dysphagia severity with the corresponding PSP-rs items (i.e., dysphagia for solids, dysphagia for liquids, using cutlery), MOCA was used to evaluate global cognition and S&E scale disease disability.

Methods: Differences between paired group at baseline and follow up were performed using paired t-test or signed-rank Wilcoxon test, as appropriate.

Results: No changes were detected in anthropometric parameters nor in measured or estimated rest energy expenditure nor in total daily energy expenditure over time ($p>0.05$). Similarly, bioimpedance analysis showed no changes in fat mass and fat free mass ($p>0.05$). Dietary habits showed a reduction of daily calories ($p<0.001$), proteins ($p<0.001$), fibers ($p=0.001$), calcium ($p=0.008$), iron ($p=0.001$), zinc ($p=0.034$), vitamin E ($p=0.006$) and folate ($p=0.038$) intake compared to baseline. The PSP-rs and MDS-UPDRS III significantly increased ($p=0.001$ and $p=0.022$ respectively), as well as the severity of solid ($p=0.083$) and liquid ($p=0.046$) dysphagia and ability to use cutlery ($p=0.046$). Moreover, S&E scale and MOCA decreased ($p=0.001$ and $p=0.004$ respectively) over time.

Discussion: As expected, after a median of 7 months follow up, disease-specific motor and cognitive characteristics showed a worsening. Dietary habits presented a lower intake of daily calories, proteins, fibers, calcium, iron, zinc, vitamin E and folate. Finally, anthropometric parameters, energy expenditure and body composition remain stable in PSP patients.

Conclusions: The worsening of dysphagia associated with a global progression of disease may explain the reduction in dietary intake. We speculate changes in dietary habits, with reduction of several macronutrients in less than a year, may not be sufficient to produce significant modifications in energy expenditure and body composition, which were found to be stable.

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## ARE GBA–PARKINSON DISEASE PATIENTS' GOOD CANDIDATES FOR DEEP BRAIN STIMULATION? A LONGITUDINAL MULTICENTRIC STUDY ON A LARGE ITALIAN COHORT

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Background: GBA mutations are known not only to increase the risk of developing Parkinson disease (PD) but also to influence the outcome. Deep brain stimulation (DBS) is considered one of the best therapeutic options for advanced PD. However, data on DBS long-term clinical outcome in GBA mutation carriers are still scarce.

Objective: To elucidate the impact of GBA variants on long-term DBS outcome.

Methods: We retrospectively collected clinical data from a multicentric Italian cohort of PD patients who underwent DBS, stratified

according to their GBA genotype (positive vs negative). We described: 1) the prevalence of GBA mutations in the DBS-PD cohort; 2) their clinical phenotype (motor and non-motor features) pre-DBS; 3) their outcomes on motor, cognition and other non-motor features after 1, 3 and (for a subset) 5 years from DBS.

Results: We included 365 subjects (244 M/144 F, age 63.4±8, age at onset 46.5±8.2, PD duration 10.4±4). GBA variants were found in 73 (20%). At pre-DBS evaluation, GBA-PD patients showed younger age, earlier age at PD onset, and a slightly shorter disease duration compared to nonGBA-PD patients. Motor, cognition and other non-motor symptoms were similar between groups, except for dyskinesias and orthostatic hypotension (more prevalent in GBA-PD). At 1-year post-DBS, both groups showed motor improvement with satisfactory control of fluctuations and dyskinesias and a significant LEDD decrease; all non-motor symptoms were also comparable. Longitudinal analysis up to 5-years post-DBS showed a prolonged motor benefit of DBS in both PD groups, except for the "on-off" phenomenon, more prevalent in GBA-PD. A deterioration of cognitive scores post-DBS was observed in both groups, with a significantly more marked worsening of GBA-PD already 3 years post-DBS. However, only 25% (8/32) of GBA-PD compared to 11% (15/140) of nonGBA-PD received a diagnosis of dementia at 5-years post-DBS. No clinically significant differences were observed in the GBA-PD group according to mutation severity prior to DBS implant and at 1-year follow-up.

Conclusion: This is the first report correlating the presence of GBA variants with DBS clinical outcomes in a large well-characterized Italian PD cohort with a relatively long follow-up. Our data indicate that GBA-PD patients have similar motor benefits from DBS as nonGBA-PD patients. Cognitive performance, although progressively worsening in both groups, shows a more rapid deterioration in GBA-PD patients, however after 5 years from DBS only a minority of patients eventually developed overt dementia.

## PROPRIOSPINAL MYOCLONUS IN ALZHEIMER'S DISEASE: A CASE REPORT

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Introduction: Propriospinal myoclonus (PSM) is a rare hyperkinetic movement disorder involving axial muscles, characterized by involuntary flexion movements of trunk, hips and knees that are painless, usually arrhythmic, often stimulus-sensitive and typically increase in supine position. PSM is often a functional movement disorder (FMD). The recording of polygraph and Bereitschaftpotential (BP) has been proposed to support clinical diagnosis, but sensitivity in studies varies between 25 and 80 %. To improve this sensitivity, the analysis of event-related EEG desynchronization patterns (ERD) has been proposed. Although cases of FMD have been described in patients with neurodegenerative diseases such as Parkinson's Disease, no cases of PSM have been previously described in patients with Alzheimer's Dementia (AD). Case report: A 61-year-old female patient with diagnosis of AD according to NIA-AA criteria, followed by the Neurology Clinic of University of Pisa, reported involuntary trunk movements that had begun about two months before the last evaluation. At the time of the examination, the patient, who had been on stable therapy for 9 months, presented with arrhythmic involuntary trunk movements that propagated to the shoulders, presented entrainment phenomenon, increased in clinostatism, decreased until disappearing with distraction maneuvers and during gait. The motor disorder appeared after the new onset of low back pain where the lumbar puncture was performed two years earlier. At that time, after the procedure, she presented back pain then she performed lumbar spine MRI, which was normal. The patient underwent clinical evaluation and polymiographic recording, with research for BP and ERD. The diagnosis of PSM was made according to Brown's criteria. During the polymiographic recording, 22 episodes of rhythmic movements in the abdomen and trunk were detected without corresponding changes in EEG activity; these movements presented cranio-caudal propagation from the rectus abdominis muscle. In addition, execution of voluntary movements of the upper limbs such as opening and closing of the hands determined the entrainment phenomenon and sometimes interruption of rhythmic involuntary movement. No BP was recorded, however, an ERD was found in the beta frequency prior to the motor event, supporting the electrophysiological evidence of a voluntary cortical genesis of the movement itself.

Discussion and Conclusion: Improving the diagnostic accuracy of FMD in patients with neurodegenerative diseases is one of the new challenges in the field of movement disorders. Currently, the diagnosis of functional PSM is supported by polymiographic findings with variable sensitivity, so research for additional and more sensitive neurophysiological biomarkers is needed.

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## APRAXIA OF SPEECH AS AN UNUSUAL MANIFESTATION OF GAD-65 SPECTRUM DISORDER– A CASE REPORT

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Objectives: Apraxia of speech (AOS) is a neurological speech disorder characterized by impaired planning and programming of movements allowing phonetically and prosodically normal speech. It is observed in patients with acquired vascular lesions or neurodegenerative diseases such as primary progressive aphasias (PPA) and progressive supranuclear palsy (PSP)[1]. The glutamic acid decarboxylase 65 (GAD65)-antibody spectrum disorder encompasses a variety of neurological disorders including stiff person syndrome (SPS), cerebellar ataxia, autoimmune epilepsy, and limbic encephalitis[2]. Herein, we report apraxia of speech (AOS) as an unusual manifestation in a patient affected by a GAD65-ataxia.

Materials: We describe a case of a 41-year-old man who presented to our clinic for progressive clumsiness of gait with "rigidity" of his left leg together with swallowing and speech difficulties.

Methods: At neurologic examination the patient exhibited an ataxic gait with spasticity of his left limbs, brisk reflexes, and Babinski sign on the left. His speech was slow, effortful, halting and hypophonic. The patient underwent cerebrospinal fluid (CSF) examination and brain MRI. A neurophysiologic study consisting in electromyography (EMG) and motor evoked potentials (MEPs) was carried out. Finally, otorhinolaryngology evaluation with laryngoscopy was performed.

Results: CSF examination showed high titre of anti-GAD65. Hence, the patient was diagnosed with GAD-65-ataxia. Brain MRI showed mild atrophy of the vermis and the cerebellar hemispheres. EMG of the vastus lateralis showed continuous high frequency firing at rest bilaterally, heightened by contraction and lasting after relaxation. EMG of the thyroarytenoid muscles at rest revealed a pattern of tonic activity, without the occurrence of bursts, with MUP of normal amplitude and duration during muscle activation and normal recruitment. MEPs were unremarkable. Laryngoscopy found no structural abnormalities. The patient underwent oral steroid therapy and intravenous immunoglobulins without substantial benefit. His symptoms improved after a plasma exchange cycle. Rituximab has been administered resulting only in little improvement. He is currently assuming methotrexate with mild benefits.

Discussion: Our patient presented a mixed clinical phenotype characterized by overlapping features of SPS and GAD-65 cerebellar ataxia. The speech disorder was inconsistent with dysarthria and spasmodic dystonia for its clinical and neurophysiologic pattern[3], thus suggesting AOS as an atypical manifestation of GAD-65 ataxia.

Conclusions: Even if with a neglected pathophysiological mechanism, AOS may represent an atypical manifestation in a GAD65-spectrum disorder which, on purely clinical ground, may be easily mistaken with other speech disorders. However, laryngeal EMG may provide helpful diagnostic clues across phonation/articulation disorders.

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## ASSOCIATION BETWEEN AVERAGE DAILY STEPS MEASURED THROUGH A COMMERCIAL SMARTWARTCH AND CLINICAL PARAMETERS IN PARKINSON'S DISEASE IN DIFFERENT DISEASE PHENOTYPES

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Objective: Commercial smartwatches could be useful for monitoring ambulatory activity in a home environment [1]. In Parkinson's disease (PD), motor impairment and reduced functional mobility are crucial aspects greatly hampering daily living independence and quality of life. However, only very few studies examined the relationship between daily steps recorded by commercial smartwatches and clinical parameters in these patients with inconsistent results [2,3].

Material and Methods: Forty-three ambulating PD patients without dementia were enrolled [28% females; age 68.7 (8.0) years; disease duration 7.3 (4.8) years; levodopa equivalent daily dose (LEDD) 616 (324) mg; median Hoehn and Yahr (H&Y) stage 2 (2-2, range 1-3)]. Average daily steps (avDS) were recorded at home through a Garmin Vivosmart 4 smartwatch for a median of 5 days (range 3-6). Data regarding motor and non-motor symptoms severity and fluctuations, presence/absence of tremor, functional mobility, quality of life, fatigue, sleep and daytime sleepiness were collected. Mann-Whitney test was used to assess difference between tremor and non-tremor patients. To assess the correlation between avDS and clinical-demographic variables, Spearman test was used.

Results: Patients took a mean 6046 (3253) daily steps. No difference in clinical-demographic and avDS between tremor and non-tremor patients were found. In the overall population, Spearman test showed a moderate positive correlation of avDS with SPPB (R=0.548; p<0.001); a weak negative correlation with MDS-UPDRS-III (R= -0.349; p=0.022), total MDS-UPDRS (R= -0.307; p=0.048), LEDD (R= -0.380; p=0.012), disease duration (R= -0.437; p=0.003), age (R= -0.431; p=0.004) and H&Y stage (R=-0.321; p=0.036). In patients with tremor (30/43, 69%), test showed a weak positive correlation of avDS with SPPB (R=0.392; p=0.032); a weak negative correlation with LEDD (R= -0.415; p=0.023), disease duration (R= -0.479; p=0.007) and age (R= -0.447; p=0.013). In patients without tremor (13/43, 31%), test showed a strong positive correlation of avDS with SPPB (R=0.842; p<0.001) and a moderate negative correlation with MDS-UPDRS-III (R= -0.629; p=0.021).

Discussion: Daily steps measured at home through a commercial smartwatch were associated with motor symptoms and functional mobility in ambulating PD patients, particularly in those without tremor. This could potentially be due to a reduced step detention performance linked to tremor or due to a more tight relationship between motor symptoms and mobility in non-tremor patients.

Conclusions: Our results suggest that mobility-related parameters measured through commercial smartwatches could add valuable and easy-to-collect information on patients status besides in-clinic evaluations, particularly in specific disease subtypes.

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## RELATIONSHIP BETWEEN BRADYKINESIA AND COGNITIVE FUNCTIONS IN PATIENTS WITH ESSENTIAL TREMOR

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Objectives: Bradykinesia in essential tremor (ET) is one of the so-called 'soft signs' configuring the diagnosis of ET-plus [1,2,3]. Cognitive disturbances may also occur in ET with a higher prevalence than in the general population [1]. Though it has been demonstrated that soft signs often occur in combination, the relationship between bradykinesia and cognitive dysfunction in ET patients has never been explored. The aims of our study is to further investigate the association between bradykinesia, as objectively assessed with kinematic analysis, and cognitive functions in ET.

Materials: 45 ET patients (23 F, mean age: 66.48±13.69). Patients underwent kinematic recordings of finger-tapping movements with an optoelectronic motion system [2,3]. A comprehensive cognitive evaluation, including the assessment of executive and visuo-constructional functions, attention, and memory, was also performed on participants.

Methods: Automatized algorithms were used for kinematic analysis, providing objective measurement of movement velocity and movement rhythm (expressed as coefficient of variation - CV, with higher values indicating a more irregular rhythm). Possible associations between kinematics and raw cognitive scores were assessed by using the Pearson correlation coefficient.

Results: We found a positive correlation between movement velocity and the Rey-Auditory Verbal Learning Test (RAVLT) immediate and delayed recall (r=0.3, p=0.04 and r=0.35, p=0.019, respectively). A negative association was found between CV and Forward Digit span scores (r=-0.3, p=0.039). Finally, CV values positively correlated with the Modified Card Sorting Test (MCST) errors (r=0.43, p=0.024).

Discussions: These results overall indicate that the lower the movement velocity and the more irregular the rhythm, the worse the performance on tests exploring memory and executive functions.

Conclusions: We here demonstrated a relationship between finger-tapping bradykinesia and memory and executive dysfunctions in ET. Our results are relevant for a better understanding of ET and ET-plus pathophysiology.

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## PERIPHERAL INFLAMMATION IS ASSOCIATED WITH A WORSE PROFILE OF CSF NEURODEGENERATION MARKERS AND LONG-TERM CLINICAL OUTCOME IN IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

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Objectives: To disentangle the dynamics of the brain-periphery interactions in idiopathic normal pressure hydrocephalus (iNPH) by examining the correlations of peripheral immunity markers with CSF neurodegeneration-associated proteins and clinical progression severity.

Materials and Methods: We conducted a single-center longitudinal retrospective study over a 12-year-long period, enrolling 38 iNPH patients and 38 sex/age-matched controls. The leukocyte population counts (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) and the neutrophil-to-lymphocyte ratio (NLR) were collected and correlated with CSF levels of amyloid-β-42, total and phosphorylated-tau in both the groups. In iNPH patients, the immune parameters and CSF biomarkers were correlated either with baseline scores of the iNPH grading scale (iNPHGS) and modified Ranking Scale (mRS) or the long-term (> 5 years) clinical outcome classified as "poor" (mRS≥5) and "positive" (mRS<5).

Results: iNPH patients had lower lymphocyte count (mean ± st.dev.: 1.89 ± 0.73 thousand/uL vs. 2.53 ± 0.80 thousand/uL, p<0.001) and higher NLR (mean ± st.dev.: 2.43 ± 1.04 vs.1.56 ± 0.47, <0.001) compared to controls. In iNPH patients, NLR directly correlated with CSF t-tau levels (r=0.50, p=0.004), even in a model adjusted for age and sex (t=2.174, p=0.039). No significant association resulted in control group. At baseline, CSF t-tau levels correlated with baseline iNPHGS cognitive subscore (t=2.43, p=0.026). At long-term follow-up, patients with "poor outcome" had higher NLR (mean ± st.dev.: 3.10 ± 1.42 vs. 2.01 ± 0.77, p=0.06) and higher CSF total-tau levels (mean ± st.dev.: 300.58 ± 114.10 pg/ml vs.175.69 ± 94.57 pg/ml, p=0.04).

Discussion: iNPH is a heterogeneous and challenging neurodegenerative condition with complex pathogenesis. While the contribution of peripheral inflammation has been ascertained in many other neurodegenerative diseases1, it needs to be adequately addressed in iNPH. Here we showed that the iNPH patients had lower lymphocyte count and higher NLR than controls, consistently with a systemic inflammatory state. Of interest, such peripheral immune changes were associated with central neurodegeneration burden and poor long-term clinical outcome. These data collectively provide novel evidence that a proinflammatory shift of the immune system might contribute to the clinical-pathological progression of iNPH, as it also occurs in other neurodegenerative diseases.

Conclusions: Increased NLR and reduced lymphocyte count emerged as the peripheral immunity signature of iNPH. Systemic inflammation was associated with a worse profile of CSF neurodegeneration markers and long-term clinical severity, suggesting a major pathogenic role with potential implications in terms of therapy or patient stratification.

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## ANTI-BASAL GANGLIA ANTIBODIES (ABGA) ASSOCIATED WITH MOVEMENT DISORDERS AND PSYCHIATRIC SYMPTOMS: A CASE REPORT

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Objective: To report the case of a 33-year-old Bangladeshi man who presented with an unusual movement disorder associated with psychiatric symptoms and anti-basal ganglia antibodies (ABGA) in serum.

Case report: The patient was a 33-year-old Bangladeshi man with aggressive behavior and gambling started two years earlier. During the same period, he also complained of constipation, epigastric pain, wheezing, and diffuse myalgias. Prior medical history was unremarkable. The patient came to our attention because of hypotension, wheezing, tachypnea, and desaturation, that were triggered by antipsychotic treatment for behavioral symptoms. He underwent orotracheal intubation as well as nasogastric tube placement for to ineffective swallowing. Neurological examination, performed after extubation, showed: hypomimia, dysarthric speech, severe sialorrhea, slowed extraocular movements with vertical gaze limitation, severe bradykinesia, diffuse muscular hypotrophy, rigidity with forced hip and knee flexion and ankle extension, dystonic posture of the hands and hyperactive deep tendon reflexes. CT scan showed bilateral calcifications in the basal ganglia, seen as paramagnetic particles on brain MRI. DATSCAN was normal. EMG showed axonal motor neuropathy at lower limbs, with diffuse denervation activity (fibrillation potentials). Cerebrospinal fluid was normal. Laboratory exams ruled out Gaucher, Niemann-Pick type C, Wilson and Lyme disease. To test autoimmune etiology, the patient underwent a panel for autoimmune encephalitis, with the positivity for ABGA in serum (research of ABGA was performed using an

immunoblotting procedure with recombinant proteins from the caudate nucleus and putamen: pyruvate kinase 60 KDa and neuron-specific enolase 40 KDa). We followed the patient over time, observing symptoms improvement: he returned to eat independently and walk without assistance. After six months, there was also an improvement in extrapyramidal symptoms. Nonetheless, behavioral symptoms, especially apathy, remained unchanged.

Discussion: Serum ABGA are commonly associated with Sydenham's chorea, and seldom found in adults. A previous study assessed the frequency of ABGA in 65 patients with adult-onset movement disorders with an unusual presentation (mainly atypical dystonia) and found 42 cases of serum ABGA positivity [1]. Dale et al. also described 20 cases of encephalitis lethargica and parkinsonism with anti-basal ganglia autoimmunity. In all reported cases, few patients had a complete recovery, showing persistence of both movement disorders and psychiatric symptoms [2]. Patients with atypical movement disorders present considerable diagnostic and therapeutic challenges to physicians, and the finding of a possible autoimmune cause in a percentage of them may help in guiding future research and therapy.

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## ASSOCIATIONS BETWEEN SEX HORMONES, CLINICAL FEATURES AND MULTIMODAL BIOMARKERS IN A COHORT OF MALE PATIENTS WITH PARKINSON'S DISEASE

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Objective: Epidemiology, clinical and pathophysiological features of PD differ between females and males, suggesting a role for sex hormones [1]. At this regard there are compelling findings from animal models [2], while human-based evidence is still scarce. By integrating neurodegeneration-related CSF biomarkers and MRI-based volumetric measurement of brain structures, we can track neuropathological changes in vivo in patients. In this study, we aimed to deepen into sex-dependent mechanisms of Parkinson's disease (PD) by analyzing the relationships between sex hormones, clinical features and multimodal biomarkers in a cohort of male PD patients.

Materials: We enrolled 63 male PD patients and 56 age-matched controls afferent to the Neurology Unit of Tor Vergata University Hospital (Rome - Italy).

Methods: For each subject, demographics and anthropometrics data were recorded. A complete clinical evaluation, including motor, non-motor and cognitive scores, was coupled to lumbar puncture for CSF biomarkers assay and blood sampling for sex hormones measurement. CSF levels of total α-synuclein (αSyn), amyloid-β-42 (Aβ42), amyloid-β-40 (Aβ40), total tau (t-tau) and phosphorylated-181-p tau (p-tau) were quantified. Aβ42/p-tau, Aβ42/Aβ40 ratios were also calculated. Serum sex hormone levels, including total testosterone, estradiol, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were determined. A subgroup of 47 PD patients underwent 3T brain MRI for volumetric measurement of bilateral subcortical gray matter structures using a 3D T1-weighted MPRAGE sequence.

Results: Estradiol and testosterone levels were higher in PD patients than in controls, independently from age ($p=0.001$ and $p=0.003$, respectively). Estradiol inversely correlated with MDS-UPDRS-III ($p=0.006$) and with disease duration ($p=0.015$). Estradiol was significantly lower in patients with motor fluctuations ($17.33 \pm 11.33$ pg/ml) than in those without ($27.9 \pm 13.6$) ($p=0.016$). Testosterone was inversely associated with CSF α-syn levels ($p=0.03$) and right-globus pallidus volume ($p=0.024$). FSH and LH had a direct correlation with age (both $p<0.0001$) and an inverse correlation with Aβ42/Aβ40 ratio and cognitive scores, which were lost in the model adjusted for age.

Discussion: Higher estradiol levels were associated to milder motoric impairment, supporting a possible neuroprotective effect, especially in the earliest stages of the disease. Testosterone levels instead were directly correlated to biomarkers of neuropathological burden, suggesting a role in the males vulnerability to PD pathology. Finally, gonadotropins might mediate age-dependent phenomena of amyloidopathy and cognitive decline.

Conclusions: This study provided evidence regarding the relationship within sex hormones and both clinical features and biomarkers of disease severity, laying the foundations for a possible therapeutic role in PD.

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## ANALYSIS OF ALFA-SYNUCLEIN DEPOSITION IN OLFACTORY MUCOSA AND SKIN NERVES OF TWO RELATED PATIENTS WITH THE SAME PARK18 VARIANT AND MILD PD PHENOTYPE

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Objectives: To describe clinical and biological findings of two related patients (mother and daughter) affected by Parkinson's disease (PD), who were found to be carriers of the same variant in exon 11 of PARK18 gene.

Materials and Methods: We performed a NGS-based genetic test to examine a panel of genes associated with PD, finding that both patients were carriers of the same mutation c.1237G>A (pGly413Arg) in the exon 11 of PARK18 gene. We used the Burghart Sniffin Sticks test for evaluation of olfactory function. We have then subjected the olfactory mucosa samples to seed amplification assay (SAA) to detect the presence of seeding activity for alpha-synuclein [1]. We investigated the presence of alpha-syn aggregates in skin sections taken from C7, thigh and distal leg, by double immunofluorescence immunohistochemical stainings [2].

Results: Our first patient is an 82-year-old woman who was diagnosed with PD at the age of 60 after the appearance of rest tremor and a long history of hypsomia. After more than 15 years since the start of treatment, she presents mild motor fluctuations without dyskinesias. Our second patient is a 50-year-old woman with a long-standing hyposmia, affected by a rigid-akinetic form of PD from the age of 46;

her actual symptoms are confined to her right hemisoma and determine a mild functional impact. For each patient, we performed an olfactory analysis and neuropathological analysis of olfactory mucosa and skin biopsy. The Burghart Sniffin Sticks test confirmed that both patients are hyposmic. SAA analysis confirmed the presence of a seeding activity for alpha-synuclein in both patients, while immunoistochemistry did not reveal alpha-synuclein deposition in skin nerves.

Discussion: The similar clinical phenomenology of our patients and the results of our analyses sustain the hypothesis that PARK18 gene could manifest as a "benign" form of PD, with a slow progression and an apparent lack of pathological alfa-synuclein accumulation in peripheric nervous system. One reason for the controversial role of this gene in previous case controls studies [3] could be the mild severity of its PD phenotype: we could consider as "healthy controls" individuals who carry the same variant and have a prodromal or non-motor prevalent form of PD (for example, with isolated hyposmia and minimal motor signs), thus underestimating the role of PARK18 gene in causing PD. Our results support the idea that the PARK18 could play a pathogenic role in determining a "benign" phenotype of PD.

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## PARKINSON'S DISEASE FOLLOWING COVID-19: ONE-YEAR FOLLOW UP OF SIX REPORTED CASES

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Objective: Here we describe a one-year follow-up of six subjects who developed PD after COVID-19 infection.

Materials: Neurological complications may occur during SARS-CoV-2 infection, covering a wide spectrum of phenotypical manifestations. We recently described six cases of PD following COVID-19, in line with a number of post-COVID-19 PD cases reported in the literature, suggesting the possibility of a close link between infection and neurodegenerative process.

Methods: The first evaluation was performed at IRCCS Mondino Foundation Hospital, Pavia, and San Paolo University Hospital of Milan between March 2021 and June 2022. In all subjects, SARS-CoV-2 infection was confirmed by means of a RT-PCR from a nasopharyngeal swab. Subjects underwent an accurate neurological evaluation and neuroimaging studies. The one-year follow-up was performed at Mondino Foundation and San Paolo University Hospital.

Results: We described six subjects, who developed PD with an average time window after SARS-CoV-2 infection of 4-7 weeks. Apparently, no relationship with COVID-19 severity emerged, no overt structural brain abnormalities were found. DaTscan was performed in four out of the six reported cases, showing altered striatal reuptake. All subjects experienced unilateral resting tremor at onset and showed a satisfactory response to dopaminergic treatment. During follow-up clinical evaluations, performed in the past 12 months, all of the subjects exhibited a significant stable motor control, and maintained a satisfactory response to the dopaminergic therapy initially set.

Discussion: The time window of clinical presentation of PD reported, suggests that the infection might have uncovered a latent neurodegenerative substrate and made it clinically manifest. Indeed, the role of neuroinflammation in the PD pathogenesis is now well established. Inflammation is a key factor in the initiation and propagation of alpha-synuclein (α-syn) aggregates, and in addition, elevated α-syn-dependent specific T cell response may be present years before the diagnosis of motor PD. Both the clinical stability, and the good response to dopaminergic treatment observed at follow-up confirm the diagnosis of PD.

Conclusions: Immune responses to SARS-CoV-2 infection have been shown to shape the individual susceptibility to develop long-term consequences. We hypothesize that, in these subjects, COVID-19 unmasked a latent neurodegenerative process. Furthermore, the clinical course resembles idiopathic-PD, supporting the hypothesis of a close connection between inflammatory processes and neurodegeneration. Thus, the long-term follow-up of these patients is crucial to define the natural history of the disease, in order to elucidate the clinical, biochemical, imaging features of this peculiar form of PD.

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## CLOZAPINE IN THE MANAGEMENT OF TARDIVE DYSTONIA: CASE SERIES AND LITERATURE REVIEW

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Tardive syndromes are iatrogenic movement disorders, characterized by involuntary repetitive body movements, caused by chronic exposure to dopamine receptor blocking agents (DRBA), mostly antipsychotics, sometimes procinetic drugs and calcium channel blockers. Tardive dystonia is an uncommon tardive syndrome, presenting with clinical features overlapping with primary dystonia, more frequent among young male patients, affecting mostly axial muscles. There are not guidelines for the treatment. Nevertheless, in a recent literature review, it is recommended the use of clozapine as a treatment and/or for drug switch. In the last two years, three patients, two male and one female, had been treated at the Movement Disorder Clinic of the Gemelli Hospital. All of them were young, treated for several years with DRBA for psychiatric conditions. DRBA treatment was ongoing when dystonia occurred, involving in all of them axial muscles and affecting neck and trunk.

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## ATROPHY OF THE CAUDATE NUCLEUS AS A POSSIBLE COMMON NEUROBIOLOGICAL SUBSTRATE FOR MOTOR AND NON-MOTOR SYMPTOMS OF PARKINSON'S DISEASE

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Introduction: Parkinson disease (PD) is the second most common neurodegenerative disorder, whose clinical features include motor and non-motor symptoms [1]. The relationship between motor and non-motor clinical features of PD still remains to be clarified. Recently, inertial sensors have become a useful tool for an accurate assessment of patients' motor performance through the analysis of quantitative measures.

Aim: To investigate the possible relationships and common neurobiological substrates between gait abnormalities and neuropsychological performance in patients with PD.

Methods: We recruited 51 patients with PD (mean [SD] age 60.5 [8.1]; M/F: 37/14) for a gait analysis investigation based on inertial sensor data acquisition. Evaluations were conducted under two different conditions: off-medication (12 hours from last levodopa administration) and on-medication (about 30 min after levodopa challenge). All patients underwent also an extensive neuropsychological (NPS) examination and MRI scanning at 3T, including acquisition of T1-weighted volumes. Univariate and multivariate regression analyses were first run including multidomain NPS test scores and a set of gait parameters to identify associations. T1-weighted volumes were used to run voxel-based morphometry (VBM) analyses of the grey matter (GM) tissue [2]. Then, we run a series of VBM analyses (ANOVA models) to identify associations between regional GM volumes and those cognitive and motor parameters resulted to be associated with each other. Imaging findings were accepted as significant for P values cluster-level corrected $< 0.05$. Finally, overlapping GM regions were evaluated to identify common regional patterns between NPS and motor performances.

Results: Multiple associations were identified between NPS and motor measures. Expected patterns of regional GM associations were found for NPS scores taken in isolation. VBM analyses also showed an overlapping region of GM volumes associated with both patient long-term memory scores and the sway area from gait analysis in off-medication. This region was centered on the right head of the caudate nucleus.

Discussion: This study highlights for the first time a possible common substrate for some motor and non-motor symptoms of PD. Interestingly, the head of the caudate nucleus is known to be implicated in the integration of cognitive (especially memory retrieval) and motor functions.

Conclusions: The caudate nucleus is a core structure in the pathophysiology of PD. The common substrate in the caudate nucleus between cognitive and motor features of PD opens interesting perspective for the definition of simple biomarkers of prognostic value to be used in clinical settings.

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## MOOD RELATED EFFECTS OF DEEP BRAIN STIMULATION IN ADVANCED PARKINSON'S DISEASE: A RESTING-STATE FMRI INVESTIGATION

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Introduction: Subthalamic deep-brain-stimulation (STN-DBS) is a widely used intervention for the treatment of advanced Parkinson disease (PD). The most important outcome of STN-DBS is improving motor symptoms and fluctuations while reducing the dose and side effects of dopaminergic therapy. Despite its great efficacy on motor symptoms, little is known on STN-DBS modulation of cognitive and neuropsychiatric symptoms. We recently identified correlations between the anatomical distribution of the volume of tissue activated (VTA) by STN-DBS and patient changes in non-motor symptoms. One of the most robust findings was an improvement of mood-depression through stimulation of an area located dorso-postero-laterally to the left STN, which we named "mood-depression-cluster" (MDC). Interestingly, MDC is anatomically crossed by the Superolateral-Medial Forebrain Bundle, which connects the midbrain to areas implicated in mood control.

Aim: To test, using resting-state functional MRI (rs-fMRI) in an independent group of PD candidates for STN-DBS, the different patterns of connectivity between the canonical VTA location and MDC.

Methods: Forty-seven patients with advanced PD eligible for STN-DBS underwent MR scanning at 3T, including rs-fMRI acquisition. rs-fMRI data were preprocessed using Conn (1) to obtain functional connectivity maps. In each subject, canonical left VTA (centered on x=-12; y=-13; z=-7) and MDC (centered on x=-15; y=-13; z=-2) were used as seed-regions to compare their patterns of connectivity with the rest of the brain. Areas of functional connectivity with seed-region were accepted as significant for P-values<0.05 (cluster-level corrected).

Results: Connectivity differences between the two seed-regions (i.e., canonical VTA and MDC) included the left nucleus accumbens septi, the left head of the putamen, the left inferior insular cortex and thalamus. These areas were significantly connected to MDC but not to canonical VTA.

Discussion: STN is regarded as the best target region for DBS in advanced PD, which induces a remarkable improvement of motor symptoms. During patients' selection for STN-DBS, severe psychiatric symptoms are considered as a contraindication. We identified a subregion nearby the left STN, whose chronic stimulation improves mood-depression. This finding is now supported by connectivity-based evidence that links MDC with a broader network related to mood control.

Conclusion: Further research on the pathophysiology of non-motor symptoms in PD and their response to neuromodulation may help improve the patient outcome of DBS. Indications for PD patient selection to DBS and stimulation programing should consider non-motor symptoms as a potential additional therapeutic target to improve patients' quality of life, in the framework of precision medicine.

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## A GRN MUTATION PRESENTING AS AN ESSENTIAL TREMOR LIKE SYNDROME AND EVOLVING INTO PARKINSONISM

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Background and Objectives: The GRN gene codes for progranulin (PGRN), a growth factor implicated in regulation of inflammation. Homozygous mutations in this gene are associated with neuronal ceroid lipofuscinosis 11 (CLN11), while heterozygous GRN mutations are a major cause of frontotemporal dementia (FTD). Mutations can also occur with other phenotypes such as Alzheimer's disease and atypical parkinsonian disorders (APD). Here, we present an interesting patient with an essential tremor-like syndrome evolved into the parkinsonism phenotype carrying a heterozygous GRN mutation (c.328C>T; p. Arg110).

Materials and Methods: A 70-year-old woman was referred to outpatient Department of Movement Disorders with a ten-year history of essential tremor like syndrome (postural tremor involving vocal cords, head, and hands). Her past medical history included insulin-dependent diabetes mellitus, obesity (BMI 30.44 kg/m²), hypertension, dyslipidemia, myocardial infarction. Maternal family history was positive for tremor (grandfather and uncle). She had Dopamine Transporter imaging (DAT-SCAN) and brain MRI, both negative, at presentation. She was prescribed propranolol, with benefit. In the following years, hyposmia, bilateral upper limbs rest tremor, mild right limbs bradykinesia, and right arm swing reduction appeared. A new scintigraphy was performed, with evidence of impairment of the left nigrostriatal dopaminergic pathway, for which dopaminergic therapy with ropinirole was started, with initial benefit. Given the subsequent accentuation of bilateral bradykinesia it was decided to add levodopa/carbidopa to ropinirole, with benefit. The patient was involved in the Rostock International Parkinson's Disease (ROPAD) study, which aims to better understand the overall contribution of genetics to Parkinson disease.

Results: A heterozygous mutation in GRN, c.328C>T p., (Arg110"), has been identified and classified as pathogenic (class 1) according to the indications of ACMG. Twelve years after onset, the patient had developed urinary incontinence, difficulty finding words and increased latency in responses. She underwent a comprehensive neuropsychological evaluation, showing mild single-domain non amnesic cognitive decline (sustained attention deficit, but visuo-spatial, and language domains were preserved; no psychiatric symptoms were present). Discussion: GRN mutations can occur with parkinsonism, usually after the development of the FTD phenotype and rarely as the predominant clinical manifestation. It is characterized by the rigid akinetic syndrome, insensitive to levodopa. Tremor is uncommon and may be postural, action, or occasionally at rest.

Conclusion: To our knowledge, this case study may represent the first case of an FTD-associated mutation presenting with parkinsonism preceded by essential tremor like syndrome, thus expanding the clinical spectrum of GRN-related disorders.

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## ATYPICAL STIFF PERSON SYNDROME WITH ANTI-IGLON5 ANTIBODIES: A CASE REPORT

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Stiff Person Syndrome (SPS) and IgLON5 disease are two apparently unrelated rare neuroimmunological disorders. The mean features of SPS are rigidity and painful spasms while the mean features of IgLON5 disease are parasomnias, bulbar symptoms, cognitive impairment, respiratory failure and IgLON5 antibodies. Herein we report a case of neuromuscular hyperexcitability overlapping with Stiff Person Syndrome associated with anti-IgLON5 antibodies positivity. An 82-year-old man presented with a 2-year history of widespread muscular fasciculations, cramps, and limb stiffness which resulted in sudden spontaneous movements in the right lower limb, unsteady gait and multiple falls. Electrodiagnostic studies (EDX), laboratory tests with an antibody panel, diagnostic imaging and lumbar puncture were performed. EDX disclosed signs of neuromuscular hyperexcitability. CSF analysis showed high concentration of tau protein and unique-to-CSF oligoclonal IgG bands. Anti-IgLON5 antibodies were positive on both serum and CSF. Brain MRI, brain PET and body CT/PET were uninformative. Lastly the patient underwent videopolysomnography (VPSG), which resulted normal. No anti-IgLON5 disease-specific "core features", previously appointed, were detected. Treatment with IV corticosteroids, followed by oral benzodiazepines prompted functional recovery, which persisted at a four-months follow-up. This case demonstrates a unique overlap between neuromuscular hyperexcitability and Stiff Person Syndrome with a so far never reported seropositivity for anti-IgLON5 antibodies. Future evaluations are necessary to confirm whether such findings could lead to a broadening of the SPS clinical and laboratory features.

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## BOTULINUM TOXIN ADMINISTRATION IN PARKINSONIAN PATIENTS WITH LATERAL TRUNK FLEXION SUGGESTING EARLY PISA SYNDROME

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Aim: Pisa Syndrome (PS) is a postural disorder, occurring in about 9% of patients with Parkinson's disease (PD), defined as a lateral trunk flexion of at least 15 degrees that can be completely alleviated by passive mobilization or supine positioning [1]. We aimed at evaluating the clinical and electromyographical response to botulinum toxin (BoNT) injection in PD patients with lateral trunk flexion suggesting a probable evolution towards clinically defined PS.

Materials and Methods: 17 PD patients with trunk lateral flexion were recruited from our Movement Disorders Clinic between 2021 and

2023. A 50 UI/ml BoNT solution was injected in various points (100 UI total) of the paraspinal muscles ipsilaterally to the trunk bending side. We assessed our patients at baseline, 1 month (1m) and 3 months (3m) after BoNT injection. Lateral flexion angle was measured by software calculator Kinovea, Perpendicular Method, on planar view photographs. Clinical scales used were: Unified Parkinson Disease Rating Scale (UPDRS), Parkinson Disease Questionnaire-8 (PDQ-8), Numeric Pain Rating Scale (NPRS), Patients' Global Impression of Change scale (PGIC). An eight-channel surface electromyograph (EMG) recorded activity of paraspinal cervical (C6-C7), thoracic (T8-T10), lumbar (L2-L4) and oblique abdominal muscles bilaterally, while video recording the patient standing with and without active flexion of the trunk, sitting and laying. Data were compared using Student's t test for dependent means.

Results: Patients showed a mean lateral bending of 6.9±3.2, 5±2.4, 6.3±5.3 degrees at baseline, 1m and 3m respectively (baseline-1m p .0019, baseline-3m p .5905), PDQ-8 scores of 3.8±2.9, 3.9±3.2, 3.9±3.6 (baseline-1m p .7175, baseline-3m p .7610), back NPRS of 3.8±3.1, 2.6±2.5, 2.5±3.4 (baseline-1m p .0129, baseline-3m p .1653). 82 and 94% of the sample reported a global improvement (PGIC scores ≥3) at 1m and 3m, respectively. Qualitative EMG signal analysis showed almost uniform improvement in global paraspinal muscle activation.

Discussion: Our population differs from previous studies as we considered patients with a pre-clinic condition of PS (lateral trunk deviation lower than 15°). BoNT is known to have a beneficial effect on PS but is still not clear whether to follow the clinic (bending side, pain) or the EMG-confirmed activation [2,3]; we obtained a significant spine angle reduction when targeting the bending side, rather than the most activated side.

Conclusions: BoNT injection ipsilateral to the trunk bending side, regardless of EMG activity, resulted in our study in a reduction of the lateral flexion at 1m, partially reverted at 3m, complemented by a subjective clinical improvement.

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## DYSBIOSIS OF GUT MICROBIOTA IN PARKINSON'S DISEASE AS A POTENTIAL BIOMARKER OF DISEASE SEVERITY AND PROGRESSION

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Objective: In recent years several studies revealed dysbiosis of gut microbiota as a well-established hallmark in Parkinson's disease (PD) [1]. However, it is still unclear whether microbiota alterations, in PD, represent a pathogenetic starting point or also a consequence of disease [2]. Therefore, our aim was to investigate microbiota alterations in PD as a potential biomarker of disease severity and progression.

Materials: Microbiota compositions was studied through 16rRNA amplicon sequencing and classified to taxonomic rank through bioinformatic analysis. Stool samples were collected through pre-analytical sample processing collection tubes, to ensure storage/conservation of DNA for at least three months.

Methods: To study microbiota as a severity biomarker, we compared faecal samples collected from three groups, representative of three different times in the natural history of the disease: healthy controls (HC), PD patients at the time of diagnosis (de-novo PD), PD patients in advanced stages, defined by H&Y stage≥3 and/or LEED>900mg (advPD). A multivaristatistical analysis was performed to identify differential abundant taxa between three groups considering the effect of potential confounding factors, like lifestyle and eating habits. To study microbiota as a prognostic biomarker, we followed longitudinally 2 groups of de-novo PD: a group with dysbiosis and a group without microbiota alterations at the time of diagnosis. The two groups underwent motor, non-motor and cognitive assessment at baseline and follow-up of 2 years.

Results: For the first study we enrolled 79 HC, 30 de-novo PD and 38 advPD. We found a progressive reduction both in alfa and in beta-diversity and a progressive reduction in Lachnospiraceae, Bacteroidaceae, Prevotellaceae and Clostridiaceae families moving from HC to de-novo PD and finally to advPD, and a reverse trend in Enterobacteriaceae and Lactobacillaceae families. For the second research line we enrolled 13 dysbiotic and 11 eubiotic de-novo PD. At two years follow up, dysbiotics showed a more severe worsening of motor impairment, non-motor symptoms and in some cognitive domains compared to eubiotics. Moreover, dysbiotic patients needed more LEED respect to patients without dysbiosis.

Discussion: We showed how, moving from the early to the advanced stages of PD, gut microbiota become gradually destructured, assuming a pathologic and pro-inflammatory arrangement. Moreover, we demonstrated that the presence of dysbiosis at the diagnosis probably underlie a more severe phenotype of the disease.

Conclusion: Dysbiosis of gut microbiota represents a key to extend our knowledge on the pathogenesis of PD and it deserves the utmost attention for its potential therapeutic implications.

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## PREDICTORS OF LEVODOPA-INDUCED DYSKINESIA IN PARKINSON'S DISEASE

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Background and Objectives: Levodopa-induced dyskinesia (LIDs) is a potential motor complication of chronic dopaminergic treatment in

patients with Parkinson's disease (PD), consisting of choreoathetoid involuntary movements associated with motor fluctuations, with a negative impact on the quality of life. The aim of this study was to determine the clinical and biological predictors of LIDs development in PD.

Materials: We retrospectively and prospectively collected data from PD patients followed up at the Movement Disorders outpatient Service, at Gemelli Hospital, Rome, Italy, between 2021 and 2023, with a diagnosis of "clinically defined PD" [1] and age between 18 and 80 years old.

Methods: All patients underwent a clinical evaluation in the best ON-medication state. Motor impairment and presence of LIDs were assessed with MDS-UPDRS parts III-IV, respectively. A minimal set of clinical and demographical data was collected (age, sex, age at disease onset, disease duration, ongoing dopaminergic therapy). A subgroup of patients underwent 123I-FP-CIT-SPECT brain imaging at diagnosis. All patients underwent venous blood sample collection and, a subgroup, lumbar puncture to collect cerebrospinal fluid (CSF). Total-alpha-synuclein (t-a-syn) levels were measured in both serum and CSF, with commercially available ELISA kits. Differences in clinical and demographical data between dyskinetic and non-dyskinetic patients were assessed with parametric and non-parametric tests as needed. Logistic regression models were employed to assess relationships between categorical and continuous variables.

Results and Discussion: A total of 104 patients were enrolled, of whom 54 underwent lumbar puncture. 123I-FP-CIT-SPECT uptake values were available for 50 patients. Longer disease duration, higher levodopa equivalent daily dose (LEDD) intake and worse MDS-UPDRS part III scores were independently associated with LIDs development, as expected [2]. With regard to biological data, no differences were found in t-a-syn levels in patients with and without LIDs, in both serum and CSF. Interestingly, the degree of putaminal dopaminergic denervation at diagnosis, measured with semiquantitative analysis of 123I-FP-CIT-SPECT uptake values, was independently associated with the development of LIDs. This association was significant also when correcting with age at disease onset, disease duration and LEDD.

Conclusion: PD patients with longer disease duration, higher LEDD intake, worse motor impairment and lower putaminal 123I-FP-CIT-SPECT uptake values are more susceptible to develop LIDs during the natural history of the disease. Conversely, t-a-syn levels did not show any relationship with the presence of LIDs. Putaminal dopaminergic denervation at diagnosis seems to represent the strongest predictor for LIDs development, independently from other modifiable and non-modifiable risk factors.

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## DEEP BRAIN STIMULATION OF GLOBUS PALLIDUS INTERNUS AND SUBTHALAMIC NUCLEUS IN PARKINSON'S DISEASE: A MULTICENTER, RETROSPECTIVE STUDY OF EFFICACY AND SAFETY

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Objectives: Deep Brain Stimulation (DBS) is an established therapeutic option in advanced Parkinson's Disease (PD). Literature data and recent guidelines remain inconclusive about the best choice as a target between the Subthalamic Nucleus (STN) and the Globus Pallidus internus (GPi) [1]. We aim to provide additional evidence by retrospectively evaluating outcomes in a group of patients recruited from two specialized movement disorders centers.

Materials: We retrospectively reviewed the clinical efficacy and safety outcomes of 48 DBS-implanted patients (33 STN-DBS and 15 GPi-DBS) at a short-term follow-up (<1 year from the surgery) and, for a subset of patients, long-term (2-5 years) follow-up.

Methods: To evaluate clinical efficacy, we collected MDS-UPDRS I, II, III ON-medication, III OFF-medication, IV, Levodopa Equivalent Daily Dose, Hoehn&Yahr Scores at all time-points. For clinical safety, we considered post-operative surgical complications (infections, brain lesions, ischemic strokes or hemorrhages) or the onset of severe side effects due to stimulation (suicides or other psychiatric disorders).

Results: We found no difference between STN-DBS and GPi-DBS in improving motor symptoms at short-term evaluation. However, STN-DBS achieved a more prominent reduction in oral therapy (L-DOPA Equivalent Daily Dose, p=.02). By contrast, GPi-DBS was superior in ameliorating motor fluctuations and dyskinesia (MDS-UPDRS IV, p<.001) as well as motor experiences of daily living (MDS-UPDRS II, p=.03). The greater efficacy of GPi-DBS on motor fluctuations and experiences of daily living was also present at the long-term follow-up. We observed five serious adverse events, including two suicides, all among STN-DBS patients.

Discussion: Both STN-DBS and GPi-DBS are effective in improving motor symptoms severity and complications, but GPi-DBS has a greater impact on motor fluctuations and dyskinesias [2], as well as on motor experiences of daily living.

Conclusion: These results suggest that the two targets should be considered equivalent in motor efficacy, with GPi-DBS as a valuable option in patients with prominent motor complications. The occurrence of suicides in STN-treated patients claims further attention in target selection.

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## THE ROLE OF T LYMPHOCYTES SUBTYPES AS POSSIBLE POOR OUTCOME PREDICTORS IN PARKINSON'S DISEASE

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Objectives: The aim of the present study is to evaluate, in a cohort of Parkinson's Disease (PD) naïve patients, whether peripheral

immunological parameters may correlate with long-term disease outcome.

Materials e Methods: 8 naïve idiopathic PD patients were included in the study. They were evaluated with UPDRS part III scale and a semantic fluency test, (particularly the animal fluency test). Based upon the prognostic model proposed and validated by Velseboer et al [1], we calculated the probability of an unfavorable outcome, intended as the development of dementia or postural instability (Hoehn and Yahr $\geq 3$) at 5 years from disease onset. Furthermore, we correlated this probability with lymphocyte count, cytofluorimetric T cell subsets and, through polymerase chain reaction (PCR), the expression of transcription factors involved in lymphopoiesis (such as STAT1, STAT3, STAT4, STAT6, RORC, TBX21, GATA3, NR4A2 and FOXP3). Statistical analyses were conducted using Pearson correlation coefficient (r) and t-student test.

Results: A positive correlation was found between a poor outcome and CD4+ T cells absolute count ($r = 0.62$, $p < 0.05$), while no correlation was found with CD3+ nor with CD8+. Subsequently, we evaluated CD4+ T cell subsets: T helper (Th)1 were positively correlated with a poorer outcome ($r = 0.60$, $p < 0.05$), while a negative correlation was found between Th2 and an unfavorable outcome ($r = -0.41$, $p < 0.05$). No correlation was found with Treg nor Th17, even if RORC expression had a significant correlation with the poor outcome ($r = 0.67$, $p < 0.05$). No additional correlation was found with the transcription factors analyzed.

Conclusion: Peripheral immune system plays a key role in the pathophysiology of PD both centrally and in the periphery. Particularly, patients display a pro-inflammatory phenotype characterized by increased Th1 and Th17 cells, a decrease of Th2 and dysregulation of Treg compartment. Whether it may be considered a predictor of clinical outcome has not yet been investigated. Even considering the small sample size, in the present study we identified a possible correlation between Th1 cells and poor outcome, suggesting that a greater pro-inflammatory state from the beginning may influence disease course.

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## DUAL-TASK GAIT INSTABILITY AS CORE FEATURE OF PARKINSON'S DISEASE WITH MOTOR FLUCTUATIONS

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Introduction: State specific objective of study: Gait alterations and instability are common during the course of Parkinson disease (PD) and can threaten patents to fall and impact quality of life. Progression of gait alterations, their response to treatment and their differences between stages of the disease is still theme to debate. Motor fluctuations are a common complication of levo-dopa therapy and are characterized by clinical motor changes during the day splitted in ON and OFF phases. Aim of the study is to analyze the differences in gait patterns between PD patients with (PD-F) and without motor fluctuations (PD-N) in PD patients.

Methods: The prospective study included consecutive PD patients with and without motor fluctuations who underwent an extensive motor assessment in supervised conditions using mobile health technology (MHT). All patients with motor fluctuations were evaluated in ON condition and patients with motor dyskinesia were excluded from the analyses. The MHT assessment include gait at normal fast and motor/cognitive dual-task conditions. Differences in step time, gait phases duration, asymmetry and variability were evaluated in PD with and without motor fluctuations adjusting for the effect of age, sex and disease severity.

Results: One-hundred four PD patients entered the study, including 62 PD-N and 42 PD-F evaluated in ON conditions (mean age of 67.56 SD=8.25, mean MDS-UPDRS III of 20.67 SD=12.48, mean disease duration 8.7 years SD=12.48). In analyses adjusted for motor severity, PD-F exhibited increased double limb support and stance time and decreased swing time compared to PD-N. The differences increased from normal and fast walking conditions to dual-task walking. Asymmetry index, and gait variability was similar between PD-F and PD-N, whereas step length was decreased in PD-F in fast conditions.

Conclusion: This multicenter study using MHT showed that PD patients with motor fluctuations have a higher instability compared to PD without motor fluctuations, even when evaluated in ON conditions. The findings are highly relevant, as they might indicate a suboptimal treatment response in ON phases and underline a higher risk of falls in this specific populations. Further larger on-going analyses combining supervised and home-based unsupervised MHT assessment are important to evaluate the fluctuations of gait disturbances during the day and their impact on risk of falls and quality of life.

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## VOICE CHANGES ANALYSIS IN PARKINSON'S DISEASE: PRELIMINARY RESULTS OF A MULTICENTRIC STUDY

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Introduction: Phonation is a complex activity that is altered in Parkinson's Disease (PD), causing hypokinetic dysarthria. An algorithm can analyze more than 6300 parameters in a vocal track, which can help identify different conditions not only involving the phonatory organs but also neurodegenerative diseases like PD. In this study, we aimed at investigating voice alterations in PD patients, using machine-learning techniques to extrapolate potential useful biomarkers that might help clinicians in the diagnosis of PD and disease progression.

Methods: In the preliminary phase of this multicentric clinical study, we enrolled subjects into two groups, one consisting of healthy controls (HC) and the other selecting patients diagnosed with PD according to the UK Parkinson's Disease Brain Bank diagnostic criteria. Subjects with cognitive impairment or respiratory, gastro-esophageal, auditory system, or vocal fold diseases were excluded. We collected their medical history and pharmacological conditions. UPDRS-III and H&Y scales were performed to define the disease stage. Additionally, clinical scales, including NMSS, MMSE, Hamilton depression scale and VHI were used. We recorded the patients' voices using a specific portable recording device in a quiet and comfortable

setting. The vocal track files were then uploaded to an online platform and analyzed offline.

Results: From the preliminary analysis of our center, results show that machine learning approaches can identify PD patients with high accuracy compared to HCs. Those findings confirm what was established in previous studies of the voice changes in PD, and the final phase of our research aims at strengthening those results, enrolling a wider sample, consisting in more than 150 patients. In addition, we demonstrate that voice changes in PD subjects can discriminate between early stage and mid-advanced stage patients, confirming the potential role of voice analysis as a biomarker in the recognition and stratification of the disease stage. Our preliminary findings are based on a sample from a single center in the context of a multi-center study. We also plan to perform an 18-month follow-up on a subset of patients to observe voice changes over time.

Conclusion: Preliminary data from this study are consistent with the literature and demonstrate that voice analysis allows discriminating PD subjects from HC with high accuracy. The sample dimension will be implemented, encompassing voice changes over time to better determine how to apply machine-learning analysis in clinical practice.
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## MOBILE HEALTH TECHNOLOGY POSTURAL ASSESSMENT AND FEAR OF FALLING IN PROGRESSIVE SUPRANUCLEAR PALSY AND PARKINSON'S DISEASE

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Objectives: Progressive Supranuclear Palsy (PSP) is a neurodegenerative disease clinically characterized by symmetric parkinsonism associated with earlier postural instability and falls compared to Parkinson's disease (PD). Mobile Health Technology (MHT) assessment can objectively evaluate postural instability under supervised conditions. The differences between postural instability characteristics and compensations mechanisms in PD and PSP are still theme of debate.

Materials: 250 subjects entered the study, namely 27 participants with PSP, 44 with PD who have experienced at least 1 fall in the last year, 63 with PD who have not experienced any fall in the last year, and 116 healthy control subjects performed static sway tests.

Methods: Static balance was evaluated with instrumented (lower back accelerometer, Rehagait®, Hasomed, Germany) 30-s trials in side by side, semitandem and tandem positions and functional reach test. The data were analysed to determine what balance parameters discriminated PSP from PD and HC and to detect the correlation of these technological measures with clinical assessment.

Results: PD with falls and PSP exhibited similar increased volume of perturbation compared to both HC and PD falls; only 44.4% of PSP patients were able to complete the functional reach tests and exhibit the worste performance in the cohort. When adjusted for severity, PSP exhibited lower volume of perturbation compared to PD with falls and higher anteroposterior acceleration and speed in PSP compared to PD without falls. The fear of falling was higher in PSP (100%), followed by PD with falls and PD. In parkinsonian patients with and without fear of falling, the volume of perturbation in static balance was higher in PD with falls compared to PSP. In PSP patients, disease severity did not correlate with age, or disease duration but with several digital parameters, including the volume of perturbation and anteroposterior speed/acceleration.

Discussion: PSP patients exhibit a similar postural instability pattern compared to PD with falls but lower perturbation volume when adjusting for severity. Different pathophysiology and compensations mechanism are thus probably related to postural instability and falls in parkinsonian patients.

Conclusions: In this study we compared postural instability characteristics in patients with PD (with and without falls) and PSP, finding significant differences in the volume of perturbation between these groups. Further studies evaluating the progression of postural instability using MHT and the efficacy of rehabilitation in different settings are pivotal to improve the general management of parkinsonian patients with falls.
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## BODY-FIRST VS. BRAIN-FIRST SUBTYPES OF PARKINSON'S DISEASE: PATHOPHYSIOLOGICAL INSIGHTS FROM EEG-BASED FUNCTIONAL CONNECTIVITY

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Objective: REM sleep behavior disorder (RBD) is highly associated with Parkinson's disease (PD) [1] and may precede the onset of motor symptoms by years. According to a recent hypothesis, isolated RBD before parkinsonism (premotor RBD, pRBD) is a marker of the PD body-first subtype, where synucleinopathy originates from the peripheral autonomic nervous system and then spreads to the brain. Conversely, in the brain-first subtype of PD, synucleinopathy would initially arise in limbic brain areas [2]. Functional connectivity (FC) could improve the understanding of clinical and pathophysiological features of these putative PD subtypes. In this study, we aim to analyze the possible differences in FC between early-stage PD patients with and without pRBD, by means of high-density EEG.

Materials and Methods: We enrolled 67 subjects, including 26 early-stage PD patients without pRBD (PDpRDB-), 17 early-stage PD patients with pRBD (PDpRBD+) and 24 healthy controls (HC). Resting-state EEG was recorded using a 64-channels system, and a source reconstruction method, based on individual brain MRI, was used to identify brain regions activity. Cortical FC in theta, alpha and beta

bands was analyzed based on weighted phase-lag index. Possible FC changes in the various frequency bands between HC, PDpRDB- and PDpRBD+ were assessed using network-based statistics.

Results: With respect to HC, PD patients showed hypoconnected networks in theta and alpha band, involving prefronto-limbic-temporal and fronto-parietal areas, respectively. When comparing the PDpRDB- and PDpRBD+ subgroups, we found a lower FC in the alpha frequency band in PDpRBD-, which involved a network composed by temporo-parietal (29.6%), frontal (22.8%) and sensorimotor (21.0%) areas (t=2.5, p=0.025). No differences were found in the other frequency bands.

Discussion: Previous evidence suggested a relationship between alpha-FC and cholinergic system dysfunctions in PD. Hence, the reduced FC in the alpha frequency band we found in PDpRBD+ patients may underlie an early alteration of brainstem cholinergic pathway, which projects widely to the cortex, in patients with the body-first PD subtype. Moreover, since alpha rhythm abnormalities have a role in PD dementia [3], our data of an early alpha FC impairment in temporo-parietal areas in PDpRBD+ support the hypothesis that patients with the body-first subtype are more prone to progress to dementia than brain-first PD [2].

Conclusions: Compared to brain-first PD, the body-first PD subtype demonstrates specific EEG-FC dysfunctions in the alpha frequency band, which may reflect an early involvement of the cholinergic subcortical system.

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## SLEEP QUALITY IN FLUCTUATING PARKINSON'S DISEASE PATIENTS: ROLE OF DOPAMINERGIC THERAPY

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Introduction: Parkinson's disease (PD) is characterized by cardinal motor symptoms (bradykinesia, rest tremor, rigidity), and several nonmotor symptoms. [1] Among these, sleep dysfunction is highly prevalent (60%-98% of PD patients). [2,3] Several antiparkinsonian drugs have been demonstrated to influence sleep quality, with conflicting results.

Objectives: To evaluate on a large cohort of advanced PD patients the role of dopaminergic treatment in influencing sleep disturbances (i.e., reduced sleep quality and excessive daytime sleepiness [EDS]).

Methods: Patients consecutively evaluated for device-aided therapies eligibility were enrolled. Sleep dysfunction was measured by means of the PD Sleep Scale-2 (PDSS-2; score ≥18 indicates poor sleep quality), and the Epworth Sleepiness Scale (ESS; score ≥10 indicates EDS). The association between dopaminergic therapy (i.e., dopamine agonists [DA], nocturnal extended-release levodopa, total levodopa equivalent daily dose [LEDD], DA-LEDD, and levodopa-LEDD) and disturbed sleep or EDS was evaluated with binary logistic regression analysis, correcting for age, sex, disease duration, motor impairment (Off-state MDS-UPDRS-III), and sleep treatment. Analysis of covariance was used to evaluate differences in PDSS-2 (total and sub-domains scores) and ESS between patients with and without DA treatment, and between patients treated with low or high doses of DA (cut-off: DA-LEDD=180 mg), correcting for the same potential confounders.

Results: We enrolled 281 patients (males: 66.5%; age: 60.3±7.9 years; disease duration: 11.6±3.7 years). 66.2% of patients reported poor sleep quality; 34.5% reported EDS. After adjusting for confounders, DA treatment showed a 2-fold lower odd of presenting relevant nocturnal sleep disturbances (OR: 0.498; p=0.035), while there was no statistically significant association between sleep quality and DA-LEDD, levodopa-LEDD, total LEDD and nocturnal extended-release levodopa. EDS was not significantly influenced by the dopaminergic regimen. We observed a significant better sleep quality in patients with DA therapy compared to those not treated with DA, with lower PDSS-2 total score (21.7±0.7 vs. 24.9±1.3; p=0.027) and lower "nocturnal motor symptoms" domain score (6.4±0.3 vs. 8.1±0.6; p=0.044). Finally, patients with higher doses of DA showed lower PDSS-2 total score compared to patients without DA treatment (p=0.043).

Conclusions: DA, in particular at higher doses, can improve overall sleep quality in advanced PD patients, especially by improving motor symptoms at night. Interestingly, improvement in sleep quality was not accompanied by a significant increase in EDS, a well-known side effect of DA. The recent increasing attention on PD non-motor symptoms may enforce the need to better understand the role of dopaminergic treatment in sleep quality.

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## HYPERTENSION IN THE OFF PHASE RESCUED BY LEVODOPA IN ADVANCED PARKINSON'S DISEASE

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Objective: High blood pressure is rarely reported in Parkinson's disease (PD). However, it is unclear how high blood pressure relates to dopaminergic state in PD. Here, we aimed to investigate the relationship between blood pressure values and dopaminergic medication state (OFF and ON) in people with advanced PD.

Materials and Methods: Consecutive subjects with advanced PD were enrolled at the Advanced Therapies MDS Centre of St George's University Hospital. Clinical characteristics, including age, gender, disease duration, and levodopa equivalent daily dose, were recorded. Motor and non-motor symptoms were evaluated using standardized rating scales. Blood pressure measurements were taken in the practically defined OFF-MED (after 12 hours without medication) and ON-MED (at 1 hour after administering 150% of morning Levodopa dose) in sitting and standing up (at 3 minutes) position. The diagnosis of hypertension was based on the 2018 ESC/ESH Clinical Practice Guidelines for the Management of Arterial Hypertension.

Accordingly, we categorized subjects in hypertensive-PD and normotensive-PD.

Results: Among 61 recruited advanced PD patients, 35 had hypertension in the OFF-MED condition as per ESC/ESH guidelines. Only 6 of these subjects had a history of hypertension and were on antihypertensive medication. After levodopa administration, 8 patients still displayed hypertension and 26 became normotensive. None of the subjects with normal blood pressure values in OFF MED, had high blood pressure in ON MED. None of the subjects had hypotension in OFF in the sitting position. Ten subjects had orthostatic hypotension both in the OFF MED and ON MED conditions. Repeated measures ANOVA with group (normotensive-PD vs hypertensive-PD) showed a significant effect of medication ($p<0.001$) and group ($p<0.001$) for blood pressure measured in the sitting position. For blood pressure measured in the standing up position, Repeated measures ANOVA showed an effect of medication ($p<0.001$), group ($p<0.001$) and an interaction between group and medication ($p<0.03$). These effects were driven by the hypertensive-PD group which had significant decrease of blood pressure by levodopa administration. Factorial ANOVA comparing the two groups of PD subjects showed higher scores of the Wearing off questionnaire (WOQ-19) ($p=0.047$) and the Gait and Falls Questionnaire Total Score ($p=0.006$).

Discussion and Conclusion: Hypertension in OFF MED is highly prevalent in advanced PD and it is associated to more severe wearing off and gait dysfunction. These results suggest that hypertension should be considered among OFF period symptoms and properly treated.

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## IRON DEPOSITION WITHIN THE BASAL GANGLIA AND THALAMUS IN EARLY DRUG-NAÏVE PARKINSON'S DISEASE PATIENTS WITH AND WITHOUT REM BEHAVIORAL DISORDERS


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Objective: Epidemiological studies suggest that Parkinson's disease (PD) patients with REM sleep behavioral disorder (RBD) present an increased risk of worse motor progression and dementia over the disease course. Iron deposition assessed by means of Quantitative Susceptibility Mapping (QSM) has been reported in several cortical and subcortical areas in patients with PD, and a relationship with the development of cognitive decline has been proposed. In this study, we aimed at exploring whether the presence of RBD is associated with a specific pattern of iron deposition in early cognitively unimpaired drug-naïve PD patients, and to correlate MRI findings with cognitive outcomes.

Materials: 3T MRI images of 58 drug-naïve PD patients (29 PD-RBD+ and 29 PD-RBD-) and 18 healthy controls, were analyzed and compared.

Methods: QSM values were extracted from 22 subcortical gray matter nuclei and 16 thalamic subregions. A partial correlation analyses were run between MRI metrics and clinical data. Finally, a ROC curve was performed to test the ability of QSM values in distinguishing PD-RBD+ from PD-RBD- patients.

Results: Compared to PD-RBD-, PD-RBD+ patients showed higher susceptibility values within the right red nucleus, left subthalamic nucleus, left anteroventral thalamus nucleus, right mediodorsal medial magnocellular thalamus nucleus, bilateral medial, left anterior and right lateral pulvinar. QSM values were found to be associated with the cognitive outcome. The ROC curve analysis showed that QSM values could significantly and accurately identify the presence of RBD in drug-naïve PD.

Discussion: This study provides evidence that higher iron deposition within different subcortical nuclei may differentiates PD patients with RBD even in the early stages. This pattern is associated with progressive impairment in executive and attention functioning.

Conclusions: We hypothesize that these findings may reflect the presence of more diffuse neuropathological changes occurring at the disease onset, potentially leading to altered cognitive processing and increased vulnerability to the future development of dementia.

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## CERVICAL DYSTONIA IN A PATIENT WITH CERVICAL HYDROMIELIC CAVITY


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Background: Cervical dystonia is a focal dystonia affecting the neck, resulting in abnormal head postures [1]. Structural lesions of the central nervous system (CNS) represent a cause of secondary cervical dystonia [2]. In the literature, 18 definite cases of concomitant dystonia and syringomyelia have been described, although a causative association between them has not been established [3]. To the best of our knowledge, we report the first case of concomitant cervical dystonia and cervical hydromyelia.

Case presentation: A 42-year-old man presented with a 12-month history of neck stiffness and involontary right head turning. He reported a minor head trauma at the age of 15 and he was not undergoing any pharmacological treatment. Neurological examination revealed cervical dystonia with right torticollis and clear gestes antagonistes, associated with right shoulder elevation and intermittent dystonic head tremor. He also presented mild gait ataxia, bilateral intention tremor, left hand adiadochokinesia and lower limbs brisk reflexes. A comprehensive clinical and laboratory work-up was performed, including blink reflex recovery cycle, somatosensory evoked potentials (SEPs), motor evoked potentials (MEPs), electromyography (EMG), 3-T brain and cervical spine magnetic resonance imaging (MRI) with gadolinium-based contrast. Neurophysiological studies showed increased blink reflex recovery cycle, prolonged latency of MEPs and SEPs and abnormal tonic activity of right trapezius, right splenius capitis and left sternocleidomastoidei muscles at EMG. Brain MRI was unremarkable, while T2-weighted images obtained from a cervical spine MRI study, showed a focal fluid-filled

cavity centrally located within the spinal cord at C6 level and lined by the normal ependymal lining of the central canal, corresponding to a large hydromyelic cavity. The clinical picture and MRI findings remaines unchanged at 6-month follow-up. The patient's dystonia was successfully treated with botulinum toxin injections.

Conclusion: This patient was diagnosed with cervical dystonia and cervical hydromyelic cavity, and as far as we know, this represents the first case described in the literature. Although a causative association has not been definitively established, a possible underlying mechanism could be the alteration of sensorimotor integration, which may lead to a disruption of the dystonia network. The results of our neurophysiology study align with this hypothesis. Further cases need to be described, and additional research is required to investigate the nature of the association between dystonia and hydromyelia, in order to advance towards improved management and treatment of this condition.

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## THE EFFECTS OF DOPAMINERGIC TREATMENT ON INTERHEMISPHERIC DISINHIBITION AND BRADYKINESIA ASYMMETRY IN PARKINSON'S DISEASE

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Objective: Previous evidence demonstrated a reduced interhemispheric inhibition (IHI) in Parkinson's disease (PD), possibly related to the asymmetry of motor symptoms. However, the effects of dopaminergic treatment on interhemispheric disinhibition and motor correlates in PD, have never been investigated. We aim to investigate whether dopaminergic therapy modulates IHI and bradykinesia asymmetry in PD.

Material and Methods: We enrolled seventeen PD patients (mean age ± standard deviation - SD: 67.5±9.2 years) and 15 healthy controls (HCs) (mean age ± SD: 64±8.1 years). Patients were studied with and without their dopaminergic therapy (ON and OFF sessions, mean LEDD ± SD: 483.8±173.2). Paired-pulse transcranial magnetic stimulation (TMS) served to measure IHI, with an interstimulus interval (ISI) between the conditioning (CS) and the test stimulus (TS) of 10 (short-latency IHI, sIHI) and 40 ms (long-latency IHI, lIHI). Objective finger-tapping measurements were obtained bilaterally with a motion analysis system5. We compared data between patients and HCs, and between patients ON and OFF medication using t-tests. We also calculated asymmetry indices (AI) of neurophysiological data. Correlations analysis was performed to test possible relations between TMS and kinematic data.

Results: As compared to HC, PD OFF medication had a reduced sIHI from the most to the less affected hemisphere ($p=0.02$). Finger tapping was slower, more irregular and characterised by the sequence effect in PD OFF medication as compared to HCs (all $p<0.05$). Interhemispheric imbalance quantified by the sIHI-AI correlated with the sequence effect of the less affected side in patients OFF medication ($R=-0.5$, $p<0.03$). Although improving movement velocity ($p=0.009$), dopaminergic treatment did not modify sIHI or the sequence effect ($R=0.23$, $p>0.05$).

Discussion: Only certain bradykinesia features are asymmetrical: the various features of bradykinesia may be underlain by distinct pathophysiological mechanisms. The differential effects of dopaminergic therapy on bradykinesia features and on their asymmetry also support the present hypothesis. We also found novel evidence of the role of interhemisperic connections imbalance in the pathophysiology of bradykinesia, somehow influenced by dopaminergic therapy.

Conclusions: We here provided further evidence on the pathophysiological role of interhemispheric disinhibition in bradykinesia asymmetry in PD with a focus on the effects of dopaminergic treatment.

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## FATIGUE AND PARKINSON'S DISEASE: FOCUS ON THE CAREGIVER'S BURDEN

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Introduction: Fatigue, defined as a decreased level of energy, or a sense of exhaustion unexplained by physical or psychological distress, is a frequent yet underestimated non-motor symptom of Parkinson's Disease (PD) [1]. It is a key determinant of patient's disability, with a severe impact on quality of life. However, the impact of fatigue on caregiver's burden has not been evaluated so far.

Objective: To assess the impact of fatigue on caregiver's burden on a cohort of PD patients

Methods: We enrolled 53 patients (males: 66.0%; age: 70.53±8.36 years; disease duration: 11.11±7.44 years) and their primary informal caregivers. Patients' fatigue was evaluated with scales validated for PD [2,3], with consistent cut-offs for defining the presence of significant fatigue, the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (mFIS). Caregiver's burden was measured by means of the Zarit Burden Interview (ZBI). We evaluated the differences in the ZBI score between caregivers of patients with and without fatigue by means of the analysis of covariance, correcting for the following potential confounders: patients' and caregivers' age, disease duration, motor disability (MDS-UPDRS-III score). Linear regression analysis, corrected for the same confounders, was used to evaluate correlations between ZBI, FSS, and mFIS scores.

Results: Significant fatigue was reported by more than 70% of patients with both scales. After correcting for potential confounders, caregivers of patients with fatigue reported 2-fold higher ZBI scores, both using FSS (34.36 ± 2.76 vs. 16.53 ± 6.08; $p=0.013$) and mFIS (36.12 ± 2.72 vs. 17.03 ± 4.80 vs; $p=0.002$) to define significant fatigue. ZBI score was significantly correlated with fatigue, in particular with total mFIS (Beta=0.712; $p<0.001$) and mFIS subdomains

(Physical: Beta=0.568, Cognitive: Beta=0.645, Psychosocial: Beta=0.408; p<0.001).

Discussion and Conclusion: Fatigue is a frequent yet underestimated symptom of PD, frequently reported even in the early stages of the disease. To the best of our knowledge, this is the first study assessing its impact on the quality of life and burden of caregivers. We showed that fatigue is an independent determinant of high caregiver's distress. A better understanding and a careful evaluation of fatigue could be of utmost importance to ameliorate not only patients' but also caregivers' well-being.

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## UNCONVENTIONAL THERAPY FOR ACUTE-ONSET LESIONAL HEMIBALLISM

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Introduction: Cerebrovascular diseases are the most common causes of secondary hypokinetic or hyperkinetic movement disorders [1]. Among acute-onset hyperkinetic movement disorders, hemiballism (HB) is the most frequent one [2]. Even though up to 90% of them may wear off within six months, involuntary movements may severely compromise patients' quality of life, so that symptomatic treatments are required. Typical and atypical neuroleptics as well as Tetrabenazine represent therapies of choice. Anecdotal reports of antiseizures medications effectiveness and successful use of botulinum neurotoxin (BoNT) injection have been rarely described [1][2][3].

Case presentation: A 78 years-old man with an history of vascular parkinsonism and undetermined onset tonic-clonic seizures, came to our attention for an acute-onset left hemiballism with homolateral hemiparesis. Brain CT scan showed a right thalamo-mesencefalic hemorrhage, while blood tests revealed acute kidney failure secondary to severe rhabdomyolysis (CPK > 80000 U/L). Due to the persistence of severe hemiballism causing cutaneous injuries and interference even with sitting balance together with the ongoing rhabdomyolysis, symptomatic therapy was required. Nevertheless, QTc interval prolongation and renal function impairment limited the dosage of neuroleptics and benzodiazepines. Despite several combined approaches including Tetrabenazine, low-dose of Quetiapine, Clonazepam and Diazepam, 20 days after the onset, the left-sided hemiballism remained severely disabling. Thus, the patient received BoNT injections in his left upper limb muscles (onabotulinumneurotoxinA 200 UI: biceps brachii, triceps brachii, teres major, deltoid) and low-dose of Topiramate (37.5 mg/die), that were followed by the gradual reduction of hyperkinetic movements. In the following months, Topiramate was gradually discontinued after about five weeks of treatment without any significant motor clinical worsening. At 6 months follow-up visit, due to severe HB rebound the patient was wheelchair-bound, so BoNT injections were repeated.

Discussion: We describe a case of disabling HB, where high-dosage of first-line therapies were contraindicated due to comorbidities. In this scenario, we decided to combine Topiramate and BoNT injections in the left upper limb muscles, where ballism was more prominent with consequent gradual reduction of involuntary movements. The discontinuation of Topiramate did not modify the clinical picture, which was, however, more severe at 6-month follow-up. So, the improvement experienced by our patient was probably ascribable to the early treatment with BoNT.

Conclusion: The present case highlights the effectiveness of unconventional therapeutic options in disabling acute onset lesional hemiballism when first-line therapies are contraindicated. Particularly, this report may encourage reflections on BoNT application in the early stage of movement disorder emergencies.

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## THEORY OF MIND AND ATTENTIONAL DEFICITS MAY DISTINGUISH FUNCTIONAL MOVEMENT DISORDERS AND PARKINSON'S DISEASE

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Objective: This work explores Theory of Mind (TOM) (the ability to attribute mental states), attentional deficits and dissociative symptoms in Functional Movement Disorders (FMDs) and Parkinson's Disease (PD) in order to identify elements that can facilitate distinction between the two pathologies. FMDs are motor manifestations not attributable to known medical conditions. The overlap of FMDs with symptoms of Parkinson's disease (PD) is frequent and distinguishing the functional component can be challenging. A neurobiologically informed model of hierarchical Bayesian inference explains functional symptoms in terms of perception and action arising from inference based on prior beliefs (priors) and sensory information. Brain damage can modify priors; loss of dopamine in the striatum is responsible for degradation of routines that overloads the attention-demanding control supporting goal-directed movements making the system vulnerable and prone to functional symptom onset that overlaps organic symptoms. The concept of altered prediction of the Baysian model is also adopted by psychosocial models on FMDs. In particular, altered TOM contributes to reduce the ability to predict mental states underlying motor behavior during social interaction leading to predicting errors whose content is the anomalous movement.

Materials and Method: Twenty-three FMDs, 23 PDs and 40 healthy controls (HCs) were recruited. Tasks exploring both affective (Reading the Mind-with-the-Eyes test-RMET) and cognitive components (Faux-pas stories) were given. The Stroop Color-and-Word test (SCWT) was adopted to explore the balance between goal-directed actions (naming) and automatic routines (reading). Classical hypothesis on dissociative symptoms related to conversion disorders was also explored by DES-II questionnaire.

Results: FMDs performed lower than HCs, with difference approaching significance (P=0.066) in RMET, and significantly lower than HCs (p<0.001) in Faux-pas stories with normal score in control questions (all p>0.1). PDs performed lower than HCs in both the RMET (p=0.027) and Faux-pas stories (p<0.001); the difference was also significant in control questions (p=0.042). Only in PDs neuropsychological tests were significantly correlated with the RMET (all <0.034); Faux-pas stories were significantly correlated with Phonological Fluency (p=0.050). In SCWT only PD produced a significant higher number of errors than HCs. Dissociative symptoms were more frequent in FMDs (p=0.018).

Discussion: Only FMDs have genuine TOM disorders, which may account for difficulties in predicting motor behavior during social interaction, whereas in PDs TOM deficits are dependent on cognitive impairment. The two groups differ in the balance between goal-directed attention and routines, and dissociative symptoms.

Conclusions: TOM and attentional disorders and dissociative symptoms may distinguish FMDs and PD.

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## EFFECTS OF SELEGILINE ON FATIGUE IN PARKINSON'S DISEASE


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Background: Fatigue is a frequent and disabling non-motor symptoms (NMS) of Parkinson's disease (PD) and no specific treatment is currently available [1]. Evidence for the role of monoamine oxidase-B receptor inhibitor (i-MAO B) in the treatment of NMS is emerging [2].

Objective: This is a single-center, prospective observational study aimed at assessing the efficacy of the selective i-MAO B Selegiline, in the treatment of fatigue in patients with PD.

Methods: Consecutive PD patients complaining of fatigue for at least three months were enrolled at the Neurology Unit, PD and Movement Disorder Division of Verona. Patients with severe NMS or chronic conditions determining secondary fatigue were excluded. Selegiline was administered with a starting dose of 5 mg/day and increased to 10 mg/day after one week. The primary outcome was the 7-point patient-rated perception of change (p-CGI) after eight weeks of treatment (T1). Secondary outcomes were changes in the mean scores of the Parkinson Fatigue Scale (PFS), Fatigue Severity Scale (FSS), and Multidimensional Fatigue Inventory (MFI) and its sub-scales. Apathy, anxiety, depression, and sleep-wake disorders were measured through validated scales.

Results: Twelve patients (8 men); mean age 64.9±11.6 years and mean disease duration 5.8±3.7 years completed the study. Two patients discontinued the medication because of minor side effects (nausea, malaise, and hypertension). After 8 week-treatment, 91.7% (n=11) of patients reported fatigue to be improved (very much-to minimally, p-CGI 1-3), while only 8.33% (n=1) did not report any change (p-CGI 4). None of the patients reported worsening fatigue. Paired samples T-Test showed a significant improvement of fatigue measured through the PFS and the sub-scale for physical fatigue of the MFI (MFI-PF) at T1 compared to baseline (p = 0.017 and p= 0.018). Other measures of fatigue (FSS and MFI-total score) showed a tendency for significance. At T1, UPDRS-III improved significantly (p = 0.03). Correlation analyses showed that improvement in PFS correlated with changes in depression, as measured by the Hamilton Depression Scales (HDS) (r 0.72, p 0.008).

Discussion: With the limitation of an open-label uncontrolled and small sample study, our results show that fatigue related to PD improved after 8 week-treatment with selegiline. All but one of the patients (91.7%, n=11) experienced a subjective amelioration of fatigue (p-CGI 1-3) and the PFS and the physical domain of fatigue significantly improved, along with a parallel reduction of motor symptoms severity (UPDRS-III). Among NMS, changes in depression influenced the positive outcome.

Conclusions: Our preliminary results suggest that Selegiline 10 mg/day might effectively relieve fatigue in PD and should be considered in the algorithm of its treatment.

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## MOCA-AOIFD: PSYCHOMETRIC AND DIAGNOSTICS OF THE MONTREAL COGNITIVE ASSESSMENT (MOCA) IN AN ITALIAN COHORT OF PATIENTS WITH ADULT-ONSET IDIOPATHIC FOCAL DYSTONIA


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Objectives: To assess the clinimetrics of the Montreal Cognitive Assessment (MoCA) in an Italian cohort of patients with adult-onset idiopathic focal dystonia (AOIFD).

Materials: N=86 AOIFD patients (blepharospasm: N=36; cervical dystonia: N=31; other phenotypes: N=19) and N=92 healthy controls (HCs) were administered the MoCA. Patients further underwent the Trail-Making Test (TMT-A/-B/-BA) and Babcock Memory Test (BMT), being also screened via the Beck Depression Inventory-II

(BDI-II) and the Dimensional Apathy Scale (DAS). Information on disease duration, disease severity and motor symptoms was also collected.

Methods: Factorial structure and internal consistency were assessed. Construct validity was tested against TMT, BMT, BDI-II and DAS scores, whilst diagnostics against the co-occurrence of a defective performance on at least one TMT measure and on the BMT. Case-control discrimination was examined. The association between MoCA scores and disease-related features was explored.

Results: The MoCA was underpinned by a mono-component structure (38.41% of variance explained) and acceptably reliable at an internal level (McDonald's ω=.67). It converged towards TMT (-.67≤rs(86)≤-.55; ps<.001) and BMT (rs(86)=.66; p<.001) scores, as well as with the DAS (rs(82)=-.37; p<.001), whilst diverging from the BDI-II. Its adjusted scores [1] accurately identified patients with cognitive impairment (i.e., 8%) at a cut-off of <17.212 (AUC=.86; sensitivity=.71; specificity=.92; positive predictive value=.46; negative predictive value=.97; positive likelihood ratio=9.41; negative likelihood ratio=.31; Number Needed for Screening Utility=.82). No association has been detected between the MoCA and disease duration, disease severity and motor phenotype. The MoCA discriminated patients from HCs (z=-5.99; OR=.50, CI 95% [.39, .62]; p<.001) with a classification accuracy of 80% (AUC=.90; sensitivity=.86; specificity=.74).

Discussion: The present study provides evidence on the clinimetric soundness and feasibility of the MoCA in AOIFD patients – by also delivering Italian practitioners and clinical researchers with disease-specific cutoffs for such a screener in this population. Indeed, the MoCA herewith proved to: 1) be valid at both factorial and construct levels; 2) be acceptably reliable at an internal level; 3) be featured by sound diagnostics; 4) be independent of disease-related features; 5) be able to discriminate patients from HCs. Considering the outcome measures herewith addressed (i.e., the TMT and the BMT), this report suggests that the MoCA is able to capture the dysexecutive-inattentive and amnestic profile that not infrequently features AOIFD patients [2].

Conclusions: The Italian MoCA is a valid, diagnostically sound, and feasible cognitive screener in AOIFD patients.

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## MOCA-PD: CLINIMETRIC PROPERTIES OF THE MONTREAL COGNITIVE ASSESSMENT (MOCA) IN AN ITALIAN COHORT OF NON-DEMENTED PARKINSON'S DISEASE PATIENTS

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Objectives: This study aimed at 1) assessing, in an Italian cohort of non-demented Parkinson's disease (PD) patients, the concurrent and convergent validity of the Montreal Cognitive Assessment (MoCA) against both first- and second-level cognitive measures; 2) delivering an exhaustive and updated evaluation of its diagnostic properties.

Materials: A retrospective cohort of N=237 non-demented PD patients having been administered the MoCA was addressed, of whom N=169 further underwent the Mini-Mental State Examination (MMSE) and N=68 the Parkinson's Disease Cognitive Rating Scale (PD-CRS). A subsample (N=60) also underwent a second-level cognitive battery encompassing measures of attention/executive functioning, language, memory, praxis and visuo-spatial abilities. Patients were free of 1) dementia due to PD, 2) further neurological/psychiatric diseases, 3) severe and/or unstable general-medical conditions and 4) uncorrected hearing/vision deficits.

Methods: Concurrent validity was assessed against the PD-CRS, whilst convergent validity against each second-level cognitive measure. Diagnostics were tested via receiver-operating characteristics analyses against a below-cut-off MMSE score.

Results: The MoCA was predictive of PD-CRS scores (β=.68; p<.001; R2=.46) and related to several second-level measures – i.e., the Stroop Color-Word Test, Trail-Making Test, Phonemic Fluency test, Verb-naming from the Esame Neuropsicologico per L'Afasia, Rey Auditory Verbal Learning Test, Design Copy test and Benton Judgment of Line Orientation test (ps<.003). Both raw and adjusted MoCA scores proved to be highly accurate to the aim of identifying patients with MMSE-confirmed cognitive dysfunctions. A MoCA score adjusted for age and education according to the most recent normative dataset [1] and <19.015 is herewith suggested as indexing cognitive impairment in this population (AUC=.92; sensitivity=.92; specificity=.80; positive predictive value=.44; negative predictive value=.98; positive likelihood ratio=4.57; negative likelihood ratio=.10; Number Needed for Screening Utility=.80).

Discussion: The present study provides Italian practitioners and clinical researchers with updated evidence on the validity and diagnostic value of the MoCA in non-demented PD patients. Indeed, the MoCA herewith proved to 1) be predictive of a disease-specific measure of global cognition (i.e., the PD-CRS), 2) converge with several second-level measures of both instrumental and non-instrumental cognitive domains/functions and 3) be diagnostically sound in detecting MMSE-confirmed cognitive impairment. Overall, the current findings align with the fact that the Movement Disorders Society recommends the use of the MoCA for cognitive screening aims in this population [2].

Conclusions: The Italian MoCA is a valid and diagnostically sound screener for global cognitive inefficiency in non-demented PD patients.

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## DIAGNOSTIC ACCURACY OF SKIN BIOPSY IN DISCLOSING EARLY PD

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Aim: To analyse the diagnostic accuracy of phosphorylated α-synuclein (p-syn) in autonomic skin fibers in identifying early Parkinson's disease (PD).

Materials and Methods: One hundred twenty participants with early parkinsonian signs (onset within the last 18 months) were included in the study. Proximal and distal skin sites were taken to analyse p-syn by immunofluorescence. Patients also underwent clinical evaluation including focused scales (UPDRS and HY, MoCA, COMPASS-31, NMSQuest) and smell analysis. Clinical evaluation was repeated over a follow-up of 18 months in all patients whereas skin biopsy was repeated in 45 patients in the follow-up. Clinical diagnosis of PD was defined according to the Movement Disorder Society (2019) criteria.

Results: Seventy patients presented clinical criteria for PD (mean disease duration 10±2 months): 45 patients at the baseline recruitment whereas 25 cases only at the follow-up. P-syn was found at baseline in 61 of these patients (87%) included 19 cases with undefined clinical picture at baseline. Fifty patients did not meet clinical criteria for prodromal PD both at baseline and follow-up. They included 21 patients with a clinical diagnosis of tauopathy, vascular PD or MSA at the follow-up. P-syn was absent in these patients at baseline and follow-up except the patient with MSA showing the typical somatic p-syn. Twenty-nine patients showed an undefined clinical picture both at baseline and follow-up and p-syn was found in 6 patients but 23 were negative. Taken into account only patients fulfilling a defined clinical diagnosis at the follow-up skin biopsy (i.e. p-syn in autonomic nerve fibers) presented 87% of sensitivity and 100% of specificity in disclosing an early PD. Skin biopsy showed the same results over the follow-up in 43 patients (96%) while 2 patients fulfilling a clinical diagnosis of prodromal PD who were negative at baseline showed p-syn over the follow-up. Patients with early PD showed higher smell dysfunctions, RBD incidence, UPDRS, HY and COMPASS-31 scales. However, p-syn was not correlated with clinical scales.

Discussion: The early diagnosis for PD is a difficult problem as not reliable biomarkers are available and the clinical picture is highly not specific during this phase of the disease. Thus, reliable biomarkers are urgently needed to identify in an early disease phase patients presenting PD.

Conclusions: Our results showed that skin biopsy and skin p-syn presented an excellent diagnostic accuracy in identifying early PD. Our study corroborates the use of skin biopsy for the diagnosis of early PD.

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## IMPACT OF DEEP BRAIN STIMULATION ON THE COGNITIVE AND BEHAVIOURAL PROFILE OF PATIENTS WITH PARKINSON'S DISEASE: A CASE-CONTROL STUDY

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Objective: Deep Brain Stimulation (DBS) is an established therapy for patients with advanced Parkinson's Disease (aPD). Despite the positive outcomes in improving motor symptoms, the effects on cognitive and behavioural functions are still debated and remain controversial [1,2]. In this single-centre study, we used a case-control design to address this issue.

Materials: Fifty-nine patients with aPD who satisfied the clinical criteria and had no major contraindication for undergoing DBS surgery were enrolled. All patients were evaluated with extensive neuropsychological testing, including standardized scales for functional impairment and quality of life (ADL, IADL, PDQ-8 and PD-CFRS), behaviour (BDI-II, BIS-11, QUIP-RS, SOGS, Apathy Scale, STAI-Y1 and STAI-Y2) and multiple cognitive domains (i.e., attention, executive functions, memory, language, visuospatial abilities). Motor symptoms were evaluated with the third section of the MDS-UPDRS and the H&Y scale. After initial screening, 30 patients underwent DBS surgery (aPD-DBS+, case group), while 29 patients did not provide informed consent for the procedure, mostly due to safety concerns (aPD-DBS-, control group).

Methods: aPD-DBS+ patients were clinically and neuropsychologically evaluated before and after 1-3 and 4-5 years from DBS surgery. aPD-DBS- patients were assessed at comparable timepoints. Nonparametric tests were used for statistical analyses.

Results: There was no significant difference in age, gender distribution, disease duration, the levodopa-equivalent daily dose (LEDD) and motor symptoms severity (MDS-UPDRS-III and H&Y) between aPD-DBS+ and aPD-DBS- at baseline (all Ps>0.05). After surgery, aPD-DBS+ patients showed a statistically significant reduction in LEDD, MDS-UPDRS-III and PDQ-8 scores, whereas aPD-DBS- showed progressive worsening over time. Notably, there was no difference in changes in behavioural functions and cognitive performances over time between the two groups, except for a mild increase in STAI-Y1 and 2 scores in aPD-DBS+ patients.

Conclusions: Our results confirmed the efficacy of DBS in improving motor symptoms and reducing the amount of dopaminergic therapy in aPD compared to patients not undergoing surgery. Importantly, in line with some previous observations, we demonstrated that DBS does not induce significant changes in the cognitive and behavioural profile of patients compared to those occurring in aPD per se [3]. These observations suggest the lack of detrimental effects of DBS on cognition and behaviour over time.

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## POTENTIAL USEFULNESS OF FAST BETA-BAND SURVEY FOR DEEP BRAIN STIMULATION PROGRAMMING IN PARKINSON'S DISEASE: A PILOT STUDY

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Objectives: Deep Brain Stimulation (DBS) is an established therapeutic option for patients with advanced Parkinson's disease (aPD). New DBS systems improved treatment tailoring and sensing-enabled technologies and allow the recording of local field potentials (LFPs), opening new avenues of scientific inquiry into basal ganglia pathophysiology [1,2].

Materials: A group of patients with aPD were clinically evaluated before and after 3 weeks and 3-6 months from DBS surgery of the subthalamic nucleus (STN) or globus pallidus internus (GPi). All patients were implanted with the Medtronic Percept® PC and quadripolar sensing-enabled directional leads (B33005).

Methods: Programming was conducted according to the standard monopolar review of DBS contacts at 3 weeks after surgery. The Brainsense survey was performed in all patients (OFF dopaminergic condition) at 3 weeks and 3-6 months after DBS surgery. The frequency and peak amplitude in the beta band range (13-30 Hz) were collected from the two middle contacts (ring configuration) of both right and left STN/GPi. Motor symptoms were assessed with the third section of the MDS-UPDRS and with H&Y scale.

Results: In more than 75% of cases, lead contacts showing the highest beta peak corresponded to the contact with the largest therapeutic window and the level chosen for chronic stimulation according to the standard monopolar review. Moreover, the contact showing the highest beta peak demonstrated good test-retest reliability across the two different time points (i.e., at three weeks and 3-6 months after DBS). After surgery, all patients showed a statistically significant improvement in the MDS-UPDRS III total scores and a reduction in LEDD at the 3-6 months follow-up.

Conclusions: We here report data from a single-centre pilot study using the new sensing-enabled DBS system for aPD patients. Performing the fast Brainsense survey to identify contacts with the highest beta peak could potentially facilitate stimulation programming by significantly reducing DBS programming time [3]. This approach may be further tested and directly compared with the standard monopolar review to assess whether the two different programming approaches produce similar clinical outcomes in larger aPD patient cohorts.

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## EFFICACY OF MULTIDISCIPLINARY INTENSIVE REHABILITATION TREATMENT IN PARKINSON'S DISEASE

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Objective: To evaluate the efficacy of an 8-week multidisciplinary intensive rehabilitation treatment (MIRT) and virtual reality training (VRT) in patients with Parkinson's disease (PD) assessed with clinical and magnetic resonance imaging (MRI) markers.

Methods: This is a prospective, parallel-group, randomized study (Ethical committee register 149/2020/PO). PD patients attending the Movement Disorders Center of the University of Catania were enrolled and randomly assigned to MIRT treatment without (group A) or with (group B) a VRT with BTs-Nirvana (BTsN). Each patients underwent a comprehensive clinical assessment at baseline (T0), after the rehabilitation treatment (week 8, T1) and after one month without (T2).

Results: Seventeen PD patients were enrolled according to Brain Bank Criteria (10 male, 7 female, age 64.3 ± 8.7 years, UPDRS-ME 56.4 ± 21.2 score). Ten patients were randomized into group A, and 7 into group B. There were no differences between the two-treatment group in demographics and clinical features at baseline. Considering the whole PD sample, patients showed an improvement in the FOG-Q score between T0 and T2 (4.3 ± 4.1 vs 3.0 ± 3.7 score, p-value 0.02), and T1 and T2 (3.6 ± 3.9 vs 3.0 ± 3.7 score, p-value 0.05). Between group analysis showed significant differences between group A and group B at T1 in TUG (11.3 ± 2.2 vs 6.1 ± 2.7 seconds, p-value <0.001), and 10-meters performances (8.5 ± 1.2 vs 5.3 ± 2.4 score, p-value 0.002).

Conclusions: This study showed that physical rehabilitation improves motor symptoms of PD patients. The use of VRT could further improve motor performance of PD patients.

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## EVALUATION OF NON-MOTOR FLUCTUATIONS IN PARKINSON'S DISEASE DURING PHARMACOLOGICAL ON PHASE. IS ALWAYS THE "ON" CONDITION BENEFICIAL?

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Objectives: Non-motor symptoms (NMS) and fluctuations (NMF) are very common in Parkinson's disease (PD) occurring in ON and OFF state and affecting patients' quality of life. Aim of the study was to evaluate NMS occurring during ON pharmacological state.

Material and Methods: Patients with diagnosis of PD according to MDS criteria were consecutively enrolled at the Movement Disorders Center of the University of Catania. For this purpose, a new questionnaire was developed considering 17 items including the main symptoms experienced by PD patients in the ON state. PD patients were evaluated in ON state, 90' after the first morning dose of dopaminergic therapy and were asked if the symptoms were present during the ON state. PD patients who experienced at least one symptom in ON were defined ON Non-Motor Fluctuators (ONMF). Additionally, clinical features, MDS-UPDRS, Hoehn and Yahr stage and levodopa-equivalent dose were collected.

Results: One-hundred and thirty-seven PD patients with a mild to moderate disease stage were enrolled (79 man and 58 woman, age 69.4 ± 9.5 years (mean ± SD), disease duration 8.0 ± 4.6 years). Seventy-seven patients were ONMF (56.6%). ONMF were associated with female gender (OR 2.81, 95%CI 1.37-5.77, p-value 0.005) and with motor fluctuations (OR 2.41, 95%CI 1.20-4.83, p-value 0.013). PD patients with short disease duration (<7 years) showed the presence of "negative" NMS such as "sonnolenza/sleepiness", "sensazione di testa vuota/light-headedness", nausea/vomito/nausea/vomiting". PD patients with longer disease duration experienced more "positive" NSM including "sentirsi pieno di energie/feel lot of energy" and "sensazione di benessere fisico/feel physical well-being".

Discussion and Conclusion: In this study we demonstrated the presence of a different pattern of NMS occurring during ON response in PD patients. PD patients with short disease duration (<7 years) showed the presence of "negative" NMS whereas PD patients with longer disease duration experienced more "positive" NSM. This could help the physician in the therapy management of PD patients.

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## GENDER DIFFERENCES IN NON-MOTOR FLUCTUATIONS IN PARKINSON'S DISEASE

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Introduction and Objectives: Non-motor symptoms (NMS) and Non-motor fluctuations (NMF) in Parkinson's Disease (PD) are common, involving several domains and affecting quality of life [1]. Aim of the study is to estimate the burden of NMF in PD patients and to evaluate the possible gender effect.

Materials and Methods: PD patients fulfilling the MDS-PD diagnostic criteria attending the "Parkinson's Disease and Movement Disorders Centre" of the University of Catania were evaluated using the Non-Motor Fluctuations Assessment (NoMoFA) Questionnaire [2]. NoMoFA items were also grouped into the following domains: cognitive, mood, sleep/fatigue, dysautonomia, hallucination/perception and miscellaneous domains were identified.

Results: One-hundred and twenty-one patients with PD (67 men, 55.4%; mean age 70.2 ± 8.9 years, disease duration 8.3 ± 4.6 years) were evaluated. All PD patients reported at least one NMS, whereas 87 (71.9%) also reported NMF (table 1). "Feel sluggish or had low energy levels" (47.2%) along with "Feel excessively sleepy during the day" (40.0%) were the most common NMF reported in the whole sample. The majority of PD patients reported presence NMF during the OFF state (79, 65.3%). At multivariate analysis, NMF were positively associated with the female gender (adjusted OR 3.13; 95%CI 1.21-8.11 p-value 0.01). Women with PD had higher NMF scores especially in depression/anxiety, sleep/fatigue and dysautonomia domains, while men with PD experienced higher NMS in cognitive, sleep/fatigue and mood domains.

Discussion and Conclusion: Our study reported the presence of a gender-related pattern in the frequency of NMS and NMF in PD patients, with female gender associated with a higher risk of developing NMF, highlighting the need for personalized treatment strategies when addressing NMF.

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## PROGRESSIVE HEMIDYSTONIA AND ANOSOGNOSIA: AN UNUSUAL PRESENTATION OF PILOCYTIC ASTROCYTOMA

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Objectives: Pilocytic astrocytoma (PCA) is a low-grade glioma, often affecting young adults, characterized by cystic masses, slow growth, and usually good prognosis. PCAs often are located in the posterior fossa, often presenting with obstructive hydrocephalus, but PCAs can have an hemispheric localization with focal signs and seizures.

Materials: We will describe the case of a 29-year-old woman, presented to our Neurology Unit, complaining of progressive hemidystonia, anosognosia and visual impairment.

Method: A detailed history, complete of previous neurological evaluations for the left-hand dystonia, and a neurological examination were obtained. We also performed a head CT scan and brain MRI. Given the need for intervention, a neuropsychological evaluation was not done.

Results: Upon examination, right eye papilledema and left-side spastic hypertonia with dystonic postures of the left hand and foot were found. Asked about the dystonia, the patient said that she has had hand dystonia for 7 years, treated as trigger finger and then as idiopathic hand dystonia with botulinum injections. The disorder progressed to a complete left hemidystonia in the last year and developed blurry vision in the previous month. About the deficits, she said that "didn't care because she was right-handed", which we interpreted as neurological anosognosia with hemispatial neglect.

Discussion: The patient revealed that she had an MRI in 2019, but never picked up the report; the retrieved images showed a right paramedian necrotic lesion and voluminous cystic lesions, compatible with PCA. A brain CT showed an increase in size of the cystic lesions, associated with transfalcial and transtentorial herniation. The patient was transferred to the Neurosurgery Unit, where a brain MRI confirmed the neoplastic lesion and its compressive effect. The patient then underwent surgical decompression and subsequent mass excision. There is a scarce literature about this topic, but according to Baizabal-Carvallo dystonia is a rare manifestation of intracranial neoplasms, being present in about 1% of cases and specifically associated with low-grade (WHO I-II) gliomas such as PCA. In most cases dystonia precedes the diagnosis by weeks or months and contralateral hemidystonia is the most frequent presentation, probably caused by compression or neoplastic infiltration of the basal ganglia.

Conclusions: After the surgery the dystonia and spasticity resolved, but a moderate left hemiparesis remained, with little improvement after physical therapy. This case prompts us to recommend brain imaging and greater attention in the presence of progressive dystonias, especially when accompanied by neuropsychiatric signs, such as anosognosia and neglect.

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## A CASE OF SYMPTOMATIC PROGRESSIVE ATAXIA AND PALATAL TREMOR (PAPT) AND INCREASED CSF TAU

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Background: PAPT is a rare neurological syndrome, which combines palatal tremor synchronous with pendular nystagmus and progressive cerebellar ataxia. PAPT can be divided into familial, symptomatic (a subgroup of secondary palatal tremor) and sporadic forms, whose causes are currently unknown. Some recent neuropathological evidence, showing 4R-Tau inclusions in neurons of patients affected, suggest sporadic PAPT could be considered a novel rare tauopathy.

Methods: Neurological examination, routine ematochemical analysis, Electromyography (EMG) of pharyngo/laryngeal muscles, magnetic resonance imaging (MRI), neuropsychological tests and cerebrospinal fluid (CSF) biomarker analysis were performed.

Results: A 70 year old male with history of right pontine-midbrain spontaneous hemorrhage, treated with surgical drainage 4 years before, came to our institution complaining insidious onset of progressive gait ataxia 8 months after discharge from neurosurgery department. Blood tests and ECG did not show any pathological sign, except for a mild increase in serum creatinine (1,65 mg/dl). Neurological examination showed left pyramidal signs and vertical and horizontal gaze palsy as result of hemorrhage besides cerebellar syndrome affecting mostly trunk, gait and speech in combination to a palatal tremor synchronous with a pendular nystagmus. MRI revealed, alongside hemosiderin deposit in midbrain and pons, bilateral T2-hyperintensity of the inferior olivary nuclei, a condition termed hypertrophic olivary degeneration (HOD), which is a typical feature of symptomatic oculo-palatal tremor. EMG of pharingo-laryngeal muscles indicated a 2 Hz pseudorhythmic activation of thyroarytenoid and cricoarytenoid muscles, coherent with a larynx myoclonus. Neuropsychological tests showed mild isolated deficits in frontal-executive functions. CSF analysis biomarker showed a major increase of both Tau (844 pg/ml) and phosphorylated Tau (113.60 pg/mL) proteins, whereas levels of Beta-amyloid were normal. Genetic screening ruled out mutations in genes underlying familial degenerative forms.

Discussion: Our findings were consistent with PAPT syndrome with onset 6-8 months after a pontine-midbrain hemorrhage. Our CSF findings, associated with clinical course and onset of cerebellar syndrome, support a degenerative process. The patient was discharged with indication to start treatment with Gabapentin (300 mg three times per day) and physiotherapy with some benefit.

Conclusions: We present the first case of symptomatic PAPT syndrome and evidence of increased CSF Tau and phosphorylated-Tau, strengthening the hypothesis of a degenerative Tau-driven underlying pathogenesis.

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## RARE ASSOCIATION BETWEEN SPINOCEREBELLAR ATAXIA TYPE 2 AND AMYOTROPHIC LATERAL SCLEROSIS: A CASE REPORT

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Objective: To describe the possible association between SCA2 and ASL.

Materials: We describe the case of a 58-year-old man who was diagnosed with spinocerebellar ataxia type 2 at the age of 38, following tests carried out for the progressive appearance of postural instability and gait ataxia. At the age of 56 he presented dysphagia and a significant decline in his ability to stand up and walk, with a reduction in autonomy and the need to use a wheelchair.

Methods: We performed electromyography and electroneurography of the four limbs and of the cranial district together with motor evoked potentials to study upper and lower motor neurons.

Results: Electromyography and electroneurography examinations highlighted the presence of moderate/severe sensorimotor axonal polyneuropathy and abundant denervation activity in progress at the level of all the muscles investigated in the upper and lower limbs. Motor evoked potentials showed reduced amplitude in cortical stimulus responses, chronodispersed morphology, slightly increased latency in the left upper and lower limbs, and non-reproducible cortical stimulus responses in the right upper limb. Referring to the revised El Escorial criteria of 2015, the patient was diagnosed with "Laboratory-supported probable ASL".

Discussion: Considering different cases described in literature over the years, SCA2 could represent an important risk factor of developing ASL. In particular, the presence of alleles of ATXN2 with 27 and 28 CAG repeats seems to slightly decrease the risk of developing the disease, which would instead be progressively increased by the presence of alleles with 29, 30, 31, 32 and 33 repeats. The exact physiopathological mechanism by which the mutation leads to an increased risk of developing the disease is currently unknown. The reduction of ATXN2 gene expression in TDP-43 ALS mouse models has been shown to prolong survival. Transcriptomic studies on mouse models have demonstrated the involvement of several pathways, including the innate immunity regulation by STING and the biosynthesis of fatty acid and cholesterol by SREBP.

Conclusion: CAG repeat expansions in ATXN2 gene have been associated with variable neurological presentations, which include SCA2, ALS, Parkinsonism or a combination of them. Further research is needed to better understand the relationship between SCA2 and ASL and explore the underlying molecular mechanisms.

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## TRANSCRANIAL SONOGRAPHY IS USEFUL IN IDENTIFY PARKINSON'S DISEASE PATIENTS WITH NORMAL WITH NORMAL 123I-FP-CIT-SPECT

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Objective: To evaluate the TCS in the patients affected by SWEDD-parkinsonism. Scans without evidence of Dopaminergic Deficit (SWEDD) represent 10% of patients clinically diagnosed as Parkinson's Disease (PD). According to new diagnostic criteria normal imaging result is defined as absolute exclusion criteria but the significance of DAT still remain unclear and this concept has to be. Recent findings argue that striatal dopamine transporter imaging does not associate with axonal nor somal loss of the nigrostriatal neurons in PD. It may reflect dopaminergic activity rather than number of surviving neurons or their striatal projection. So new methods are required. Hyperechogenicity of Substantia Nigra (SN), detected by Transcranial sonography (TCS) could represent a useful tool to identify these patients.

Material and Methods: 3 patients were observed in Movement Disorder Center of Neurological Clinic of Sassari. All received a clinical diagnosis of tremor-dominant PD according to the new criteria and normal [123 IFP-CIT SPECT scans. TCS was performed a 2.5 MHz transducer using a transtemporal window. Hyperechogenicity of area of SN was defined as an echogenic area above of 0.20 cm2.

Results: Patient 1: female; 55 years old; age at motor symptoms onset: 47 y; disease duration at SPECT: 8 y; disease duration at TCS: 8 y; midbrain hyperechogenicity ( right: 0,41 cm2, left 0,38 cm2); III width: 6,3 mm. patient 2: female; 76 years old; age at motor symptoms: 74 y; disease duration at SPECT: 1 y; disease duration at TCS: 2; midbrain hyperecgogenicity (right:0,46 cm2, left:0,33 cm2); III width: 4,7 mm. patient 3: male; 70 years old; age at motor symptoms: 53 y; disease duration at SPECT: 14 y; disease duration at TCS: 17 y; midbrain hyperechogenicity (right: 0,28 cm2, left 0,22 cm2); III width: 6,1 mm.

Discussion and Conclusions: Clinical diagnosis of PD with normal dopaminergic functional imaging is challenging and still debated, and maybe alternative diagnosis could be considered. TCS, which detects midbrain hyperechogenicity, found in up to 90% of patients with PD, could be a useful tool in identify these patients, when presynaptic dopaminergic nerve terminals are still preserved.

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## PAINFUL LIMB SPASMS AT PRESENTATION OF ACUTE LENTICULO-CAPSULAR STROKE

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Aims: Movement disorders (MDs) can develop following stroke, usually in relation to basal ganglia (BG) lesions [1,2]. We present a case of painful spasms following lenticulocapsular stroke.

Materials and Methods: A 62-year-old woman with diabetes, hypertension and no known neurological history presented to our attention after the appearance of acute-onset left sided hemiparesis (arm > leg). Emergency brain CT and CT angiography were normal; intravenous fibrinolysis with altepase 0.9 mg/kg was administered for suspected acute stroke, without immediate benefit on the left sided weakness. Few hours after symptom-onset, the patient developed painful spasms of the left foot characterized by ankle flexion and successive forced extension-inversion, lasting several seconds, with frequency of several episodes per hour, associated with ipsilateral quadriceps twitching contractions.

Results: Blood exams, including electrolytes and CPK/LDH were normal. Serial electroencephalograms and electroneurography/electromyography were unremarkable; the spasms eventually spontaneously subsided after two days. Brain MRI showed a T2 - Fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) hyperintense lesion involving the posterior portion of the right lentiform nucleus and the ipsilateral posterior arm of the internal capsule, with concomitant apparent diffusion coefficient (ADC) hypointensity, consistent with acute right lenticulocapsular ischemic stroke. The patient was discharged after 2 weeks, with marked improvement of the lower limb weakness and modest improvement in the upper limb. After 50 days, she is free from spasms.

Discussion and Conclusions: Based on the clinical and imaging presentation, we think that the patient's spasms could be of central origin. MDs, both hyper- and hypo-kinetic, can arise following stroke, typically in relation to BG lesions [1,2]. Advocated mechanism for MDs in BG stroke is the disruption of the critical BG contribution to motor processing through the different cortico-subcortical motor loops. Among MDs, dystonia has been reported in association with lentiform nucleus involvement, particularly when the putamen is interested but even in case of pallidal lesions [2,3]; a proposed mechanism is that putaminal lesions could have predominant effect on the BG indirect pathway, with consequent cortical hyperexcitation and appearance of contralateral hypermor symptoms [3]. Moreover, lesions of the globus pallidus could possibly decrease pallidal inhibitory output causing thalamo-cortical hyperactivation, and, accordingly, dystonia [3]. We speculate that some of the aforementioned mechanisms may underlie the observed foot spasms and muscle contractions, and we feel that the patient's symptoms may actually be similar to dystonia on pathophysiological grounds. Painful spasms are an uncommon presentation in the setting of BG stroke [1].

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## NEUROLEPTIC MALIGNANT SYNDROME IN HUNTINGTON'S DISEASE: A CASE REPORT AND LITERATURE REVIEW

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Objective: Huntington's disease (HD) is the most common neurodegenerative chorea in adults and is caused by an autosomal dominant inherited CAG trinucleotide expansion in the huntingtin gene. The purpose of this study is to estimate the incidence of neuroleptic malignant syndromes (NMS) in Huntington patients treated with tetrabenazine (TBZ) and/or dopamine receptor blocking agent (DRBA) drugs and discuss the measures to avoid this potentially life-threatening condition.
Methods: This is a review of the literature and description of a clinical case [1-2]. In addition, we consulted the 5th data set of the Enroll-HD study (PDS5), a longitudinal, observational, multinational study of families with HD, including manifest and premanifest HD gene carriers. We selected cases of NMS in Huntington's disease patients who were treated with TBZ and/or DRBA and presented at least one of the core symptoms of NMS (rigidity or hyperthermia) and determined which and how the drugs induced NMS, the clinical manifestations, and the potential risk factors.

Results: We identified 12 cases of NMS in HD patients (mean age of disease onset: 32.2±14.8 years, three with Westphal variant) treated with DBRA and/or TBZ, 9 were undergoing multiple drug treatments. All patients described had a long clinical history (mean: 13.7±3.7 years) and an advanced stage of disease before the onset of NMS. Eight of them were bedridden with symptoms such as akinetic rigidity, dysphagia, and dehydration, suggesting a correlation between the long clinical history of the disease and the onset of NMS. Eleven patients manifested NMS during drug-therapy changes: 7 during substitution of one drug for another, 3 during dosage modification, and one following introduction of a new drug. Only one patient during unmodified TBZ treatment. Three patients manifested the atypical form of NMS (hyperthermia without rigidity), two under TBZ and one under haloperidol. Finally, five cases of unspecified fever in polytherapy with TBZ and DBRA were reported in the ENROLL dataset. After NMS, ten patients made a full recovery, while two died.

Conclusions: The available data suggests that NMS is potentially underestimated in patients with Huntington's, partly due to the difficulty in identifying the atypical form of NMS [3]. The advanced stage of disease, extra-pyramidal signs, abrupt changes in therapy, polytherapy, and dehydration are the main risk factors for NMS in Huntington's patients. As neurodegeneration progresses, the treatment plans require a periodic review, they must be managed with caution, and clinical manifestations associated with therapeutic changes must be carefully monitored.

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## AUTONOMIC DYSFUNCTION IN PARKINSON'S DISEASE PATIENTS TREATED WITH LEVODOPA-CARBIDOPA INTESTINAL GEL: A SYSTEMATIC REVIEW

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Objective: Autonomic dysfunction in Parkinson's disease (PD), encompassing cardiovascular (CV), genitourinary (GU), and gastrointestinal (GI) symptoms, severely affect patient's quality of life. We systematically review the current literature to assess the safety and efficacy of levodopa/carbidopa intestinal gel (LCIG) infusion on autonomic dysfunction in PD patients.

Methods and Materials: Following the PRISMA guidelines, we systematically searched PubMed for studies (only in English), including non-motor symptoms (NMS) outcomes, regarding autonomic dysfunction in LCIG-treated PD patients. We collected data on study design, clinical and demographic features, Unified Parkinson's Disease Rating Scale (UPDRS), Non-Motor Symptoms Scale (NMSS), and safety outcomes in terms of reported adverse events (AEs) possibly related to LCIG. Device and procedure-related AEs were not considered. We evaluated improvement, stability, or worsening of CV, GU, and GI symptoms at four timepoints: <6 months (T1), 6 months (T2), 12 months (T3), and >12 months (T4), according to clinometric scale change in comparison to baseline evaluation.

Results: Thirteen studies were included for an amount of 1340 PD patients. NMS were evaluated using NMSS, UPDRS I, and SCOPA-AUT (questions 15, 16). Regarding CV symptoms, an improvement has been reported in 2/4 (50%), 5/8 (62.5%), 3/4 (75%), and 1/5 (20%) studies, respectively, at T1, T2, T3, and T4. Stability has been reported in 6/13 studies (46%). Regarding GU symptoms, an improvement has been reported in 4/4 (100%), 6/7 (85.7%), 3/4 (75%), and 5/5 (100%) studies, respectively, at T1, T2, T3, and T4. Stability has been reported in 2/12 studies (16.6%). Regarding GI symptoms, an improvement has been reported in 3/4 (75%), 6/6 (85.7%), 3/4 (75%) and 1/5 (20%) studies respectively at T1, T2, T3 and T4. Stability has been reported in 4/12 studies (33%). No studies reported worsening. Concerning safety, seven studies reported LCIG-related AEs, precisely four reported CV AEs in 16 patients, three GI AEs in 96 patients, and none GU AEs.

Discussion: To our knowledge, this is the first qualitative/quantitative assessment of studies evaluating the efficacy and safety of LCIG therapy on autonomic dysfunction in PD patients. Although data is not sufficient to pose definite indications, our analysis suggests that LCIG infusion can help reduce the burden of autonomic symptoms in advanced PD patients.

Conclusion: LCIG is relatively safe and may help manage autonomic symptoms in patients with advanced PD. Prospective studies addressing autonomic dysfunction in LCIG-treated PD patients should be performed to make this evidence more robust.

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## MEDITERRANEAN DIET ADHERENCE IN PATIENTS WITH PARKINSON DISEASE AND GLUCOCEREBROSIDASE MUTATIONS

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Background & Objectives: In recent years, the Mediterranean diet has been widely studied for its potential protective effects against several chronic diseases [1], including Parkinson Disease (PD) [2]. However, the relationship between PD, GBA mutations and the adherence to Mediterranean diet has still not been explored. We aim to investigate a possible correlation between PD clinical features and Mediterranean diet adherence in a group of GBA-related PD (GBA-PD) patients compared to idiopathic PD (iPD).

Materials & Methods: We analyzed clinical motor and non-motor data (UPDRS part I-IV; SCOPA-AUT, BDI-II, HADS-D, HADS-A, RBDSQ, UPSIT, MoCA) and dietary habits (MEDAS questionnaire) in 51 GBA-PD and 84 iPD patients. PD groups were also stratified by low/ high adherence to the Mediterranean diet using the MEDAS cut-off score of 8. Within group analyses according to low/high diet adherence and between PD groups comparison were also performed.

Results: GBA-PDs showed an earlier age of disease onset and higher scores at UPDRS part I, BDI-II, HADS-D, HADS-A, compared to iPDs. No significant differences were found in MEDAS scores as well as UPDRS (part II, III and IV), MoCA, SCOPA-AUT, RBDSQ and UPSIT scores between the two groups. GBA-PD patients with low diet adherence showed higher BDI-II, HADS-A and HADS-D scores as compared to GBA-PD patients with high diet adherence, while no difference was detected when comparing low diet adherence vs high diet adherence in the iPD group. We also report a significant correlation between a low Mediterranean diet adherence and higher scores in BDI-II (p=0.0312) in the GBA-PD group.

Discussion & Conclusion: These findings show an interesting association between adherence to the Mediterranean diet and mood disorders in PD-GBAs. Further studies are needed to confirm these results and to investigate the underlying mechanisms of this association. If confirmed, these findings may have important implications for the development of personalized dietary interventions for PD patients with genetic mutations.

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## THE INFLUENCE OF FRAILTY ON PARKINSON'S DISEASE PROGRESSION: A LONGITUDINAL STUDY

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Objectives: Previous evidence suggests that frailty is a risk factor for Parkinson's disease (PD) development and can influence PD clinical expression. However, the possible influence of frailty on PD progression has been not investigated. The aim of this longitudinal study was to elucidate the role of frailty, assessed by Frailty Index (FI), on PD motor and non-motor symptoms progression.

Materials: One-hundred and fifty patients participated and one-hundred and nine patients completed follow-up at three years. Patients underwent a clinical evaluation that included the administration of standardized clinical scales aimed at assessing motor and non-motor manifestations. To evaluate frailty levels we administered a FI, specifically designed for patients with PD and previously validated by our group.

Methods: Spearman correlation coefficient was used to investigate possible correlations between FI score and motor/non-motor symptoms severity at the baseline and the follow-up assessment. Linear regression models were used to explore possible associations between baseline FI score and PD progression.

Results: At baseline, FI score correlated with motor symptoms, motor complications and non-motor symptoms severity. Furthermore, an inverse correlation between FI score and cognitive performance was observed. At follow-up assessment, we confirmed the positive correlation between FI score and motor and non motor manifestations. In addition, we observed a correlation between FI score and the stage of disease, not observed at baseline. Linear regression models showed a significative association between baseline FI and motor and non-motor symptoms progression.

Discussion: Our findings confirmed that frailty levels modulate the clinical expression of patients with PD. The novel finding of the present study was that frailty levels may also influence motor and non motor symptoms progression in PD.

Conclusions: FI may represent a useful tool to assess and predict disease progression in PD and to decode the clinical variability that characterized PD.

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## NEURAL CORRELATES OF BRADYKINESIA IN PARKINSON'S DISEASE: A KINEMATIC AND FMRI STUDY

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Objectives: Bradykinesia is one of the cardinal signs of Parkinson's disease (PD) and is usually assessed during repetitive movements. The aim of the study was to investigate the neural correlates of hand tapping performance in patients with PD relative to healthy controls.

Materials: Fifteen PD patients and 15 age- and sex-matched healthy controls were included.

Methods: All the subjects underwent brain magnetic resonance imaging (MRI) including a hand tapping functional MRI (fMRI) task: subjects were asked to alternatively open and close (hand tapping) their right hand as fast and as ample as possible. Hand tapping speed and amplitude was measured during the fMRI task using an optical fiber data glove.

Results: During the fMRI hand tapping task, patients with PD showed reduced hand tapping amplitude and reduced activity of frontoparietal areas and sensorimotor regions including supplementary motor area (SMA), pre/postcentral gyri, pallidum and cerebellum

compared to healthy controls. Decreased activity of SMA, cerebellum lobule VIII and caudate correlated with reduced hand tapping amplitude.

Discussion: As expected, patients with PD showed a worse hand tapping performance in terms of reduced movement amplitude relative to healthy controls. Interestingly, we found a correlation between bradykinesia and brain activity. In particular, areas strongly involved in motor planning such as SMA and caudate correlated with reduced movement amplitude. This study has the major strength of collecting objective motor parameters and brain activity simultaneously, providing a unique opportunity to investigate the neural correlates of bradykinesia in PD.

Conclusions: A reduced recruitment of cortical, cerebellar and basal ganglia areas implicated in motor programming is a hallmark of bradykinesia in patients with PD.

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## SPONTANEOUS AND EVOKED PAIN IN PARKINSON'S DISEASE WITH MOTOR FLUCTUATIONS: AN OBSERVATIONAL, PROSPECTIVE, CLINICAL AND NEUROPHYSIOLOGICAL STUDY IN PATIENTS UNDER L-DOPA AND OPICAPONE ADD ON THERAPY

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Objective: We aimed to evaluate the effectiveness of opicapone on spontaneous and evoked pain -by electrical stimulation- in Parkinson's Disease (PD) patients suffering from motor fluctuations and chronic pain.

Materials and Methods: This is a prospective, single center study in fluctuating patients with stable therapy. Patients with PD and motor fluctuations were consecutively enrolled. Main inclusion criteria were pain intensity with an NRS≥4, no modification of dopaminergic drugs and analgesic therapy with FANS, Hoehn and Yahr stage I–III during OFF time; motor fluctuations (>1.5 hours' OFF time/day). Clinical and neurophysiological assessments were performed before and after 12 weeks of treatment with opicapone 50 mg/day as add-on therapy to levodopa. Primary outcome: Numeric Rating Scale (NRS). Secondary outcomes: King's Pain Scale for Parkinson's Disease (KPS), Brief Pain Inventory (BPI), Clinical Global Impression of Change (CGI), Parkinson's disease Questionnaire 39 (PDQ-39), non-motor Symptoms Scale (NMS), and pain threshold and tolerance.

Results: 12 out of 28 eligible patients were enrolled (disease duration 9±4). Patients showed a significant reduction of pain in the NRS scale (p=.003). We also found significant changes (reduction) in the secondary outcomes as KPS (p=.008), BPI intensity (p=.011), UPDRS III (p=.002) and IV (p=.011) but not significant changes in the BPI total and interference, PDQ-39, and NMS as well as in the tactile threshold, pain threshold and tolerance. CGI showed an improvement in 8 patients (n=2 very much/much improved; n=6 minimally improved), while no change was observed in 4 patients. We found a significant correlation between changes (reduction) in the UPRDS III and the BPI Intensity (r=.817, p=.001) and NRS scores (r=.611, p=.035), and also a significant correlation between UPDRS IV and KPS (r=.627, p=.029) and BPI Intensity (r=.689, p=.013). None of the patients reported treatment-emergent adverse events.

Discussion: Score changes of the primary outcome NRS and secondary outcomes indicated that patients experienced a relief of pain along with a parallel reduction of motor symptoms and motor complications as suggested by UPDRS III and IV. Opicapone, a once daily, long-acting COMT inhibitor [1] may improve pain through alleviation of motor complications, as suggested by the correlation between a reduction of pain and the reduction of UPDRS IV score, as also confirmed by previous studies [2, 3].

Conclusions: Our preliminary results suggest that opicapone 50 mg/day might be effective for the management of motor complications of PD and related pain, and it is safe.

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## DEEP BRAIN STIMULATION FOR MEDICALLY REFRACTORY TREMOR IN WILSON'S DISEASE: A SINGLE CASE AND REVIEW OF THE LITERATURE

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A 41-years-old woman was referred to our outpatient clinic for a five year slowly progressive onset of speech impairment and tremor involving the arms and head. She had previously received a genetically confirmed diagnosis of Wilson's disease (WD) at the age of three years. At the admission neurological examination showed: a) action and postural tremor of the upper limbs (left more than right); its amplitude increased with a longer duration of posture (i.e wing-beating tremor); b) horizontal head tremor (i.e. "no-no"); c) voice tremor. Brain T2-MRI showed the typical "face of the giant panda sign"( i.e. normal intensity of red nuclei and lateral portions of substantia nigra pars reticulata with high signal intensity of tegmentum and hypointensity of the superior colliculus) with no other evidence of basal ganglia structural changes. Because of first line (primidone and propranolol) and second line (topiramate, pregabalin, clonazepam) therapy agents for tremor were unsuccessful, a surgical approach was proposed; the patient underwent to Deep Brain Stimulation (DBS) of ventral intermediate (Vim) thalamic nucleus. High stimulation output led to a significant reduction of her tremor amplitude of both arms and head; speech impairment remained stable and no potential DBS-related side effects were reported. Vim has emerged as the most effective and established target for medically refractory tremor in patients with essential tremor (ET) [1]. Even though the pathophysiology of tremor is different between WD and ET our experience and published evidence support the potential role of Vim DBS as an effective and safe approach in carefully selected WD patients, although the presence of structural changes in the basal ganglia may limit the therapeutic success of the surgical procedure [2].

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## A JUVENILE CASE OF PARKINSON'S DISEASE ASSOCIATED WITH MAPT MUTATION

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Objective: We describe heterogeneous clinical manifestations in a 51 years old man with PD and carrying a mutation in MAPT gene.
Methods: Subject underwent serial neurological visits, Genetic Analysis, brain magnetic resonance imaging (MRI), brain DAT-SPECT, brain PET-FDG and neuropsychological assessments.

Results: We present the case of a man who was diagnosed with PD at the age of 47 years, beginning with right upper limb bradykinesia. The brain SPECT DATscan confirmed low uptake in the left caudate and putamen while the Brain MRI showed mild ventricular dilation. Therapy with dopamine-agonist, rasagiline and levodopa was started. Interestingly the gene analysis identified a pathogenic variant in exon 10 of MAPT gene (c. 1853C>T; p.Pro618Leu). Further diagnostic investigations highlighted left insular and temporo-parietal hypometabolism through Brain PET-FDG and deficit of attentive, executive e visuospatial skills. In the following years motor symptoms worsened, impulse control disorder occurred (with hyperphagia, hypersexuality, gambling and drug abuse) and the patient presented traits of aggression, requiring psychiatric intervention.

Conclusions: Tauopathies refer to a wide range of phenotypically diverse diseases characterised by the aberrant aggregation of tau in neurons and/or glia, tau dysfunction is sufficient for widespread central nervous system neurodegeneration. In this case we increase the knowledge about the possible role of tau dysfunction in non-motor clinical manifestation of Parkinson disease.
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## BEYOND CLASSIC PHENOTYPES OF CHOREA: WHAT IS THE ACTUAL SIGNIFICANCE OF INTERMEDIATE ALLELES IN THE HTT GENE?

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Introduction: In the context of Huntington's Disease (HD), the pathological significance of intermediate alleles remains controversial. Intermediate alleles are expansions of CAG sequences ranging from 27 to 35 repeats in the HTT gene. Previous studies have shown that intermediate alleles are frequent in the general population, but an increasing number of cases of subjects with "Huntington-like" phenotypes have been recently reported [1]. Furthermore, previous studies suggest that intermediate alleles may also be associated with α-synucleinopathies, such as PD, DLB, MSA [2] [3]

Case Report: A 48-year-old woman presented to our Clinic with a history of involuntary right-hand movements that began at age 39 and progressively worsened in frequency and intensity over time. These symptoms disappeared during the night's rest. The patient reported no neuropsychiatric disturbances and appeared normal on psychiatric examination. The patient did not refer to a family history of neurological diseases or other relevant pathologies. The patient performed a brain MRI about two years after the onset of symptoms, which was unremarkable, while she had not performed a DAT-Scan exam yet. Recent blood tests were normal (CBC, liver and kidney function, serum electrolytes, vitamin B12, folic acid, ceruloplasmin, glycated hemoglobin, ANA, ANCA, HIV test), except for mild hypercholesterolemia and hypereosinophilia. A clinical diagnosis of HD was previously made, but the patient did not show a good response to treatment with Xenazine. At neurological examination, the patient showed resting and intention tremors in the hands bilaterally and in the head. The ambulation was autonomous with a slight reduction of the pendulum movements to the right, and a slight bilateral plastic hypertonicity (right>left). L-DOPA trial was performed with remarkable improvement in tremor and rigidity. Therapy was set up with L-DOPA 200+50 mg TID, and Xenazine 25 mg TID. Genetic testing was requested for Huntington's Disease and Monogenic Parkinsonisms. Genetic testing for CAG amplification of the HTT gene showed the presence of a normal allele of 15 repeat units, and an intermediate allele of 27 repeats.

Conclusions: This case provides clinical evidence to support the hypothesis of a possible association between intermediate CAG repeat and movement disorders other than HD, like early onset parkinsonism or atypical choreas. However, this hypothesis needs to be confirmed by further clinical cases and scientific evidence.
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## POST TRAUMATIC DYSTONIA ASSOCIATED TO PRRT2-RELATED PAROXYSMAL KINESIGENIC DYSKINESIA (PKD): CASE REPORT AND REVIEW OF LITERATURE

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Objectives: To describe a patient with history of peripheral injury, who developed paroxysmal dyskinesias associated with dystonia and was found to be carrier of a mutation in the PRRT2 gene.

Results: This case report describes a 19-year-old male with a negative family history for neurological diseases, who presented a 3 years history of paroxysmal dyskinesias consisting of brief episodes of involuntary contractions in the right limbs, associated with cervical dystonia, first only during physical activity and later during habitual voluntary movements. The episodes described (about 20 episodes per day) lasted approximately 10-15 seconds and resolved spontaneously. The patient reported a sports-related cranial and mandibular trauma with left orbital, maxillary, and ethmoid fractures 6 months before the onset of the motor symptoms, leading to prolonged immobilization. Our clinical examination revealed a torsional posture of the right upper limb during repetitive movements of the contralateral upper limb. An EEG and a brain and cervical MRI were performed, which resulted normal. Genetic analysis revealed the presence of a heterozygous mutation in exon 2 of the PRRT2 gene, which causes a reading frame shift in the protein and the consequent insertion of a premature stop codon

(p.Arg217Profs*8), compatible with the status of a subject affected by PKD. A therapy with carbamazepine 200 mg daily has lead to the complete resolution of paroxysmal disorders.

Discussion: Peripherally-induced movement disorders (PIMD) should be considered when involuntary or abnormal movements emerge shortly after an injury to a body part. The spectrum of PIMD is broad but dystonia is the most common phenomenology [1]. It has been proposed that in some patients with PIMD there are some pre-existing genetic risk factors [2]. We performed a systematic research of the literature, identifying 87 clinical studies which reported the phenotype of patients with PRRT2-PKD, and post-traumatic onset was never reported.

Conclusions: This case highlights the importance of genetic predisposition in PIMD patients and expands the genotype phenotype correlations in PRRT2-PKD patients.

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## THYROID DYSFUNCTION AND IDIOPATHIC ADULT-ONSET DYSTONIA: DATA FROM THE ITALIAN DYSTONIA REGISTRY

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Background: A few earlier observations and a recent controlled study pointed to the recurrence of thyroid diseases in idiopathic adult-onset dystonia (IAOD).

Objective: The aim of this study was to analyze the frequency of hyperthyroidism and hypothyroidism in a large multicentre cohort from the Italian adult dystonia registry (IADR) and the relationship of thyroid disease with the phenotypic expression of dystonia.

Material and methods: On May 2023, the IADR included 1698 IAOD patients from 42 centers. Patients who were diagnosed with hypothyroidism and hyperthyroidism were selected and compared with patients who had not been diagnosed with any thyroid disease.

Results: Among the 1698 IAOD patients, 202 (11.9%) were diagnosed with thyroid dysfunction: hypothyroidism was diagnosed in 159 patients (9.4%; 95% CI, 8.0% - 10.8%) and hyperthyroidism in 43 (2.5%; 95% CI, 1,8% - 3.2%). No thyroid disease was diagnosed in the remaining 1496 patients. Since the prevalence of both previously diagnosed hypothyroidism and hyperthyroidism in our cohort tend to be greater than in the European population (see below), we thus analysed both thyroid dysfunctions combined. Patients who carried thyroid dysfunction (n. 202) and those who did not (n.1496) were comparable for sex (135/202 vs. 938/1496, $p = 0.3$) but no for age ($66.5 \pm 11.4$ vs. $64.3 \pm 13.9$, $p = 0.01$). Phenotypic analysis yielded a higher age of dystonia onset in the thyroid group ($54.4 \pm 14$ vs. $52.3 \pm 15.1$), that was however no longer detectable after adjustment for age and education. The anatomical distribution of dystonia and spread of dystonia over the follow up did not significantly differ between dysthyroid and euthyroid groups.

Discussions and Conclusion: The frequency of diagnosed thyroid dysfunction in our sample tend to be higher than the prevalence of both previously diagnosed and undiagnosed thyroid dysfunction in the general European population (hypothyroidism, 3.05% [95% CI 3.01%-3.09%]; hyperthyroidism, 0.75% [95% CI, 0.73%-0.77%]). Further strengthening the relevance of our estimates that referred to diagnosed thyroid disease, results of studies in the general population also indicated that 85% of the thyroid dysfunction was subclinical. Since the majority of adult cases with thyroid disease are caused by autoimmune mechanisms, the increased frequency of thyroid disease in IAOD might reflect an autoimmune contribution to dystonia. Our findings would also stimulate investigation on the relationship between thyroid, related hypophyseal hormones, and IAOD.

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## GAIT IMPAIRMENT AND NEUROGENIC ORTHOSTATIC HYPOTENSION ARE INDEPENDENTLY ASSOCIATED IN PARKINSON'S DISEASE

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Objectives: Orthostatic hypotension (OH) and gait impairment are frequent non-motor sources of disability of Parkinson's disease (PD). An association between OH and ambulatory capacity impairment in PD was evaluated also in patients asymptomatic for postural lightheadedness, and wearable sensors demonstrated good sensitivity and specificity to predict risk of falls related to OH. Still, the impact of neurogenic OH (nOH) on gait features need to be clarified. This cross-sectional study aimed to assess the influence of nOH on postural and spatiotemporal gait parameters in a cohort of advanced PD patients by means of wearable inertial sensors.

Materials: Patients with advanced PD were evaluated during their "best-ON" state by means of APDM Mobility Lab™ motion sensors for gait and balance assessment and screened for the presence of nOH using a standardized procedure at bedside.

Methods: Gait/balance parameters were evaluated during a Sway test, a 3-meters Timed-up and go (TUG) test, a 360° Turn Test and a Two-minute walk test (2MWT). The bedside assessment of nOH was performed using the ΔHeart Rate/ΔSystolic Blood Pressure (ΔHR/ΔSBP) ratio, after 5 minutes of supine rest, and then after 3 minutes of active upright tilt. Analysis of covariance was performed to evaluate differences in gait and balance features between the two groups, adjusting for age, disease duration, and Hoehn and Yahr stage (H&Y).

Results: A total 81 patients were enrolled, 18 with nOH (22.2%) and 63 without nOH (77.8%). The two groups showed similar age (62.3±7.3 vs 60.3±8.3, p=0.18), levodopa equivalent daily dose and H&Y stage, while disease duration was longer in patients without nOH (10.2±2.3 12.8±5.4, p=0.03). After correcting for age, disease duration, and H&Y stage, patients with nOH exhibited at the 2MWT lower stride length (p=0.011), lower gait speed (p=0.010), and longer time of double support (p=0.042). No significant differences were found for the other tests.

Discussion: Wearable inertial sensors showed worse gait performances during a prolonged walking test in PD patients with nOH, even after correcting for principal confounders of the advanced disease. Like previously suggested, we hypothesize a detrimental effect of orthostatic hypotension during prolonged walking in PD patients with suspected autonomic failure. Management of nOH could improve gait impairment of these patients, reducing falls, fractures, and other important PD complications.

Conclusion: nOH was independently associated with worse gait features in PD patients, highlighting the possible impact of this non motor feature on mobility.

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## ANTI-AMPHIPHYSIN-IGG-SEROPOSITIVE PARANEOPLASTIC SYNDROME: A RARE CAUSE OF STIFF PERSON SYNDROME

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Objectives: Amphiphysin is a 128 kDa intracellular protein that promotes cleavage of neuronal synaptic vesicles. Amphiphysin-immunoglobulin G (IgG) autoimmunity was first recognized in stiff-person syndrome, a rare neurological condition characterized by muscle stiffness and painful muscle spasms associated with breast cancer. Herein, we report a case of anti-amphiphysin-mediated paraneoplastic Stiff Person Syndrome in a patient with medium to high-grade invasive ductal breast carcinoma and serum and cerebrospinal fluid (CSF) anti-amphiphysin IgG.

Materials and Methods: A 49-year-old female patient was admitted to our department with a two-year history of right-sided neck and upper limb pain, left foot stiffness, diffuse muscle spasms, and recent onset of hypophonia. Due to the muscle spasms, she was struggling to walk, climb stairs, sleep, and carry out her work activities. One year before the onset of neurological symptoms, the patient received a diagnosis of medium to high-grade invasive ductal left-sided breast carcinoma. Thus, she had a mastectomy, and hormonal therapy is still ongoing. On neurological examination: gait ataxia with intra-rotation of the left foot, dystonic attitude of the right upper limb with hyperflexed forearm on the arm, winged scapula. Passive mobilization of this body segment caused pain, and humeral and antebrachial extension movements were severely limited.

Results: Brain and spinal cord MRI showed mild cerebellar vermis atrophy and discogenic myelopathy extending from C4 to C5. CSF standard analysis revealed mild damage to the blood-brain barrier and systemic oligoclonal IgG. According to the medical history of subacute onset of a stiff person-like syndrome, we also investigated onconeural antibodies. A high titer of anti-amphiphysin IgG was detected both in CSF and serum, with no trace of anti-GAD antibodies.

Discussion: Plasmapheresis was initiated, resulting in a gradual improvement of dystonia and ataxia.

Conclusions: It is mandatory to assess onconeural antibodies in each young patient affected by dystonia or any other movement disorder with a history of malignant tumor. Anecdotal evidence and clinical experience suggest that amphiphysin Ab-associated SPS may not respond to IVIg. Plasmapheresis may be considered as the first-line treatment for Anti-Amphiphysin-IgG-seropositive Stiff Person Syndrome.

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## EXPLORING THE IMPACT OF FATIGUE ON CAREGIVER BURDEN IN PARKINSON'S DISEASE

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Objectives: Fatigue is a common and disabling non-motor symptom (NMS) in Parkinson's disease (PD), affecting up to 60% of patients [1]. It has been suggested that fatigue experienced by people with PD may considerably aggravate caregiver burden [2]. The aim of this study was to evaluate whether PD-related fatigue had a significant impact on caregiver burden.

Materials and methods: Demographic and clinical data were obtained from patients with PD recruited at the Centre for Neurodegenerative Diseases and the Aging Brain, Tricase (Italy), as part of the Non-motor International Longitudinal Study (NILS), a global cohort study. Fatigue was assessed using the Fatigue Severity Scale (FSS), while Caregiver Burden Inventory (CBI) were completed in carers. Univariate and multivariate linear regression models were performed to assess whether patient-related fatigue was a significant predictor of caregiver burden, while controlling for age, sex, disease duration, motor and NMS burden, anxiety, depression and cognitive performance.

Results: A total of 61 patients (mean age 67.84±10.33; 70,5% males; mean disease duration 4.95±4.19) were included in the study. Mean total FSS score was 40.95±16.85, while mean total CBI score was 15.39±18.44. Significant clinical predictors of CBI score in univariate linear regression models were disease duration ($p<0.001$), NMS burden ($p<0.001$), anxiety and depression scores ($p<0.001$), cognitive performance ($p=0.008$) as well as FSS score ($p<0.001$). These were then included as independent variables in a multivariate linear regression model with CBI as dependent variable: only FSS score and disease duration remained significant predictors of caregiver burden ($p<0.001$ and $p=0.003$ respectively).

Discussion: Despite its high prevalence, fatigue remains underrecognized and undertreated in the management of PD, leading to a significant burden on patients and their caregivers. We showed that fatigue, as measured by FSS, emerged as a major determinant of worsening caregiver burden in PD, when compared to other previously recognised factors, such as disease duration, motor performance and specific NMS, in particular anxiety, depression and cognitive impairment.

Conclusion: Our findings highlight the significant impact of patients' fatigue on their caregivers' burden. The existing literature lacks studies exploring this association using validated assessment tools as FSS [3]. Our study fills this gap and emphasises the importance of including the evaluation of fatigue, and therefore its management, in clinical practice to improve the well-being of both patients with PD and caregivers.

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## SLEEP QUALITY AND AUTONOMIC DYSFUNCTION IN A-SYNUCLEINOPATHIES

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Aims: Clinical observations suggest a close relationship between the severity dysautonomic symptoms and RBD in Parkinson's Disease [1]. We aimed to determine whether PD patients with clinical history of RBD have more severe dysautonomia and whether sleep quality is correlated with autonomic dysfunction. Cardiovascular autonomic control was assessed through heart rate variability (HRV) analysis, a non-invasive method quantifying the activity of the two branches of the ANS.

Materials and Methods: We enrolled 15 PD patients (8 RBD+, 7 RBD-), at the Neurology Unit of Policlinico Hospital, Milan, Italy. ECG and respiratory traces were recorded for 10 minutes in supine position; subsequently, a segment of 250 ± 50 beats was selected for the HRV spectral and symbolic analysis. Sleep quality was evaluated using a wireless monitoring patch for 1 night (RootiRx; 3 channels: ECG, thoracic effort and actigraphy). Questionnaires for subjective evaluation of sleep quality and autonomic symptoms were administrated.

Results: PDSS score negatively correlated with LF/HF, an index of sympathetic modulation, suggesting that sleep impairment is related to a sympathetic predominance. Low sleep efficiency and higher Wake time After Sleep Onset (WASO) scores were associated with higher sympathetic modulation (0V%) and reduced parasympathetic modulation (2UV%). Moreover, RBD+ patients had higher COMPASS-31 scores and worse sleep quality, assessed by PDSS.

Discussion: Our preliminary data showed that altered sleep quality is significantly associated with cardiovascular sympathetic predominance in PD patients and that RBD+ patients have severer global autonomic dysfunction.

Conclusion: Overall, this suggests that the link between altered sleep and autonomic dysfunction in PD should be more deeply investigated.

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## LATERAL TRUNK DEVIATION AND PISA SYNDROME: BOTULINUM TOXIN TREATMENT IN THE SHORT- AND IN THE LONG-TERM

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Objective: Lateral trunk flexion is a frequent, disabling complication of Parkinson's disease (PD) with uncertain management options [1,2]. We aimed to evaluate long-term use of botulinum toxin (BoNT) in PD-lateral trunk flexion.

Materials: 13 PD patients with a lateral trunk flexion >5° were evaluated for posture, quality of life (8-Item Parkinson's Disease Questionnaire -PDQ-8-), and back pain (visual analogue scale -VAS-) before (T0) and one month after (T1) BoNT. Posture was then followed-up at each next BoNT course by validated measurements based on patients' pictures taken while standing in relaxed trunk position and at their best effort to avert the back [3].

Methods: Patients were treated by US- and EMG-guied Onabotulinumtoxin-A injections in the longissimus (50 Units) and iliocostalis lumborum (50 Units) at the same side of flexion at T0. All following treatment courses were personalized for each patient based on muscular hyperactivity on EMG when sitting without support.

Results: Comparing T0 vs. T1, we didn't observe a significant improvement of the lateral trunk flexion angle (from 11.2±4.6 to 12.4±7.5 for relaxed posture -p=0.507-; from 9.7±4.7 to 12±7.7 with effort -p=0.196-). VAS score changed from 6±3 to 5±3.3 (p=0.606) and PDQ-8 score from 23.6±20.3 to 19.8±14 (p=0.878). 30.8% of patients were treated once, 15.4% twice, and 53.8% beyond 12 months (≥ 3 BoNT courses). The duration of lateral trunk flexion was different between long- and short-term groups (2.4±2.2 vs 6.2±6.8; p=0.057); albeit not significant, the T0 lateral trunk flexion angles at rest and with effort were lower in the long-term treatment group (10.4±2.8 vs. 12.2±6.2 and 8.6±2.6 vs. 11.1±6.5). In the long-term group, the mean angle of flexion was 10.4±2.8 at T0 and 9.2±6.4 at last follow-up (p=0.237).

Discussion: This is the first study analyzing the effect of BoNT for treating PD lateral trunk flexion in the long term. Patients who benefit the most and decide to continue BoNT treatment are those with a shorter duration of the trunk flexion, which may suggest that patients should be treated early. Also, our data suggest that the personalized approach based on EMG and US characteristics of paravertebral muscles is more efficacious than a standardized protocol.

Conclusion: BoNT treatment, tailored according to EMG and US-guidance, could be considered a safe and efficacious treatment to prevent worsening of lateral trunk flexion in PD.

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## TRANSCRANICAL PULSE STIMULATION IN PARKINSON'S REST TREMOR: A PILOT STUDY

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Introduction: Transcranical Pulse stimulation (TPS) is a recent, safe and painless non-invasive brain stimulation technique that has been proved to ameliorate cognitive performance in neurodegenerative diseases [1]. There is not yet a study investigating the effectiveness of this stimulation on PD patients, especially in terms of rest tremor.

Objective: Therefore, the goal of this paper is to explore a possible effect of TPS on the PD rest tremor circuit, stimulating the motor cortex (M1) of the contralateral most affected side.

Materials and Methods: The study included only patients suffering from Parkinson Disease accordingly to MDS criteria, attending the Movement Disorders Outpatient Clinics of the University Hospital of Trieste. All patients displayed a rest tremor, referred as frustrating, and accepted to undergo a single session of TPS. All subjects were tested with UPDRS III and accelerometer recording the upper limbs tremor at T0 (before TPS), T1 (right after TPS) and T2 (24-hours after TPS). At the end of the study, patients were asked to fill a questionnaire about a potential improvement of the PD symptoms (tremor, rigidity, bradykinesia).

Results: 14 PD tremor dominant patients were recruited and underwent all items. In our cohort of patients, the efficacy on the UPDRS was displayed in 13 individuals. The reduction up to 19 points was evaluated after 24h. The mean UPDRS decrease reached 7 points in the next day. On the accelerometer graphic, a cut of the width of the tremor was evaluated in 12 patients at T2. We appreciated a mean width reduction of the tremor reached the 57% compared to baseline. 13 patients were satisfied with the TPS session and reported a subjective improvement of the tremor. No adverse effect were reported.

Discussion and Conclusions: TPS is a harmless, non-invasive brain stimulation method that is well tolerated by the patients. This technique can be safely practiced on M1 to help in reducing the PD rest tremor in the next 24 hours after stimulation. This is supported by a clear improvement of the tremor symptoms highlighted by both the clinician (decrease in UPDRS III and reduction in the width of the tremor) and subjectively by the patient. More studies or a larger group of are needed to better understand an eventual long-lasting function of this technique on PD rest tremor.

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## ACUTE RESPIRATORY FAILURE AS COMPLICATION OF MULTIPLE SYSTEM ATROPHY: DOES LARYNGEAL STRIDOR PLAY A ROLE?

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Laryngeal stridor is one of the several breathing disorders that can occur in multiple system atrophy (MSA), described as a strained, high-pitched, harsh respiratory sound, caused by narrowing of rima glottidis, that can be present both during sleep and wakefulness and has been associated with a worse prognosis. Respiratory complications in MSA can determine acute respiratory failure, but it is not known the role that stridor plays. We present the case of a 69-year-old man with akinetic-rigid syndrome not responsive to levodopa, admitted in an Intensive Care Unit for respiratory acidosis requiring intubation. The patient reported a four-year history of progressive slowness of movements associated with constipation, urinary incontinence and episodes, especially during sleep, of noisy and wheezing breaths.

At the neurologic examination the presence of an akinetic-rigid parkinsonism was found. Functional respiratory and polysomnographic studies revealed dysventilatory syndrome with a restrictive pattern and mild sleep apnea syndrome while laryngoscopy excluded any structural lesion and revealed normal vocal cord motility. Neurovegetative testing showed orthostatic hypotension. The patient was discharged with the diagnosis of clinically established MSA-P according to MDS criteria and the prescription of continuous positive airway pressure (CPAP) during sleep (CPAP) in order to treat laryngeal stridor. This case shows as, in patients with MSA, stridor can be associated with acute respiratory insufficiency, and it is crucial to recognize it quickly and provide the patient with ventilatory support treatment.
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## HEMICHOREA AS FIRST MANIFESTATION OF POLYCYTHEMIA VERA: A CASE REPORT


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Background: Acquired lateralized chorea is mainly caused by stroke, metabolic disorders and autoimmune diseases, while Polycythemia Vera represents a rare etiology of this neurological disorder. [1]

Case presentation: In October 2022, an 84-year-old man was admitted to our Neurology Department 5 days after a sudden onset of involuntary movements at the right side of the face and right limbs. His medical history included hypertension, atrial fibrillation and left cerebellar infarction the previous year. His home therapy included Cardioaspirin, Amiodarone, Enalapril, Simvastatin and Pantoprazole. On hospital admission, high blood pressure was recorded, and blood tests were normal except for elevated hemoglobin (19.7 g/dl) and high hematocrit (70%). Neurological examination showed non-stereotyped involuntary movements involving right orofacial muscles and right limbs, interpreted as hemichorea. Brain MRI documented cerebral small vessel disease, while it was negative for acute cerebrovascular event. A brain 18F-FDG PET was also conducted, revealing hypometabolism in the left thalamus. Further investigations revealed JAK2V617F mutation in peripheral blood. Therefore, diagnosis of polycythemia Vera was made according to 2016 WHO criteria. The patient underwent a phlebotomy (about 250 mL). As a result, the hematocrit level decreased to 45%, and complete resolution of hemichorea was observed three weeks after the treatment. Subsequently, treatment with oncocarbide was initiated, aiming to maintain the hematocrit level below 47%. Since the hematocrit levels normalized, there have been no further episodes of involuntary movements.

Discussion: In our case, the detection of polycythemia occurred simultaneously with the onset of involuntary movements. Furthermore, the decrease in hematocrit levels through phlebotomy strongly correlated with the improvement of the symptoms. This association implies that chorea could potentially arise as a consequence of Polycythemia Vera, with hyperviscosity potentially influencing pathophysiological processes. [2] Elevated hematocrit levels increase blood viscosity, impairing cerebral blood flow and consequently metabolism in basal ganglia and thalamus, without ischemic lesions. [3] Indeed, in our case, brain MRI did not reveal any sign of recent brain injury, while PET-FDG demonstrated decreased activity in the left thalamus, providing evidence of localized metabolic alterations consistent with the patient's symptoms.

Conclusions: Our case underlines the importance to consider polycythemia vera as a potential etiology of acute onset of hemichorea, when polyglobulia is present and other diagnoses have been excluded. In such cases, regression of symptoms can be observed following phlebotomy. Furthermore, FDG-PET may represent a supportive diagnostic tool in order to reveal a metabolic dysfunction especially when routine imaging examinations are negative.
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## PERSONALITY AND PSYCHOPATHOLOGICAL CHARACTERISTICS IN FUNCTIONAL MOVEMENT DISORDERS


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Introduction: Aim of the present study was to assess personality and psychopathological characteristics in patients with functional movement disorders (FMDs) compared to patients with organic weakness (OW).

Methods: Personality characteristics were assessed with the Rorschach test coded according to Exner's comprehensive system and the Structured Clinical Interview for DSM-5 (SCID-II). Alexithymia was assessed with the Toronto Alexithymia Scale (TAS-20) total score and sub-scales Difficulties in Describing Feeling (DDF), Difficulties in Identifying Feeling (DIF) and Externally Oriented Thinking (EOT).

Results: Thirty-one patients with FMDs (27 women; age 40.2±15.5 years; education 11.7±3.2 years; disease duration 2.3±2.5 years) and 24 patients affected by OW (18 women; age 35.8±16.3 years; education 11.9±2.9 years; disease duration 3.4±2.8 years) were enrolled. At the Rorschach, FMDs presented a significantly higher frequency of Popular (P) and sum of all Human content codes (SumH>5) responses and avoidant coping than OW. Moreover, FMDs presented significantly higher scores than OW in TAS-20 total score and sub-scales DDF and DIF.

Conclusion: FMDs presented "conformity behaviors" and excessive interest in others than usual, a maladaptive avoidant style of coping and a difficulty in verbalizing emotional distress. These psychopathological characteristics, may "favor", acting together, the occurrence of FMDs.
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## GENERALIZED MILD CHOREA IN A YOUNG MALE, AFTER CARDIAC ARREST DUE TO ANAPHYLACTIC SHOCK

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Purpose: Post-hypoxic movement disorders (PMD) after cardiac arrest are under-reported phenomena most probably related to basal ganglia dysfunction; ballism and chorea are the most frequently occurring movement disorders associated with basal ganglia infarction. Chorea is one of the major types of involuntary movement disorders originating from dysfunctional neuronal networks interconnecting the basal ganglia and frontal cortical motor areas. The syndrome is characterized by a continuous flow of random, brief, involuntary muscle contractions and can result from a wide variety of causes. We report a case of a young male with a medical history relevant only for asthma, who presented a generalized chorea, prevalent to left side of the body, few days after a cardiac arrest due to anaphylactic shock and concomitant swab positive for COVID19.

Methods: An MRI of brain performed after several days showed hyperintense lesions in T2 weighted and FLAIR sequences involving globus pallidus, bilaterally; blood exams revealed the presence of p-ANCA antibodies with a moderate title. A diagnosis of Churg Strauss wasn't stated for absence of the main diagnostic features, except for asthma.

Results: The irregular movements regressed with introduction of very low dosage therapy with tetrabenazine. At 3-month follow-up neurological examination was negative and so the therapy was suspended, at 6-month follow-up irregular movements where still absent.

Conclusions: In conclusion, our patient showed a generalized chorea due to bilateral globus pallidus infarcts, caused by cardiac arrest after anaphylactic shock; the other possible intervening etiologies (COVID19, presence of p-ANCA) are less likely.

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## TIC SUPPRESSION IN GILLES DE LA TOURETTE SYNDROME, A TRANSCRANIAL MAGNETIC STIMULATION-ELECTROENCEPHALOGRAPHY STUDY

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Introduction: The role of the primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC) in Gilles de la Tourette syndrome (GTS), although relevant to the inhibition of tics, is poorly understood [1,2]. The only studies that have characterized these areas in GTS involve functional magnetic resonance, characterized by poor temporal resolution [1,2]. On the other hand, transcranial magnetic stimulation with EEG co-registration (TMS-EEG) can investigate the dynamics of these areas with a perturbational approach and with greater temporal precision. The aim of our study is to search for excitability alterations of M1 and DLPFC in patients with GTS that could explain their role in tic suppression.

Materials and Methods: 10 subjects with GTS and 10 healthy subjects, matched for age and sex, were enrolled. Each subject underwent M1 and DLPFC stimulation in real condition (110% of the resting motor threshold, RMT) and sham (same intensity as real, using a coil sham) in two conditions: release of tics (free blink in healthy subjects) and voluntary inhibition of tics (inhibition of blink in healthy people). TMS-EEG data were preprocessed with standard pipelines, and the epochs thus obtained were averaged to obtain transcranial evoked potentials (TEPs). Each patient underwent administration of a battery of validated scales for the evaluation of the motor symptoms of the syndrome and the severity of psychiatric comorbidities. The local excitability of each area (15-60 ms) and the modulation between conditions were compared by mixed-model ANOVA.

Results: Compared to healthy controls, GTS patients exhibited reduced M1 excitability during the tic release condition and reduced M1 modulation during the tic suppression condition. Furthermore, greater modulation of M1 during tic suppression corresponded to less severity of motor symptoms and psychiatric comorbidities. Modulation of DLPFC during tic suppression correlated inversely with the severity of motor and psychiatric symptoms.

Discussion and Conclusion: The reduced excitability and modulation of M1 during tic suppression in patients with GTS is a possible expression of entrainment of M1 by subcortical circuits, which makes it refractory to TMS stimulus and voluntary modulation. Although not different from healthy volunteers, also the modulation of DLPFC seems to have a role in the inhibitory control on involuntary movements, in line with the generally known inhibitory role of this area [3].

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## HIGH-DENSITY ELECTROENCEPHALOGRAPHIC CORRELATES OF GAIT DISORDERS IN POST-STROKE PATIENTS

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Aim: Stroke causes sensorimotor impairments that disrupt motor skills performance, including balance and gait. In the clinical scenario of stroke recovery, tracking how individual human brains adapt is critical for therapy outcomes. However, the neurophysiological changes underlying this condition are still debated. This study aims to characterize alterations in electroencephalographic (EEG) signal dynamics as biomarkers of gait disorders.

Materials and Methods: EEG signals were acquired from 20 stroke patients and 21 control participants age-matched using a high-density recording system (128 channels) during 14 meters of straight walking (three phases: acceleration, 10 meters, deceleration) and 5 min of resting-state. Mini-BESTest and Gait dynamic index were used to assess the dynamic balance and functional gait abilities, respectively. Weighted Phase Lag Index (wPLI) analysis was used

to characterize functional connectivity within four regions: Centroparietal (CP) and Frontocentral (FC) in the right/left hemispheres. Statistical analyses were performed using a t-test between groups in alpha and beta bands. The correlations between the straight walking wPLI and clinical scales were obtained through Pearson's correlation analysis.

Results: A pairwise between groups t-test of straight walking task analysis revealed significant reductions of functional connectivity in stroke patients as compared to healthy participants in both alpha and beta bands. These reductions observed in stroke patients correlate with the clinical scales. Furthermore, the t-test showed increments of wPLI during the walking task compared to the resting state in both groups.

Discussion: According to the literature [1], decrements of wPLI in both bands in stroke patients compared to healthy participants suggest alterations in functional connectivity. The increased connectivity observed during the straight walking could be due to the task constraints that imply a reorganization of connectivity in both groups compared to the resting state. The correlations between sensor pairs and clinical assessments suggest that alterations of functional connectivity provide a neurophysiological marker of gait disorders in post-stroke patients.

Conclusions: WPLI is an interesting method for detecting abnormal changes in the dynamics of EEG signals associated with stroke. Furthermore, these changes are associated with clinical outcome measures. These results may open interesting new approaches to stroke rehabilitation.

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## DRIVING ABILITIES, PARKINSON'S DISEASE, AND THE WEARING-OFF MANAGEMENT: INSIGHTS BY THE OPICAR-PARK STUDY

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Objectives: To assess driving abilities, and to compare the use of OPICapone versus other add-on strategies on virtual CAR driving performances of PARKinson's disease with motor fluctuations.

Materials: Driving Questionnaire by the Oregon University was adopted to assess real driving performances. All subjects received a virtual driving evaluation with a driving simulator on a standardized path with traffic lights, jam, pedestrians, and a parking challenge after a training with calculation of learning curve (calculated in seconds) of various driving items. A customized virtual driving rating scale (VDRS) with reaction times (RT) and learning curves (LC) was adopted to assess simulated driving performances. All patients were assessed with the WOQ9 at screening, and with UPDRS and MoCA at the various time points.

Methods: The study had a prospective observational design. Parkinson's disease patients (PD) reporting motor fluctuations were consecutively enrolled according to the following criteria: non-demented PD without sensory disturbances who received an add-on therapy to levodopa in the previous 6 months (PD1, iMAO and other; PD2, opicapone); WOQ9≥2; still on driving. Enrolled subjects received a V1 during their pharmacological "best on" and a V2 during their "wearing-off". A matched healthy population was also recruited (HC).

Results: 36 PD patients and 12 HC were recruited. Mean age and sex did not differ across groups. PD patients described worse real driving performances ("maintaining the lane" item; $p<0.05$). VDRS, RT and LC were significantly altered in PD vs HC ($p<0.01$). The motor impairment (UPDRS-III) and the WOQ9 were associated to the VDRS at V2. At a sub analysis, PD2 were younger than PD1 and had higher WOQ-9 and LEDD values. Moreover, after correcting for the age, PD2 subjects showed better VDRS ($p<0.05$) and reaction time ($p<0.05$) at V1 and better learning curves at V2 than PD1 ($p<0.05$).

Discussions: PD is associated with history of driving impairment and lower performances at driving simulation. This is influenced by the the detrimental motor performance that is observed during the wearing-off. Patients on opicapone performed better than others during the best-on and showed a better learning profile at V2 despite the wearing-off condition.

Conclusions: This is the first study investigating the role of motor fluctuations and the effect of therapies on PD driving abilities [1,2]. A possible positive effect of opicapone on driving abilities has been detected. Further studies are needed to elucidate how to shape the PD pharmacological therapy on the patient needs, focusing on driving.

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## NEUTROPHIL-TO-LYMPHOCYTE RATIO AND LYMPHOCYTE COUNT REFLECT ALTERATIONS IN CENTRAL NEURODEGENERATION-ASSOCIATED PROTEINS AND CLINICAL SEVERITY IN PARKINSON DISEASE PATIENTS

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Introduction: Peripheral inflammation has recently been associated with Parkinson's disease (PD) [1], although correlations between peripheral immune activation and clinicopathological stage of PD remain unclear. Neutrophils and lymphocytes are the two major leukocyte populations of the innate and adaptive immune responses, respectively. The neutrophil-to-lymphocyte ratio (NLR), is now considered a meaningful biomarker for conditions accompanied by systemic inflammation due to various underlying causes such as infections, trauma or stroke.

Objectives: In this study we evaluated the peripheral immune profile of a well-characterized cohort of PD patients, examining correlations with both CSF biomarkers of neurodegeneration and key clinical parameters, in order to better understand the complex dynamics of brain-periphery interactions in PD.

Materials and Methods: Leukocyte population counts (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) and the NRL were collected and compared in 61 PD patients and 60 sex/age matched controls (CTRL). Immune parameters were correlated with CSF levels of total α-synuclein, amyloid-β-42, total and phosphorylated tau, and with scores on major motor and non-motor scales.

Results: PD patients had lower lymphocyte counts and higher NLR than CTRL patients. In PD patients, lymphocyte count was directly correlated with CSF α-synuclein levels, while NLR showed an inverse correlation with CSF amyloid-β42 levels. Lymphocyte count also correlated negatively with HY stage, while NLR positively with disease duration.

Discussion: The purpose of the study was to evaluate leukocyte populations and NLR in a cohort of PD patients, assessing the possible association with CSF biomarkers and disease burden. The study found that PD patients, compared with controls, had lower lymphocyte counts and higher NLR. The lower lymphocyte count was found to correlate with greater severity of motor disturbances and lower CSF total α-syn levels. Increased NLR was found to correlate with lower CSF levels of Aβ42 and longer disease duration. Increased NRL may underlie a systemic inflammatory state secondary to increased release of cytokines and pro-inflammatory molecules. Lymphocyte counts and NLR correlated positively with total α-syn levels and inversely with CSF Aβ42 levels, thus revealing a link between peripheral inflammation and central neuropathology.

Conclusions: In this study, it was shown that, in PDs, peripheral immune system alterations, such as relative lymphopenia and increased NLR, are associated with increased clinical severity and changes in neurodegeneration-associated proteins centrally, particularly in the α-synuclein and amyloid-β pathways.

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## NEGATIVE MYOCLONUS IN SEVERE CHRONIC RESPIRATORY FAILURE: A CASE REPORT

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Background: Negative myoclonus (NM) is an unspecific motor disorder that can characterize a variety of neurological conditions. NM is a shock-like involuntary jerky movement caused by a sudden, brief interruption of muscle activity [1]. Patients with transient myoclonus represent about 30% of all patients with myoclonus who visit an emergency room (ER) for a movement disorder. We describe a patient who de novo developed almost continuous NM triggered by respiratory hypercapnic acidosis.

Clinical Case: A 64-year-old woman was referred to our attention because she experienced continuos brief loss of the muscular tone of the arms, clearly predominating in the upper limbs. She complained of episodes characterized by drops of her upper limbs, which caused the patient to let objects fall. She was taking at home pregabalin 25 mg TID for neuropathic pain and O2 medication for a clinical picture of OSAS.

Methods: At ER a brain CT scan was unremarkable while an arterial blood gases analysis (ABGA) showed severe respiratory hypercapnic acidosis (pH 7.29, pCO2 125.98 mmHg, pO2 64.2). Polygraphic EEG recordings, including the EMG tracing of the deltoid and wrist extensor muscles showed an abrupt and brief period of electrical silence when the patient was asked to extend the arms and dorsiflex the hands in a sustained posture. EEG recordings showed intermittent frontal and bilateral sharp waves without any temporal correlation with NM. The interruption of tonic muscle activity occurred without conjunction with epileptiform EEG abnormalities. An MRI brain study was unremarkable.

Results: To exclude the possibility that pregabalin might have caused the symptom the medication was abruptly stopped. Further, after BIPAP placement we observed a progressive improvment of ABGA values risulting in remission of NM. At this time, polygraphic video EEG recording was normal. Noteworthy, pregabalin medication 25 mg TID was restarted at home but at the present follow-up the patient was asymptomatic for NM.

Discussion: In our case a direct relationship between NM and respiratory hypercapnic acidosis was found. NM is commonly seen in patients with hepatic failure whereas respiratory failure is not commonly associated with NM [2-3]. After resolution of hypercapnia, pregabalin was restarted but no clinical events where observed.

Conclusions: A complete respiratory function screening should be taken into account in the diagnostic workup of NM.

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## MOTOR AND NON-MOTOR CORRELATES OF HYPOSMIA DETECTED BY THE ITALIAN OLFACTORY IDENTIFICATION TEST (IOIT) IN AN ITALIAN COHORT OF PARKINSON'S DISEASE PATIENTS

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Objectives: To characterize olfaction in a cohort of Parkinson's disease (PD) patients and to investigate the relationship between olfactory impairment and both motor and non-motor features and other clinical characteristics (duration, stage and severity).

Materials: One hundred fifty-four patients with idiopathic PD without dementia (Mini-Mental State Examination score >25) were included in the study.

Methods: Odor identification ability was tested using the validated Italian Olfactory Identification Test (IOIT) (33-testers), specifically designed for the Italian population [1]. A comprehensive spectrum of motor (tremor, bradykinesia, rigidity, postural stability, gait, masked face, speech, voice, posture) and non-motor features (urinary symptoms, depression, sleep disorders, constipation) was assessed, using Unified Parkinson's Disease Rating Scale (UPDRS-III), modified Hoehn and Yahr (mH&Y) staging and a semi-structured interview. Patients were divided into 3 clinical phenotypes: tremor-dominant type (TDT), akinetic-rigid type (ART) and mixed type (MXT) [2].

Results: Hyposmia was found in 141/154 (93%) patients (mean mH&Y:1.99±0.6, mean UPDRS-III:23.4±11.56, mean age 66.96±9.2 years, mean disease duration 5.57±4.9 years). Hyposmic patients were older than those with normal olfaction (p=0.012). mH&Y score≥2 was associated with a higher probability of being hyposmic (OR=1.18, p=0.01). IOIT score did not significantly differ between TDT, ART and MXT PD patients. IOIT score directly correlated with patients' age

(p<0.001), disease duration (p=0.01) and mH&Y score≥2(p<0.05). Clinical features associated with higher IOIT score were freezing of gait (FOG) (+2.38, p=0.027) and camptocormia (+2.31, p=0.022).

Discussion: In line with previous studies [3], our investigation highlighted that worse IOIT scores were more likely to associate with camptocormia and FOG among motor symptoms, but not with non-motor symptoms. These results suggest that more severe olfactory impairment is associated with more severe disease manifestations, such as camptocormia and FOG, and it is comparable across clinical phenotypes (TDT, ART, MXT).

Conclusion: Assessing olfactory dysfunction through IOIT may help identify PD patients at higher risk of developing severe motor features (camptocormia and FOG). Overall, IOIT may be a useful tool not only for supporting PD diagnosis but also for providing prognostic information about motor function. Follow-up studies are warranted to confirm IOIT's ability to predict more severe motor symptoms in PD patients.

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## THE ACUTE EFFECTS OF SUBTHALAMIC DEEP BRAIN STIMULATION ON CARDIOVASCULAR AND SUDOMOTOR FUNCTION ASSESSED BY HEAD-UP TILT TEST AND SUDOSCAN

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Objective: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for advanced Parkinson's disease (PD), but its effects on the autonomic nervous system are not well understood. Aim of this study is to investigate the acute effects of STN-DBS on cardiovascular and sudomotor regulation using objective neurophysiological tests.

Materials and Methods: Ten patients with advanced PD who had undergone STN-DBS implantation were enrolled in the study. Patients with certain medical conditions or medications affecting the autonomic nervous system were excluded. Heart rate (HR), blood pressure (BP), and respiratory rate were recorded at rest and during a head-up tilt test (HUTT). Sudomotor function was assessed by measuring electrochemical skin conductance (ESC) using Sudoscan. The patients were evaluated under three conditions: under DBS ON and therapy OFF (DBS ON/Th OFF), 30 minutes after switching off the DBS (DBS OFF/Th OFF) and 30 minutes after switching on the DBS and administering melevodopa/carbidopa 100/25 mg (DBS ON/Th ON). Statistical analysis was performed using t-tests.

Results: A significant reduction in systolic BP was observed at the 10th minute of HUTT in the DBS ON/Th ON condition (p 0.036). No other significant differences were found in HR, BP, or ESC conductance among the three conditions.

Discussion: Most of the previous studies regarding the effects of STN-DBS on autonomic symptoms are based on subjective questionnaires. This study applied objective neurophysiological tests to evaluate autonomic control. Our findings did not show significant differences in HR, BP, or sudomotor function between conditions, except for the decrease in systolic BP at the 10th minute of HUTT during DBS ON/Th ON. This reduction in BP is likely attributed to the acute effect of levodopa therapy rather than direct STN stimulation. The results align with previous studies that found no changes in BP or its responses to tilting in PD patients receiving STN-DBS. Regarding sudomotor function, this study did not find a significant effect of DBS on sweating, consistent with previous literature data.

Conclusion: STN-DBS does not appear to have a direct impact on cardiovascular and sudomotor autonomic regulation. However, it may indirectly improve cardiovascular reactivity by reducing levodopa load.

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## POLYNEUROPATHY, TREMOR AND MR ABNORMALITIES IN KLINEFELTER SYNDROME

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Introduction: Klinefelter syndrome (KS) represent a genetic disorder interesting the sexual chromosomes, with an extra-X chromosome added to the normal karyotype (XXY) Neurological deficits are often present in Klinefelter Syndrome (KS). Tremor, expecially essential tremor, is quite a characteristic tract of the disease. Leukoencephalopathy in MRI hyperlucency spots in white matter is sometimes described. Polyneuropathy is another neurological problem described in KS, although rarely described. Leucoencephalopathy has also rarely been described in KS. We report three cases of KS patients carrying all these three alterations: tremor, sensory-motor polyneuropathy and leukoencephalopathy.

Study subjects: We report three patients affected by KS (XXY) occurred in the last 10 years in our Universitary Department of Neurology. They were 42, 45 and 51-year-old male with numbness, tingles and pain in both the feet, difficult in walking too, with frequent falls. They complained a postural tremor of the upper extremities, with frequency of 12 Hz, exacerbated by anxiety and stress. Neurological examination highlighted an high frequency hand tremor, slightly prevalent in the right side, and reduced sensibility in lower extremities; deep tendon reflexes were symmetrically diminished in lower extremities. Brain MRI showed a pattern of hyperlucency spots in white matter, referred as vascular leucoencephalopathy. Nerve conduction studies showed decreased amplitude and conduction velocities in both motor and sensory fibers.

Discussion: Klinefelter syndrome, 47 XXY, is the most common chromosomal aberration among men. Tremor is one of the most frequent neurological problem described in KS. Although tremor is reported at a younger age, our patients are older than forty. In the report by Harlow et al. the average age of tremor onset in KS was twenty years. The presence of white matter alterations is also reported in different reports, with a distribution of lesions typical of the vascular encephalopathy. The presence of Polyneuropathy is another

neurological pathology less often described in patients with Klinefelter syndrome. There are few reports of these in literature. The Authors considered the polyneuropathy a potentially hypogonadic complication of KS or a complication of pathologies strictly related to the KS, such as Diabetes mellitus or Thyroid disfunction.

Conclusion: In conclusion, the presence of cromosomal alteration typical of KS, would address the presence of tremor, PNP and leukoencephalopathy and do brain MRI, EMG and cognitive tests in these patients in order to find these pathologies and treat them.

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## A NEWLY IMPLEMENTED NGS-BASED METHOD TO DETECT GBA1 VARIANTS IN PATIENTS WITH PARKINSON'S DISEASE


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Objectives: Heterozygous variants in GBA1, encoding for the lysosomal enzyme β-glucocerebrosidase, are the most common genetic risk factor for PD, accounting for 5-15% of all PD cases. Sequencing of the whole GBA1 coding region (11 exons) is a burdensome task, both employing conventional techniques such as Sanger sequencing as well as more innovative strategies such as standard NGS. In particular, the high degree of homology (96-98%) between GBA1 and its pseudogene GBAP1 often leads to recombination events that eventually produce complex alleles which are misaligned and missed by the standard NGS pipelines. We aim to implement a new rapid and cost-effective next-generation-sequencing (NGS)-based technology to sequence GBA1 gene in Parkinson's disease (PD) patients.

Materials and Methods: The experiment was designed to start from a specific long-range PCR which amplifies a unique 7kb amplicon encompassing the GBA1 gene and excluding the neighboring pseudogene GBAP1. This was used as a template to create NGS libraries, which were amplified using Nextera technology and then run on an Illumina MiSeq instrument. In parallel to standard bioinformatic analyses, a tailored pipeline was used, masking GBAP1 pseudogene on the reference sequence and forcing the alignment of sequencing reads against the genomic coordinated of GBA1 gene only. To assess the validity of this approach we studied selected PD patients who were already tested with conventional techniques (Sanger sequencing or standard NGS).

Results: The tailored pipeline displayed a significant increase in read depth and mapping quality compared to the standard bioinformatic analysis. All known GBA1 variants were correctly called and identified using this approach. In several PD patients resulting GBA1-negative with conventional strategies this novel method identified previously missed GBA1 pathogenic variants, particularly those originating from the pseudogene (gene conversions and fusions).

Conclusions: The proposed NGS-based approach appears a cost-effective and reliable alternative for GBA1 sequencing, holding promise to increase speed analysis and variant detection rate compared to conventional strategies.

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## AGE AT ONSET AND FUNCTIONAL STRIATAL CONNECTIVITY IN DRUG-NAÏVE PATIENTS WITH PARKINSON'S DISEASE


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Objective: Compelling evidence suggests that age at onset may significantly affect the clinical picture of Parkinson's disease (PD), in terms of motor and nonmotor symptoms as well as rate of disease progression and development of complications. We investigated the potential effect of age on the whole-brain functional connectivity (FC) from different striatal subregions in a cohort of early PD patients using resting-state functional MRI (rs-fMRI).

Materials: 147 drug-naive PD patients and 38 healthy controls were enrolled. Non-hierarchical cluster were applied to stratify PD patients according to age at onset in 3 subgroups: 32 "early/young", 69 "early/intermediate" and 46 "early/old".

Methods: Clinical assessments as well as rs-fMRI were performed at baseline. Longitudinal clinical data were also collected at 4-year follow-up. Using connectivity-based parcellation, we obtained three regions-of-interest (ROIs) for different striatal functional subregions: sensorimotor, limbic and associative.

Results: "Early/old" PD were presenting with more severe motor and cognitive impairment relative to "early/young" patients. No differences were detected in terms of disease duration between the PD subgroups. The sensorimotor ROI showed increased FC with the left superior frontal gyrus, precuneus and cerebellum, and decreased FC with right lingual gyrus, paracentral lobule and left inferior frontal gyrus in "early/young" compared to "early/old" PD. The limbic ROI showed increased FC with the right temporal gyrus and decreased FC with the posterior cingulate cortex (PCC) in "early/young" compared to "early/old" PD. The cognitive ROI showed increased FC with the cerebellum and decreased FC with PCC in "early/young" compared to "early/old" PD. "Early-young" PD presented a higher risk to develop treatment-related motor complications after 4 years.

Discussion: Specific changes in the striatal FC are associated with age at onset in PD patients. This pattern is related with better motor outcome at baseline and increased vulnerability to develop treatment-related motor complications overtime.

Conclusions: These results may suggest the presence of early compensatory mechanisms occurring in the early stages, that may potentially become dysfunctional under chronic dopaminergic stimulation, likely shifting towards those maladaptive changes of the striatal dopaminergic firing which have been hypothesized to underlie the development of motor complications over time.

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## DATA-DRIVEN CLUSTERING OF NEURODEGENERATIVE DISEASES BASED ON EEG SPECTRUM POWER-LAW DECAY: THE DACNES STUDY

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Background: Neurodegenerative diseases are common causes of impaired mobility and cognition in the elderly. Among them, tauopathies (including Alzheimer's Disease, Progressive Supranuclear Palsy and Corticobasal Degeneration) and α-synucleinopathies (including Parkinson's Disease and Multiple System Atrophy) were considered. The neurodegenerative processes and relative differential diagnosis were addressed through a qEEG non-linear analytic method.

Objectives: To test accuracy of the power law exponent β applied to EEG in differentiating neurodegenerative diseases and to explore differences in neuronal connectivity among different neurodegenerative processes based on β.

Methods: N = 230 patients with a diagnosis of tauopathy or α-synucleinopathy and at least one artifact-free EEG recording were selected. Welch's periodogram was applied to signal epochs randomly chosen from continuous EEG recordings. Power law exponent β was computed as minus the slope of the power spectrum versus frequency in a Log-Log scale. A data-driven clustering based on β values was performed to identify independent subgroups.

Results: In bilateral frontal-temporal regions, β values were significantly higher for Parkinson's Disease with respect to the atypical parkinsonism; in parietal areas, differences remained significant only for Progressive Supranuclear Palsy and Corticobasal Degeneration. Data-driven clustering based on β differentiated tauopathies (overall lower β values) from α-synucleinopathies (higher β values) with high sensitivity and specificity. Tauopathies also presented lower values in the correlation coefficients matrix among frontal sites of recording.

Conclusions: Statistically significant differences in β values were found between tauopathies and α-synucleinopathies. Hence, β is proposed as a possible biomarker of differential diagnosis and neuronal connectivity.

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## FRONTOTEMPORAL DEMENTIA PHENOTYPE IN LATE-ONSET HUNTINGTON DISEASE WITHOUT CHOREA

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Introduction: Huntington disease is a neurodegenerative disorder with autosomal dominant transmission, caused by CAG-repeat expansion in the IT15 gene in chromosome 4, typically characterized by movement disorders such as involuntary choreic movements, gait disturbance, extrapyramidal rigidity and dystonia, associated with neuropsychiatric and cognitive disturbances. Disease onset and severity of manifestations varies depending on repeats number. Age of onset is usually between 40 and 50 years of age, but older presentations are possible and usually associated with more prominent motor onset rather than psychiatric or behavioural, and with a lower number of CAG repeats. We here report a case of HD presenting as behavioural frontotemporal dementia (bvFTD), without movement disorder, in which diagnosis was prompted by [18F]FDG PET/MRI findings.

Case report: A 77-year-old Caucasian man came to our attention for behavioural alterations (irritability, lack of inhibition and hypersexuality) and memory deficits starting at age 75. He had a past history of post-traumatic stress disorder (PTSD) after a car accident treated with SSRI, and treated skin melanoma. In his family, an 80-year-old sister was affected by dementia. In the following months, he developed memory and attention deficits, occasional outdoor space disorientation. brain CT scan revealed mild global brain atrophy, redominantly in temporo-mesial areas. Neuropsychological examination showed mild impairment of attention, executive functions, working memory, visuospatial and visuoconstructive functions (MMSE score: 25/30). Behavioural evaluation showed presence of apathy, lack of inhibition and sleep disturbances. Neurological examination revealed no pyramidal and extrapyramidal signs; however, it documented disrupted pursuit and slow saccades, failure in performing Luria sequence. A diagnosis of possible bvFTD was made. CSF examination documented a normal cell and protein count, normal total tau and phosphorylated tau (whereas amyloid deposition was confirmed with decreased beta1-42/1-40 ratio [0.041]). Brain [18F]FDG PET/MRI highlighted a subtle hypometabolism in bilateral fronto-mesial cortex and discrete hypometabolism in both caudate nuclei. Genetic testing for the most frequent causes of FTD including GRN, MAPT, TARDBP, FUS and c9orf72 resulted negative. A search for CAG expansion in HD gene prompted by the presence of mild caudate hypometabolism, and 41 CAG repeats were found (NM_002111.8:c.53AGC[18]; c.53AGC[41]). A diagnosis of HD with bvFTD phenotype was made.

Conclusion: In our case low number of CAG repeats may explain the late onset and bvFTD clinical presentation. HD is a rare cause of FTD. Decreased metabolism in caudate should rise the suspicion of HD also in atypical and very-late onset patients, even in the absence of motor symptoms.

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## A CASE OF AUTOSOMAL RECESSIVE SPINO-CEREBELLAR ATAXIA TYPE 10 (SCAR10) CAUSED BY HOMOZYGOUS MUTATION IN THE ANO10 GENE: CLINICAL PRESENTATION AND FUNCTIONAL SIGNIFICANCE

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This report describes a case of Autosomal Recessive Spino-Cerebellar Ataxia Type 10 (SCAR10) resulting from a pathogenic variant in the ANO10 gene. SCARs are a group of inherited neurodegenerative disorders characterized by progressive ataxia with cerebellar atrophy. Unlike autosomal dominant SCAs, most ARSCAs are caused by single-nucleotide exon mutations, making the disease challenging to diagnose using traditional sequencing methods. SCAR10 is a rare variant of SCAR caused by mutations in the ANO10 gene. The pathogenesis of SCAR10 is not well understood, but it is thought to involve impairment of endosomal retrograde trafficking and the endolysosomal pathway. The case report describes a 44-year-old male patient with a 13-year education level and a history of gait unsteadiness since childhood. The patient presented with progressive cerebellar ataxia, gait and balance impairment, upper limb coordination problems, and speech and swallowing difficulties. Neurological examination revealed dysarthria, dysphagia, hearing loss, strabismus, and limitation of eye movements. The patient also exhibited pyramidal manifestations, but no peripheral neuropathy's signs. A brain MRI showed a severe diffuse cerebellar atrophy. Genetic testing identified the homozygous variant c.289delA(p.Met97Ter) in the ANO10 gene. The ANO10 gene encodes the endoplasmic reticulum transmembrane protein 16K (TMEM16K), which is involved in various cellular processes, including phospholipid distribution, calcium regulation, apoptosis, and endosomal transport and sorting. Changes in TMEM16K function can impact these processes and contribute to the development of SCAR10. The identified variant in the ANO10 gene is a pathogenic variant and has been reported in a few other individuals with SCAR10. This case report expands our limited knowledge about SCAR10 and provides further evidence of the association between ANO10 gene mutations and the clinical presentation of the disease. Understanding the functional significance of TMEM16K and its role in cellular processes may help in the development of targeted therapies for SCAR10 and related disorders. Further research is needed to elucidate the genotype-phenotype correlation and explore potential treatment options for SCAR10.

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## BRAIN PARENCHYMA SONOGRAPHY FINDINGS IN PATIENTS AFFECTED BY PARKINSON'S DISEASE ASSOCIATED WITH GBA GENE MUTATIONS

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Objective: The aim of this study is to describe the Brain Parenchyma Sonography (BPS) finding in a series of Parkinson's disease associated with GBA mutations (PD-GBA) patients which could be consider as a biomarker both in early and advanced stages of PD-GBA.

Methods: Case series of patients with diagnosis of Parkinson's disease admitted to the Neurological Department of the University Hospital of Sassari.

Discussion: PD-GBA is a common cause of early onset PD, with a peculiar phenotype characterized by prominent non-motor features and even in the early stages of the disease. Single-photon emission computed tomography (SPECT) with DaT has high specificity and sensitivity, but in early stage of disease can be negative [1]. BPS have been shown to be a useful tool in identifying early and already premotor stage of PD [2] through the detecting of bilateral substantia nigra (SN) hyperechogenicity. Previous studies have found that BPS findings in PD-GBA is similar to those of patients with sporadic PD [3].

Results: 6 patients affected by PD-GBA were investigated by BPS. Four patients carried the N370S mutation, one patient carried the E365K mutation and one patient was found to be carrier of a new mutation c.1312C>T. The age at onset of the motor symptom was 52,2 years (range 40-59). Upon execution of BPS, the average duration of the disease was of 8,5 years (range 1-25). A DaT SPECT showed bilateral dopaminergic denervation in 4 patients and unilateral in 2; a BPS revealed bilateral and symmetric hyperechogenicity of SN in 3 patients, asymmetrical hyperechogenicity, contralateral to the site of motor onset, in the others 3.

Conclusions: GBA mutation carriers with PD have greater hyperechogenicity similar to sporadic PD. The mechanism underlying parkinsonism in these patients is still debated. The presence of this sonographic finding is consistent with iron deposition. Larger simple size is needed to explore possible differences in nigral echogenicity in PD patients with different genotypes.

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## NEUROGENIC ORTHOSTATIC HYPOTENSION IN PARKINSON'S DISEASE: IS THERE A ROLE FOR LOCUS COERULEUS MAGNETIC RESONANCE IMAGING?

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Objective: To test whether degeneration of the Locus Coeruleus (LC) is associated with Orthostatic Hypotension (OH) in Parkinson's disease (PD).

Materials and Methods: OH is a common and debilitating non-motor symptom in PD but the mechanisms underlying its development remain largely elusive. Peripheral and central noradrenergic denervation are both likely to play a key role. LC is the main noradrenergic nucleus of the brain and its early degeneration in PD has been put in relation with a variety of non-motor symptoms, including OH, but with inconsistent results. A total of 22 cognitively intact PD patients and 52 age-matched healthy volunteers underwent 3T magnetic resonance (MRI) with neuromelanin-sensitive T1-weighted sequences. For each subject, a template space-based LC-MRI was used to calculate LC signal intensity (LC-contrast ratio) and the estimated number of voxels (LC-Vox) belonging to LC. In a case-control study we compared the LC-MRI parameters in 11 PD patients with OH (PDOH+) versus 11 without OH (PDOH-) (matched for sex, age and disease duration) using one-way analysis of variance followed by multiple comparison tests. We also tested for correlations between subject's LC-MRI features and orthostatic drop in systolic blood pressure (SBP).

Results: PDOH- and PDOH+ did not differ significantly ($p>0.05$) based on demographics and clinical characteristics, except for blood pressure measurements and SCOPA-AUT cardiovascular domain ($p<0.05$). LC-contrast ratio and LC-Vox measures were significantly lower in PD compared to HC, while no differences were observed between PDOH- and PDOH+. Additionally, no correlation was found between the LC-MRI parameters and the orthostatic drop in SBP or the clinical severity of autonomic symptoms ($p>0.05$). Conversely, RBD symptom severity negatively correlated with MRI-LC parameters.

Conclusions: Our results failed to indicate a link between the LC -MRI features and the presence of OH in PD but confirmed a marked alteration of LC signal in PD patients.

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## PARA-INFECTIOUS ACUTE CEREBELLITIS IN A YOUNG WOMAN CAUSED BY MYCOPLASMA PNEUMONIAE: A CASE REPORT


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Introduction: Acute cerebellitis occurs more frequently in childhood, however some cases are described in adulthood. The aetiology of acute cerebellitis in adults is often undetermined. It may be associated with medications, infections, para-infectious processes, auto-immune disorders and para-neoplastic syndromes.

Case Report: A 26-year-old North-African woman presented to our Emergency Department complaining for subjective vertigo associated with headache, blurred vision, nausea, diarrhoea and night sweats since three days. Medical history revealed nasal polyposis, allergic asthma, episodic vertigo and an anxiety disorder, not requiring chronic treatments. Neurological examination showed opsoclonus, postural and action tremor. Hence, she was admitted to the Neurology Clinic. During the first hours of hospitalisation she worsened with new onset of dysmetria, gait instability, till inability to keep an upright position. MRI showed bilateral peri-cerebellum leptomeningeal enhancement. Cerebrospinal fluid (CSF) examination revealed an elevated leukocyte count (13.7/microL, 100% lymphocytes) and protein (43 mg/%). Due to the occurrence of fever, acyclovir, ceftriaxone and levofloxacin were started, without a clinical meaningful benefit. Extensive microbiological analysis on blood, cerebrospinal fluids, throat swab, urine and stool did not reveal any pathogen. Blood serology at the admission showed dubious results for Mycoplasma pneumoniae immunoglobulin M (IgM), while immunoglobulin G (IgG) title was negative. Tests for auto-immune antibodies were negative both in plasma and CSF. Total-Body CT and FDG-PET-RM ruled out malignancies or infectious foci. Opsoclonus was investigated with nystagmography. The clinical situation dramatically improved after high-dose steroid treatment (methylprednisolone 1 g/day for 3 days and then de-escalating): firstly, nausea disappeared, and then, opsoclonus and tremor improved. Meanwhile, a follow up MRI showed a partial resolution of the leptomeningeal enhancement. Ten days from the admission, serology tests demonstrate plasmatic IgM for Mycoplasma turned positive (with negative IgG). After a rehabilitation treatment, the patient was discharged. After a 15 days hospitalisation, the neurological examination showed reduced opsoclonus and a low intensity postural and action tremor, with restoration of gait ability.

Discussion: This is a rare case of acute cerebellitis with opsoclonus in an adult woman associated to Mycoplasma Pneumonia acute infection. Patient was responsive to high dose of intravenous steroids. In case of acute onset cerebellitis and/or opsoclonus, mycoplasma pneumonie infection should be ruled out and early treatment started.

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## NEUROPHYSIOLOGICAL MARKERS OF MOTOR RESERVE IN PARKINSON'S DISEASE


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Objectives: Motor reserve is defined as the resilience mechanisms of the brain coping with neurodegeneration in idiopathic Parkinson's

Disease (PD). [1] Several different mechanisms have been proposed for motor reserve. However, motor reserve has never been investigated on PD patients with clinical unilateral signs and bilateral binding reduction at dopamine transporter (DAT) imaging using a rigorous neurophysiological method.

Materials: In this cross-sectional case-control study, we included 16 PD patients and 28 healthy control subjects. Patients were included if their motor symptoms and signs were unilateral (Hoehn and Yahr stage =1/5, confirmed by two independent raters) but DAT density (assessed using [123I] Ioflupane SPECT imaging) was significantly reduced in the bilateral putamina (Putamen z-score > 0.5).

Methods: Patients and healthy control subjects were extensively investigated using the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS; part III was videorecorded), Hoehn & Yahr (H&Y) stage. Transcranial magnetic stimulation (TMS) was performed on primary motor cortices (M1) in both presymptomatic and symptomatic hemispheres in patients and on dominant hemisphere for HC. TMS testing included cortical excitability and plasticity assessment and the analysis of interhemispheric inhibition (IHI). Data analyzed with paired and unpaired t-test, one-way and two-way repeated measures analyses of variance, multiple regression models, logistic regression. We also used ROC curve to identify a Motor Reserve Coefficient (MRC).

Results: TMS testing revealed asymmetries in corticospinal excitability measures with higher values in the symptomatic hemisphere. Here we also found lower M1 plasticity (compared to the asymptomatic hemisphere). Finally, we found reduced IHI from presymptomatic to symptomatic hemisphere. Interestingly, reduced putamen binding was predicted by reduced ICF in symptomatic hemisphere and by higher plasticity and reduced IHI in presymptomatic hemisphere. Putamen/caudate ratio was directly associated with corticospinal excitability in presymptomatic hemisphere and inversely associated with cortical plasticity in symptomatic hemisphere. MRC distinguished presymptomatic from symptomatic hemisphere (AUC 0.9844). MRC was associated in presymptomatic hemisphere with PAS increment, IHI and corticospinal excitability reduction.

Discussion: Cortical response to nigrostriatal degeneration induced by PD involves a M1-putamen network, sustaining an increased corticospinal excitability, and cortico-M1 connections, responsible for excitability and plasticity changes, depending on caudate activity and becoming more effective with binding reduction in putamen. The balance between these networks results in motor reserve, where cortical plasticity seems to be the main actor.

Conclusion: These new insights on motor reserve networks in PD are essential to develop novel neuromodulation approaches, aimed at reducing motor burden in daily life.

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## CLINICAL PRESENTATION OF FACIO-SCAPULO-HUMERAL DYSTROPHY AND PROGRESSIVE SUPRANUCLEAR PALSY OVERLAP

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Facio-scapulo-humeral dystrophy (FSHD) is a common type of muscular dystrophy characterized by gradual weakness, particularly in the facial and scapular muscles. While individuals with FSHD generally have a relatively long life expectancy, approximately 20% of FSHD patients become reliant on wheelchairs by their fifties. A 60-year-old man, who had been diagnosed with FSHD during his childhood, visited our Movement Disorder outpatient service due to progressive slowness and fatigue. Over the past five years, the patient had experienced a continuous decline in motor function. Initially, his difficulties were attributed solely to his genetic condition. However, concerns arose when his clinical condition worsened significantly, accompanied by the emergence of cognitive and behavioral abnormalities. Neurological examination revealed signs of atypical parkinsonism that had been concealed by FSHD for many years. Specifically, the weakness in his face masked the lack of facial expression (hypomimia), the weakness in his spinal muscles disguised the stooped posture (camptocormia), and the low muscle tone concealed the presence of rigid movements associated with extrapyramidal symptoms. An MRI scan of the brain confirmed a diagnosis of progressive supranuclear palsy (PSP). The symptoms of FSHD can obscure the initial signs of a subsequent neurodegenerative disorder. In cases of FSHD, a late deterioration in motor symptoms should be seen as a warning sign indicating the possible onset of an accompanying neurological condition. The convergence of a neurodegenerative disorder with FSHD significantly impacts the prognosis of the patient and therefore necessitates an early diagnosis to establish appropriate management.

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## EARLY-ONSET PARKINSON'S DISEASE IN WOMEN: ROLE OF HORMONAL EXPOSURES

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Objective: To assess the demographic characteristics and the exogenous/endogenous exposure to estrogen and progesterone related hormones in an incident cohort study from 1991 to 2020 in Olmsted County, Minnesota (USA).

Materials: We used the Mayo Clinic Data Management tool to identify patients with a diagnosis of Early Onset Parkinson's disease. A movement disorder specialist reviewed all medical records to confirm the clinical diagnosis of EOPD, defined as patients with motor symptoms onset between the ages of 21 and 50.

Methods: Medical records of EOPD patients were reviewed to identify their BMI, hormonal exposure, history and features of EOPD.

Results: 87 incident EOPD female patients were identified (90% white, 7% Asian and 3% other/unknown). Median age at motor onset was 43.1 years; the cardinal motor symptoms were tremor (85%), bradykinesia (83%), rigidity (77%) and impaired postural reflex (11%). 28

patients (32%) had a normal BMI (<25), 21 patients (24%) were overweight (BMI 25-30) and 51 patients (44%) were obese (BMI>30). 49 (56%) used hormonal contraception: 32 (54%) ethinyl estradiol and progesterone, 15 (25%) progesterone only and 8 (14%) medicated IUD. The majority of patients had at least one pregnancy (84%): with a median number of 3 pregnancies and 2 deliveries after full term pregnancy, whereas 29% had at least one miscarriage. Menopause had occurred in 63% of the patients (75% patients non-provoked menopause and 24% surgical menopause), with a median age of menopause of 47.6 years; only 10% were menopausal before the onset of EOPD.

Conclusions: Our study reports a high frequency of obesity and exogenous hormonal exposure in female patients with EOPD. The role of exogenous hormones and obesity-correlated hyperestrogenism on the pathogenesis of PD is still controversial, while is unexplored in EOPD. Further studies are needed to address the causality of such observations.

## ARM SWING REDUCTION IN PARKINSON DISEASE: A STUDY WITH A NETWORK OF WEARABLE SENSORS

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Objective: Patients with Parkinson 's disease (PD) commonly manifest arm swing reduction during gait [1]. Previous kinematic studies performed in a laboratory setting using traditional gait analysis have shown decreased arm swing range, amplitude, and velocity in PD compared with controls. The pathophysiology of arm swing abnormalities in PD is still under debate since it is thought to reflect bradykinesia as well as limitation of articular range of motion secondary to upper limb rigidity [2][3]. The present study aims to examine arm swings in PD patients while performing the timed-up and go (TUG) test, in an ecological experimental setting, using a network of wearable sensors. A second aim of the study is to correlate the collected instrumental measures with specific UPDRS subitems for bradykinesia, rigidity, and tremor.

Materials & Methods: We recruited a total of 44 PD patients in the early stage of the disease (H&Y<2) and never exposed to L-Dopa (drug-naïve) and 31 age-matched healthy controls. We performed a novel frequency-based analysis of arm swings during gait extracting data by a network of wearable sensors. The collected data were FFT transformed, and the frequency content was further analyzed. The Spearman's test was used to assess possible correlation among specific harmonic features and clinical scores for bradykinesia, rigidity, and tremor.

Results: The kinematic analysis demonstrated that arm-swing reduction in PD patients can be objectively described in terms of decreased amplitude of all harmonics extracted from upper limb movements. Specific kinematic features highly correlated with rigidity and, in a lesser extent, with bradykinesia; there was no significant correlation with upper limb tremor.

Discussion & Conclusions: The kinematic analysis based on our wearable sensors network allowed us to demonstrate arm-swing reduction objectively during gait in patients with PD while performing a TUG test in an ecological experimental setting. Our findings also suggest that reduced arm swings in PD more likely reflect the severity of rigidity rather than bradykinesia in the upper limb. The findings overall gain new insights into the pathophysiology of abnormal arm swings in PD.

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## EARLY ONSET PARKINSONISM, PHYSIOPATHOLOGY THEORY AND THERAPY

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Introduction: Parkinson disease (PD) is a progressive neurodegenerative disorder characterized by loss of nigrostriatal dopaminergic neurons and it manifests at variable age. Early onset (< 50 yrs) PD is frequently associated with genetic mutations.

Description: Genetic mutations are common in PD especially in the Mediterranean including Sicily and some have a documented pathogenetic role. Those most relevant in early onset PD are Parkin (PARK-2) and PINK1 (PARK-6) both causing autosomal recessive forms characterized by greater prevalence of dystonia, sleep disorders, common motor and psychiatric complications. Heterozygous carriers (only one altered allele) may present a greater risk of disease stressing the importance of genetic counselling. Parkin is a protein of 465 amino acids, expressed in different tissues and at neuronal level in cell body and presynaptic nerve terminals. Parkin is involved in the transcription and replication of mitochondrial DNA, its over expression prevents mitochondrial swelling and stress-induced apoptosis. Where the action of Parkin fails, there is an increase in intracellular levels of $Ca^{2+}$, which is responsible for cell death. In addition, it activates the process of mitophagy. PINK1 is a protein of 581 highly conserved amino acids. Under physiological conditions the high membrane potential of healthy mitochondria is exploited to import PINK1 into the inner membrane, where it will be cut by PARL (presenilin-associated rhomboid like), the protein is then exported to the cytoplasm and will undergo degradation. As a result of a toxic insult and membrane potential variation, internalization does not occur and the protein accumulates on the outer membrane of damaged mitochondria, where it serves as a signal for the recruitment of Parkin and the initiation of the mitophagy process.

Therapy: Therapy in early onset genetic PD considers the use of levodopa possibly in combination with MAO-B (rasagiline, safinamide) and COMT (opicapone and entacapone) inhibitors and should include deep brain stimulation therapy and infusion treatments both providing excellent benefit.

Conclusion:

- Early and late onset PD differ in symptomatology and progression of the disease between.
- Early onset PD has often a genetic cause, mutations alter mitochondrial function and do not cause aggregates of oligomers of phosphorylated synuclein
- Therapy should be optimized early given the risk of motor and psychiatric complications

## ARE DIETARY COMPONENTS POTENTIAL RISK/PROTECTIVE FACTORS OF PARKINSON'S DISEASE?

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Aim of the study: Parkinson's disease (PD) is a multifactorial disease. Previous studies identified several modifiable risk and protective factors for developing PD. Among possible modifiable factors, dietary components may play a relevant role but the relationship between PD risk and diet factors/patters is still poorly understood. The aim of this multicentric case-control study was to investigate the potential influence of dietary components and patterns on PD development in a large sample of patients.

Materials: Six hundred and ninety-four case patients were recruited from among consecutive outpatients with PD who attended six Italian Movement Disorders Centers. PD was diagnosed by neurologists who were experts in movement disorders according to published standard criteria. Six hundred twelve healthy controls were enrolled among the relatives of neurologic outpatients without PD who visited participating outpatient neurology departments during the study period. Healthy controls were frequency-matched to cases by 5-year age stratum, sex, and referral center.

Methods: Dietary factors were explored using a validated 77-item food-frequency questionnaire. The questionnaire was administered in person by a medical interviewer in each centre. Cases and controls were asked to specify the side of the portion of each food and the frequency of consumption. Age-, sex- and referral center-adjusted multivariate logistic regression models were used to investigate possible associations between the risk of PD and the 77 dietary components examined. Factor analysis was used to examine possible relationship between PD risk and diet patterns.

Results: The multivariate logistic regression models showed that eight dietary factors had an independent positive association with PD. These included pizza, prosciutto, artichoke, cruciferae, biscuits, chocolate snacks, sugar and soft drinks. Five factors were inversely associated with PD development and included whole wheat bread, raw carrots, citrus fruits, coffee and beer. The factor analysis identified two diet patterns. The first one ("Western pattern") included meat, sweets, pasta, pizza and potatoes and was positively associated with PD risk. The second one ("Prudent pattern") included vegetables and fruits and there was a trend for an inverse association with PD risk.

Discussion: Our findings demonstrated a relationship between PD risk and dietary components and patterns. This relationship may depend on the ability of different foods to influence the "gut-brain axis" that is thought to play a pivotal role in PD development.

Conclusions: Dietary factors may influence PD risk. Future strategies aimed at preventing PD development should take into account diet components among the modifiable risk/protective factors.

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## COGNITIVE AND AFFETTIVE THEORY OF MIND IN PATIENTS WITH FUNCTIONAL MOVEMENT DISORDERS

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Background and Aims: Functional movement disorders (FMD) are a heterogeneous group of abnormal motor manifestations, alterable by attention or distracting maneuvers, not attributable to a known neurologic disease. It has been recognized that psychosocial and affective-emotional factors play a role in FMD, at least as risk factors. Silveri et al. reported disorders of Theory of Mind (ToM) in FMD [1]. ToM is the ability to predict others behavior by inference of their mental states. The affective component is responsible for understanding others' emotions, while the cognitive component is related to the knowledge of others' mental states, beliefs, thoughts, and intentions [2]. The aim of this study was two-fold: 1) to confirm whether FMD might be related to ToM disorders and 2) to explore the relationship between ToM abilities and neuropsychiatric and behavioral dimensions.

Materials and Method: Eighteen Italian-speaking FMD subjects underwent the Yoni task to assess ToM affective and cognitive dimensions, balanced for level of difficulty (first and second order). This computerized task also contains control items (Physical) [3]. Patients were also administered several questionnaires for measuring depression (BDI-II), anxiety (BAI), dissociative experiences (DES-II), alexithymia (TAS-20), pain (BPI), health-related quality of life (SF-12), and fatigue (MFI-20). The severity of symptoms was rated by the Simplified-FMD Rating Scale (S-FMDRS).

Results: No differences emerged in the Yoni task accuracy between cognitive, affective, and physical condition on the first-order items ($p>0.1$). However, a significant between-condition difference emerged on the second-order items ($p<0.001$); in particular, pairwise comparisons revealed that FMD subjects scored worse on the cognitive and affective items than the control items ($ps\leq0.001$). Accuracy on the second-order ToM items was negatively correlated with anxiety (Spearman's rho=-0.587, p=0.005), the TAS-20 subscore "difficulty describing feelings" (Spearman's rho=-0.465, p=0.026) and MFI-20 fatigue global score (Spearman's rho=-0.436, p=0.035) and mental score (Spearman's rho=-0.446, p=0.032).

Discussion: The results are consistent with the hypothesis that a ToM disorder might underlie FMD. The Yoni task showed the decay of the more complex ToM inferences both cognitive and affective second-order levels of reasoning. The first level of cognitive and affective ToM

seemed to be preserved. Moreover, these data contribute to highlight the relationship between disorders of social cognition and emotion regulation.

Conclusions: FMD could represent an experimental model to explore the overlap between organic and non-organic illness and help clinicians to reconsider some of the symptoms that are present in patients with neurological disorder.

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## INSULAR DOPAMINE DEFICITS IN PRODROMAL ALPHA-SYNUCLEINOPATHIES

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Objectives: Nigrostriatal dopaminergic alterations in iRBD have been associated with a higher risk of phenoconversion to α-synucleinopathies [1]. However, in a very early phase iRBD patients often result negative at DAT-SPECT imaging. Thus, we aimed to i) evaluate striatal and extra-striatal dopamine binding characterizing iRBD and ii) test the ability of extra-striatal dopamine alterations in predicting phenoconversion.

Materials: In this multicenter study, consecutive polysomnography-confirmed iRBD (n=50), drug-naïve PD (n=50) and age-matched control (n=50) underwent a standardized neurological examination and dopaminergic imaging with 123I-FP-CIT Brain SPECT. iRBD subjects were further classified in RBD-DAT- (n=36), and RBD-DAT+ (n=14) according to visual rating assessment. For all iRBD patients, we collected conversion to clinical diagnosis at follow-up (mean time= 3.16 years).

Methods: Between-groups differences in 123I-FP-CIT striatal and extra-striatal binding were evaluated both with ROI-based and voxel-wise analyses - in age, sex, and center adjusted models. An ANCOVA model- adjusted for age, sex, center, and DAT-SPECT positivity at baseline- was applied to test demographic and dopaminergic differences between iRBD converters and stable over time. Cox regression analysis was used to assess the ability of extra-striatal alterations characterizing iRBD to predict longitudinal clinical progression over follow-up time – adjusting for DAT-SPECT positivity at baseline.

Results: Both ROI-based and voxel-wise analyses showed an early involvement of the left insula in RBD-DAT- with an additional impairment in nigrostriatal regions extending from RBD-DAT+ to PD conditions. In the whole iRBD sample, insular binding was lower in those who converted to α-synucleinopathies over time. A lower insular binding was significantly associated with a greater conversion to α-synucleinopathies with a hazard risk ratio of 3.64 [C.I. 95% 1.22-10.89].

Discussion: Insular dopaminergic deficits are an early signature of iRBD, even before DAT-SPECT positivity according to cut-off used in clinical practice. Moreover, insular alterations are associated with a greater risk of conversion to α-synucleinopathies over time - therefore being a promising biomarker of progression.

Conclusions: Together, these results suggest insular dopaminergic deficits as core features of iRBD, even before the nigrostriatal deficits and motor impairment.

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## DETECTION OF FATIGUE IN PARKINSON'S DISEASE PATIENTS AND CORRELATION WITH OLFACTORY AND COGNITIVE IMPAIRMENT, APATHY AND NON-MOTOR SYMPTOMS

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Objective: Although fatigue represents a frequent non-motor symptom in patients affected by Parkinson's disease (PD), correlations with motor and other non-motor symptoms are often underevaluated. Our aim was to identify the presence of fatigue in PD patients, and subsequently to analyze the correlations between fatigue and apathy, olfactory and cognitive impairment, and motor symptoms.

Materials and Methods: One hundred and seventy-three PD patients (105 males/68 females) were enrolled. Mean age ± standard deviation at enrollment was 70.1± 9.1 years. Participants with PD were recruited during regular out-patient follow-up visits. PD was diagnosed according to the Postuma criteria [1]. Fatigue was evaluated by the PD Fatigue Scale (PFS) with the score of 3.3 considered the cut-off [2]. Motor impairment in PD patients was assessed using the Modified Hoehn and Yahr Scale and the Unified PD Rating Scale (UPDRS) part III. Montreal Cognitive Assessment (MoCA) was used for cognitive evaluation. Olfactory impairment was examined using the "Sniffin' Sticks" test. Apathy was evaluated by the self-report version of the Starkstein Apathy Scale.

Results: Using the PFS cut-off score of 3.30, 68 PD patients with PD (39.3%) were considered affected by fatigue. Multivariate linear regression analyses analyzing motor and non-motor features showed that both apathy ($p<0.001$) and UPDRS part III ($p<0.002$) were the strongest predictors related to the severity of fatigue.

Discussion and Conclusions: In our study, we confirm as fatigue represents a frequent condition among parkinsonian patients. Our findings highlighted the fact that fatigue in PD patients may arise from the convergence of both motor and non-motor disturbances.

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## DISTINCT STRIATAL CONNECTIVITY PATTERNS IN PATIENTS WITH PARKINSON'S DISEASE WITH AND WITHOUT URINARY SYMPTOMS

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Objectives: To investigate the possible association of urinary symptoms with whole-brain functional connectivity (FC) alterations from distinct regions-of-interest (ROI) of the striatum in a large cohort of drug-naïve Parkinson's disease (PD) patients applying a seed-based analysis approach to resting-state functional MRI data.

Materials: Seventy-nine drug-naive PD patients (45 PD-urinary+/34 PD-urinary-) and 38 healthy controls (HC) were consecutively enrolled.

Methods: Motor, nonmotor and cognitive assessments were performed. Using an a priori connectivity-based domain-specific parcellation, we obtained three ROIs for different striatal functional subregions, sensorimotor, limbic, and cognitive, from which seed-based FC voxelwise analyses were conducted over the whole brain. Clinical data were also correlated with imaging findings.

Results: No demographical/clinical differences were found between patients' subgroups. In PD-urinary+ compared to PD-urinary- patients the sensorimotor ROIs showed increased FC with the right premotor area, supplementary motory area and primary motor area, and decreased FC with the right angular gyrus; the limbic ROI showed increased FC with the left anterior prefrontal cortex (aPFC). In PD-urinary+ patients compared to HC, the sensorimotor ROI showed increased FC with the bilateral fusiform gyri; the limbic ROI showed increased FC with the right superior temporal gyrus, and decreased FC with left insula, left anterior cingulate cortex and right aPFC; the right cognitive ROI showed increased FC with the left insula. In PD-urinary- compared with HC, the sensorimotor ROI showed decreased FC with the bilateral substantia nigra; the limbic ROI showed decreased FC with the bilateral aPFC. Correlation analysis showed that FC alterations between striatal subregions and fronto-parietal areas correlated with motor/cognitive outcomes in PD-urinary+.

Discussion: We found specific FC changes potentially associated with urinary dysfunction in PD: ) increased FC between striatal regions and insula/anterior dorsolateral PFC, aiming at inhibiting the urinary urge while in social context; ii) increased FC between striatal regions and motor and premotor/supplementary motor areas as an attempt to recruit the pelvic floor muscles and overcome urinary frequency and urgency to delay micturition; iii) decreased FC between striatal regions and parietal, insular and cingulate cortices as an early biomarker for altered autonomic and behavioral sensorimotor integration of the timing of voiding; iv) increased FC between striatal regions and temporo-occipital areas as a compensatory mechanism for altered sensorimotor control.

Conclusions: Our findings revealed that a specific pattern of striatal FC may be associated to altered stimuli perception and sensorimotor integration in PD patients. These results may potentially help clinicians to design tailored rehabilitation programs.

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## PROGRESSIVE IMMUNE-MEDIATED CEREBELLAR ATAXIA IN A PATIENT WITH PRIMARY SJÖGREN'S SYNDROME AND CONCOMITANT HASHIMOTO ENCEPHALOPATHY: A CASE REPORT

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Objective: To describe a patient with progressive cerebellar ataxia with Primary Sjögren's Syndrome (PSS) and concomitant Hashimoto encephalopathy.

Case report: A 68-year-old Iranian woman with a history of breast cancer without relapses after surgery. In the last year, she developed a progressive cerebellar syndrome. She also reported outbursts of uncontrolled crying, impulsivity, and dry mouth. The neurological examination was remarkable for the presence of mild dysarthria, gait ataxia, and behavioral abnormalities. A neuropsychological assessment was performed, which revealed a dysexecutive syndrome. Brain MRI documented cerebellar atrophy which was more severe in the vermis. Cancer screening (paraneoplastic autoantibodies and whole-body PET/CT) was negative. Anti-nuclear antibodies (ANA 1/1280 with speckled granular pattern), antibodies against Extractable Nuclear Antigen (ENA anti-Ro 60 and 52), anti-thyroid peroxidase (TPO) and anti-thyroglobulin (TG) antibodies were detected in the blood. The Schirmer test was positive. The Cerebrospinal Fluid (CSF) showed mild protein elevation and the presence of oligoclonal bands with pattern IV. A diagnosis of Sjogren's Syndrome was made according to the 2016 ACR-EULAR classification criteria. The neurocognitive impairment and the presence of anti-thyroid antibodies make also possible the diagnosis of Hashimoto encephalopathy. The patient was treated with methylprednisolone 1 g daily for 5 days with a slight improvement of cerebellar ataxia and impulsivity.

Discussion: This is a case of progressive cerebellar ataxia in a patient with PSS and concomitant Hashimoto encephalopathy. Neurological involvement in PSS is a common extra glandular manifestation but cerebellar involvement is rare and the pathophysiology is still unclear. The prevalence is 1.5%, with a high female-to-male ratio, a mean age at onset from fifth to sixth decade, a detection of anti-Ro positivity and evidence of mild cerebellar atrophy. [1] Most of the cases reported so far show mild protein elevation and the presence of oligoclonal bands in the CSF, suggesting an active role of autoantibodies in CNS damage. [2] Because of the concomitant presence of HE, the cerebellar involvement in this case cannot be attributed with certainty to either autoimmune disease. Despite this, high-dose glucocorticoid therapy, prescribed as the initial treatment or during neurological exacerbations, remains the first-line therapy. Corticosteroid-sparing immunosuppressive therapy might be indicated in those cases with a progressive course. [3]

Conclusion: Primary Sjögren's Syndrome and Hashimoto encephalopathy are rare but potentially treatable causes of progressive cerebellar syndrome. Early diagnosis is of paramount importance to start timely a specific therapy and stop the CNS damage.

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## GENDER DISPARITY IN ACCESS TO ADVANCED THERAPIES FOR PATIENTS WITH PARKINSON'S DISEASE

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Objective: The objective of this study was to investigate the presence of any gender disparity in the access to advanced therapies for patients with Parkinson's disease (PD).

Materials and Methods: All patients consecutively referring to the Parkinson's and Movement Disorder Center of L'Aquila from April 2011 to May 2023, and screened for the possible access to advanced therapies for PD, were investigated. All clinical data were retrospectively reviewed, with attention being paid to anagraphical and clinical data of patients finally undergoing advanced therapies.

Results: 626 medical records were reviewed (mean age±SD 73.3±9.9; 67% males). Out of them, 172 patients (mean age±SD 70.0±10.0; 73% males; median Hoen Yahr level: 3, minimum 1 maximum 5) were considered clinically eligible for advanced therapies. Specifically, 133 were considered eligible for MRI Guided Focused Ultrasound Thalamotomy (mean age±SD 70.0±8.9; 77% males), 25 patients for Levodopa/carbidopa intestinal gel (LCIG) infusion (mean age±SD 71.2±6.3; 56% males), 12 for Deep Brain Stimulation (DBS) (mean age±SD 71.2±6.3; 75% males), and 2 for subcutaneous apomorphine (mean age±SD 63.5±0.7; 50% males). With respect to MRgFUS, 95 patients already underwent the procedure (mean age±SD 70.4±9.6; 73% males), while 38 patients are still waiting for the treatment (mean age±SD 68.9±9.2). No sex differences were found in all groups in relation to age (MRgFUS group: males vs females 70.2±8.9 vs 70.8±8.9, p 0.809; LCIG group: males vs females 71.8±4.6 vs 70.5±8.21, p 0.234; DBS group: males vs females 77.2±8.1 Vs 67.3±8.6, p 0.843) and disease duration (MRgFUS group: males vs females 8.3±4.4 vs 9.6±6.7, p 0.419; LCIG group males vs females 11.5±3.8 vs 15.4±5.4; p 0.154; DBS group: males vs females 15.0±9.62 Vs 15.50±7.78, p 0.796). In the whole group, a higher mean Levodopa equivalent daily dose (LEDD) was reported in men (mean LEDD±SD 551± 356 mg) then in women (mean LEDD±SD 456± 278 mg), although the difference was not statistically significant (p 0.215).

Discussion: To date, no data are available about the different access among sexes to advanced therapies for PD. The higher prevalence of PD in men than in women explains only in part the reported management gender disparity that is higher than that expected.

Conclusions: Motor fluctuations and dyskinesias, that are the main indications for advanced therapies, are more frequent in women that in men. Therefore, the above gender disparity deserves further investigation to identify the factors accounting for the discrepancy in the access to advanced therapies.

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## POST-COVID PARKINSONISM: A SYSTEMATIC REVIEW OF CLINICAL PRESENTATIONS

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Objectives: Among neurological manifestations associated to Covid-19, few cases of parkinsonism with a close temporal relationship with SARS-CoV-2 infection have been reported. The objective of this review is to provide a critical appraisal of all the reported COVID-19-related cases of parkinsonism. We assessed the quality of reporting and propose a phenomenological and diagnostic classification based on clinical features and current diagnostic criteria.

Materials and Methods: A comprehensive PubMed search was conducted for cases of parkinsonism occurring in temporal connection with Covid-19 published until May 2023. The methodological quality of reports was assessed by two independent reviewers, applying a tool assessing different domains. Parkinson's disease was diagnosed based on MDS criteria for clinically established early PD and multiple system atrophy according to consensus MDS criteria. Reports were grouped into consistent phenomenological sets.

Results: The search strategy identified 25 cases of parkinsonism following a confirmed SARS-CoV-2 infection. Quality was rated low in 12 cases (48%), moderate in 11 (44%), high in the remaining two cases (8%). Cases were grouped into four consistent categories according to phenomenology. Eleven patients matched criteria for clinically established early PD or clinically probable PD, 1 for clinically probable MSA. Five cases were assessed as acquired parkinsonism, while eight remained unclassified.

Discussion: We found a moderate or low overall quality in most of the reviewed reports. Adherence to CARE checklist was insufficient in most cases highlighting the need for a systematic approach of data collection and reporting. We identified four main clinical categories notwithstanding a certain degree of heterogeneity. The putative role of Covid-19 in causing or accelerating a preexisting neurodegenerative condition have been previously discussed, but these hypotheses are not supported by robust evidence. These include: direct CNS invasion; hypoxic damage, neuroinflammation or immune-mediated events. Evidence of a direct pathogenic connection between SARS-CoV-2 infection and parkinsonism was lacking in all cases, raising

the question whether Covid-19 was indeed the cause or was instead a coincidental occurrence. SARS-CoV-2 infection may otherwise have acted as an environmental trigger to facilitate onset or progression of parkinsonism.

Conclusions: Whether parkinsonian syndromes may occur following Covid-19 infection remains a yet unexplored possibility. High quality reports fulfilling CARE guidelines are therefore crucial in order to extend evidence derived from single observation to clinical care. Prospective cohort studies collecting patients affected by Covid-19 are needed to observe the real impact of Covid-19 on a potential rise in parkinsonism cases.
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## RESTLESS LEG SYNDROME AND PRIMARY HYPERPARATHYROIDISM: AN INTRIGUING RELATIONSHIP


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Objectives: Restless leg syndrome (RLS) is an invalidating neurological disorder with a complex and still largely unknown pathophysiology. RLS may be observed in Parkinson's disease (PD) and in renal failure, but idiopathic cases are also common. Few reports and small studies associated RLS with parathyroid metabolism. Herein, we aim to analyze a cohort of patients affected by primary hyper and hypoparathyroidism, investigate the prevalence of RLS, and the associated risk factors.

Materials: A total of 94 patients, 57 affected by primary hyperparathyroidism and 37 by iatrogenic hypoparathyroidism were consecutively recruited. Patients affected by peripheral neuropathy, iron deficiency, PD, and rheumatological disorders were excluded.
Methods: All patients underwent neurological examination, the Revised IRLSSG diagnostic criteria for RLS were administered, and if the diagnosis was met, the RLS severity scale was dispensed. Retrospective records including baseline serum levels of parathyroid hormone (PTH), calcium, phosphorus, 25-OH-vitamin D, and creatinine, but also data on parathyroidectomy, renal lithiasis, bone fractures, T-scores, and the presence of osteoporosis were collected.

Results: RLS was diagnosed in 14 patients with hyper PTH (32%) compared to 3 patients with hypoPTH (8%) (p=0.04). The mean score severity of RLS was 16 (0-27) which is defined as moderate. Out of 11 patients with hyper PTH and RLS that had undergone parathyroidectomy, 8 of them reported improvement of RLS symptoms after the procedure. Patients with hyper PTH who had undergone surgery had a higher prevalence of RLS compared to those who did not undergo the procedure (p=0.036). PTH and calcium levels were higher in patients with RLS than those without, the latter showing the strongest correlation.

Conclusion: Our study shows that primary hyperparathyroidism is associated with the presence of RLS. Their relationship may be in part related to electrolyte imbalance. Patients with hyper PTH and who have undergone therapeutical parathyroidectomy have a higher prevalence of RLS, implicating a more severe disease at baseline. Surgery however alleviated but did not completely resolve RLS symptoms. Possibly hyper PTH, via renal, intestine, and bone reabsorption with the release of calcium levels in the blood, may act on the central nervous system (together with the hormone itself) by facilitating the nociceptive processing through the neuroendocrine system, a result which should be further investigated.
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## NEUROIMAGING CORRELATES OF POSTURAL INSTABILITY IN PARKINSON'S DISEASE


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Objective: Neuroimaging correlates of postural instability (PI) in Parkinson's disease (PD) are largely unknown [1-2]. In this study, we aimed to identify the brain structures associated with PI in PD patients, using different MRI approaches.

Methods: One-hundred and forty-two patients with PD and 45 control subjects were enrolled in the study. PI was assessed using the MDS-UPDRS-III pull-test item (PT) [3]. A whole-brain regression analysis identified brain areas where grey matter (GM) volume correlated with the PT score in PD patients. Voxel-based morphometry (VBM) and Tract-Based Spatial Statistics (TBSS) were also used to compare unsteady (PT=1) and steady (PT=0) PD patients. Associations between GM volume in regions of interest (ROI) and several clinical features were then investigated using a multivariate regression analysis.

Results: PI was present in 44.4% of PD patients. The whole-brain approach identified the bilateral inferior frontal gyrus (IFG) and superior temporal gyrus (STG) as the only regions associated with the presence of postural instability. VBM showed reduced GM volume in fronto-temporal areas (superior, middle, medial and inferior frontal gyrus, and STG) in unsteady compared with steady PD patients, and GM volume in these regions was significantly associated with the PT score after correcting for confounding factors.

Conclusions: This study demonstrates a significant atrophy of the IFG and STG in unsteady PD patients, suggesting that these brain areas may play a role in the pathophysiological mechanisms underlying postural instability in PD. This result paves the way for further studies on postural instability in parkinsonism.

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## MOTOR OUTCOMES AND POSSIBLE PREDICTIVE FACTORS FOR DIRECTIONAL DEEP BRAIN STIMULATION

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Background and Aim of the Study: Deep Brain Stimulation (DBS) is a well-established therapeutic approach for patients with advanced Parkinson's disease. Directional stimulation (DS) extended the therapeutic window by increasing the side effects threshold and minimizing the impact of suboptimal lead placement as compared to conventional stimulation (CS)3, although its superiority in motor outcomes is still debated. We aimed to assess possible predictive factors for DS use and its motor outcomes as compared to CS.

Methods: Patients with DBS implant compatible with DS with at least six-months follow-up were included. Subjects were divided into two subgroups (DS vs CS), according to the stimulation settings at the latest follow-up. Motor outcomes were compared between the two groups. Predictive factors for the use of DS were evaluated.

Results: A total of 42 patients were included. At the latest follow-up, DS and CS subgroups showed the same population (21 subjects each). DS seemed to achieve better, although not significantly superior, motor outcomes, in particular in the stimulation-induced improvement of the Unified Parkinson's Disease Rating Scale (UPDRS) III in off-medication state (DS 31% vs CS 24%, p=0,9) and in the reduction of the Levodopa Equivalent Daily Dose (LEDD) (DS 47% vs CS 40%, p=0,6). Moreover, UPDRS scores in items evaluating axial symptoms decreased significantly after DS (6,9 vs 4,3, p=0,01). Such improvement seemed to be more prominent in the DS group as compared to CS, although statistical significance was not achieved (DS 37,1% vs CS 12,8%, p=0,8). Among those considered at baseline (demographic variables, disease duration, motor phenotype, Hoehn & Yahr stage, LEDD, motor impairment, axial symptoms, improvement after levodopa challenge), no clear predictive factor for DS use was highlighted.

Conclusions: In our study DS seemed to achieve better motor outcomes as compared to CS, although such trend resulted not statistically significant, possibly due to the limited sample size and short follow-up period. In particular, a significant improvement in axial symptoms was obtained with DS, whereas it was not reached with CS. No clinical feature at baseline correlated with future DS use, again possibly due to limited numerosity. Larger study samples and longer follow-up periods are needed to elucidate whether DS, along with the renown milder side effects, achieves better motor outcomes as compared to CS.

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## EFFICACY AND STABILITY OF TREATMENT WITH MAO-B AND COMT-INHIBITORS IN PATIENTS WITH PARKINSON'S DISEASE AND MOTOR FLUCTUATIONS: A RETROSPECTIVE STUDY

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Objective: To compare the efficacy and stability of three add-on options (safinamide (SF), rasagiline (RS), and opicapone (OP)) for treating Parkinson's disease (PD) patients with motor fluctuations.

Methods: Data were retrospectively collected from PD patients at Sant'Andrea Hospital from January 2012 to January 2022. Patients had at least 12 months of observation. The primary objective was to determine differences in treatment stability, in terms of months without pharmacological changing, among the add-on options.

Results: Data from 61 subjects (78 observations in total) were analyzed. Baseline characteristics did not significantly differ among the groups. Therapy stability duration (months) did not differ significantly (p=0.595). However, patients on OP therapy had higher LEDD values (p=0.009) and were younger (p=0.042) than those on RS therapy. RS therapy had a higher discontinuation rate (45%) compared to SF therapy (p=0.015). RS patients more frequently switched MAO inhibitors (p=0.003), while SF patients often replaced a previous MAO inhibitor (p=0.001).

Discussion: Therapy stability did not significantly differ among the add-on options. Differences in LEDD and age at add-on starting suggest variations in patient characteristics and treatment strategies.

Conclusion: RS, SF, and OP are valid, effective, and well-tolerated add-ons with similar therapy stability. OP is commonly used in patients with MAO inhibitors, while SF is preferred as a first-line add-on for initial motor fluctuations. Add-on therapy choice currently relies on individual patient evaluation for personalized medicine. Further studies are needed to validate these findings.

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## CEREBELLAR CHANGES ON MR SPECTROSCOPY IN HEREDITARY SPASTIC PARAPARESIS

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Background and Aim: Hereditary spastic paraplegia (HSP) is a group of neurodegenerative disorders characterized by underlying wide genetic and clinical heterogeneity. The core clinical presentation is a pyramidal syndrome which starts in the lower limbs. They can present as pure or complex forms. In the latter, a wide range of clinical symptoms and signs are reported, including cerebellar ataxia. The aim of this study was to explore in-vivo cerebellar metabolic alterations with proton MR spectroscopy (1H-MRS) technique in patients with pure and complicated HSP.

Methods: We enrolled 20 patients with HSP (51.3±11.2years, 8F). To date the genetic diagnosis was available for 13 patients (subtypes: 1 SPG3A, 6 SPG4, 1 SPG7, 1 SPG10, 1 SPG15, 1 SPG26, 1 with ABCD1 mutation and 1 with MFN2 mutation). The neurological evaluation included the Spastic Paraplegia Rating Scale (SPRS). Three patients had mild cerebellar signs. A cohort of 20 matched healthy control subjects (HC) was also recruited (48.5±12.4years, 8F). The participants underwent a standardized high-field (3T scanner) MR protocol including single voxel (6 ml volume) 1H-MRS within the left cerebellar hemisphere. Metabolites content was quantified with the automatic software LCModel and evaluated relative to creatine (Cr), marker of energy metabolism. In particular, N-Acetylaspartate (NAA), marker of neuronal integrity, choline (Cho), marker of membrane turnover, and myo-Inositol (mI), marker of glial cells, were evaluated. Tissue fractions within the 1H-MRS VOI were estimated and included as nuisance covariates. Voxel-based morphometry of cerebellar volumes was also performed.

Results: NAA/Cr was lower in HPS patients compared to HC (1.19±0.18 vs 1.55±0.23, p=0.0003) also when three patients with clinical cerebellar involvement were excluded (p =0.0002). NAA/Cr correlated with SPRS (r=-0.451, p=0.046) and with the cerebellar grey and white matter volume loss (GM: r=0.427, p=0.006; WM: r=0.482, p=0.002)

Discussion and Conclusion: 1H-MRS disclosed biochemical alterations in the cerebellar hemisphere of HSP patients, even in the absence of cerebellar signs. Such alterations correlated with both volume changes and disease severity. These results support the hypothesis of a shared vulnerability of cerebellar and corticospinal neurons for common pathophysiological processes.

## ASSESSING SMELL PERFORMANCE IN ESSENTIAL TREMOR PLUS PATIENTS

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Objectives: Essential tremor (ET) plus is a heterogeneous syndrome of bilateral upper limb action tremor with either rest tremor or soft signs, which has been suggested to represent a prodromal stage of Parkinson disease (PD) in some cases. Hyposmia is a prodromal symptom of PD, which can be detected with the University of Pennsylvania Smell Identification Test (UPSIT). To get a deep phenotyping of ET plus with rest tremor we evaluated smell performance in these patients and compared it with that of patients with Parkinson's disease and with that of healthy subjects (HS).

Materials: We used a shorter version of the Italian adapted UPSIT test with 8 items, able to discriminate between PD patients and HS using a cut-off point of $\leq 6$.

Methods: Kruskal-Wallis nonparametric test was performed to compare the 8-item UPSIT scores between the three groups using SPSS software, version 26.0.

Results: The study sample consisted of 35 ET plus patients, 42 PD patients and 38 HS. The three groups were homogeneous in terms of age (70.89 ± 8.96 vs. 65.38 ± 6.88 vs. 63.71 ± 6.93, ET plus, PD and HS, respectively, $p = 0.20$) and sex distribution (men/women: 62.9%/37.1% vs. 57.1%/42.9% vs. 57.9%/42.1%, ET plus, PD and HS, respectively, $p = 0.863$). The mean UPSIT score was significantly different between the groups [Kruskal-Wallis chi-squared = 42.649; df = 2; $p < 0.05$]. Post-hoc analyses demonstrated the mean UPSIT score in ET plus patients was significantly different from both PD (5 ± 3 vs 3 ± 3, $p<0.05$) and HS (5 ± 3 vs 7 ± 3, $p<0.05$). Twenty-eight (80%) ET plus patients exceeded the proposed cut-off (i.e., $\leq 6$) for pathological smell performance, so nearly 50% of ET plus patients were evaluated with 40-item UPSIT Italian version. Only two patients exceeded the pathological cut-off (i.e., $\leq 21$).

Discussion: A small fraction of ET plus with rest tremor has a smell performance in the pathological range therefore they should be closely monitored. The remaining fraction of ET plus with rest tremor has a normal smell, in these patients rest tremor is not a prodromal of Parkinson's disease.

Conclusions: The assessing of smell performance in Essential tremor plus with rest tremor contributed to a deep phenotyping. However, the 8-item UPSIT had poor diagnostic performance because it was unable to discriminate between ET plus with resting tremor and HS.

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## "MY EAR IS CLICKING": A CASE OF SECONDARY PALATAL TREMOR

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Background: Palatal tremor (PT) is a rare disorder involving soft palate. The underlying etiology and differential diagnosis could be wide and challenging. In this regard, the choice of the best work-up is essential.

Case presentation: A 54-year-old male patient complained a two-year history of rhythmic, low-frequency palate movement with audible click. Other symptoms were slight dysphagia for liquids and non-progressive balance disorder described as retropulsion with some near falls. Clinical assessment disclosed bilateral palatal tremor at approximately 1,5Hz with preserved palatal motility. No dysarthria,

no rhinolalia, no phonatory click were found. In addition, rotatory gaze-evoked bilateral nystagmus with delayed vertical saccades and unsteady walk with positive Romberg sign were observed. Brain MRI showed SWAN hypointensities involving ponto-mesencephalic junction, pons and the bulbo-pontine junction, left cerebral peduncles, cerebellar folia, postero-inferior portion of the left cerebellar hemisphere, extended to bilateral dentate nuclei. Within these lesions, there were two cavernous angiomas and a developmental venous anomaly (DVA) located in the cerebellar hemispheres. Furthermore, MRI revealed degenerative hypertrophy of both bulbar olivary nuclei.

Discussion: PT can be essential/idiopathic (EPT) when not attributable to a structural cause and symptomatic (SPT) when secondary to lesions involving the dentato-rubro-olivary pathway. A common feature is the hypertrophic olivary degeneration (HOD) that represents the vacuolation of the nucleus and the enlargement of cell bodies due to olivary deafferentation. Patients with SPT usually present other symptoms, while patients with EPT usually report ear clicks rather than the sensation of throat involuntary movements. EPT can be also voluntary (intentional contraction of tensor veli palatini) or psychogenic. Distractibility and entertainability are present in both psychogenic and non-psychogenic EPT, making distinction harder. Conversely, common features in EPT, not typical in SPT, are audible click, disappearance of tremors during sleep, no other clinical signs/symptoms or structural lesions. In our case, despite the presence of a click, PT presentation associated with cerebellar syndrome led us to perform MRI that showed diffused and confluent not recent microhemorrhagic lesions involving both brainstem and cerebellar vermis and hemispheres caused by multiple cavernous angiomas and a DVA. The pivotal role of MRI consists also in providing us with the finding of bilateral HOD, a very specific sign of SPT, which further supports the hypothesis of an EPT.

Conclusions: PT can be secondary to several different etiologies involving the dentato-rubro-olivary pathway: it is mandatory for patients with this disorder to undergo MRI in order to exclude consistent lesions.

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## A MACHINE LEARNING APPROACH FOR DETECTING IDIOPATHIC REM SLEEP BEHAVIOUR DISORDER


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Background and Purpose: Growing evidence suggests that Machine Learning (ML) models can assist the diagnosis of neurological disorders. However, little is known about the potential application of ML in diagnosing idiopathic REM sleep behavior disorder (iRBD), a parasomnia characterized by a high risk of phenoconversion to synucleinopathies [1]. This study aimed to develop a novel model using ML algorithms to identify iRBD patients and test its accuracy.

Methods: Data were acquired from 32 participants (20 iRBD patients and 12 controls). All subjects underwent a videopolysomnography. In all subjects, we measured the components of heart rate variability (HRV) during 24 h recordings and calculated night-to-day ratios (cardiac autonomic indices). Discriminating performances of single HRV features were assessed. ML models based on Logistic Regression (LR), Random Forest (RF) and eXtreme Gradient Boosting (XGBoost) were trained on HRV data. The utility of HRV features and ML models for detecting iRBD was evaluated by area under the ROC curve (AUC), sensitivity, specificity and accuracy corresponding to optimal models.

Results: Cardiac autonomic indices had low performances (accuracy 63–69%) in distinguishing iRBD from control subjects. By contrast, the RF model performed the best, with excellent accuracy (94%), sensitivity (95%) and specificity (92%), while XGBoost showed accuracy (91%), specificity (83%) and sensitivity (95%). The mean triangular index during wake (TIw) was the best discriminating feature between iRBD and HC, with 81% accuracy, reaching 84% accuracy when combined with VLF power during sleep using an LR model.

Conclusions: Our findings demonstrate, for the first time, that ML algorithms can accurately identify iRBD patients. Our model could be used in clinical practice to facilitate the early detection of this form of RBD.

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## ENLARGED PERIVASCULAR SPACES AND CEREBRAL SMALL VESSELS DISEASE BURDEN IN PARKINSON'S DISEASE: ASSOCIATIONS WITH NON-MOTOR SYMPTOMS FOCUSING ON SLEEP DISORDERS


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Objectives: This preliminary study aims to investigate associations between enlarged perivascular spaces (EPVS) as part of the cerebral small vessels disease (SVD), and non-motor symptoms (NMS) burden in Parkinson's disease (PD) patients. We hypothesized that EPVS and SVD burden via the glymphatic system can contribute to the NMS burden and we focused our attention on sleep disorders.

Methods and Materials: We retrospectively evaluated 64 PD patients from an Italian cohort of the Non-motor Longitudinal International Study (NILS) database: 17 female and 47 male patients, average age of 67.2 years (29-84 y), mean disease duration 4.75 years (0-23 y), mean Hoehn and Yahr stage 2.05. Patients underwent baseline brain 3.0 Tesla MRI-scan: a visual assessment of baseline basal ganglia (BG), centrum-semiovale (CSO), hippocampus (H), midbrain (M)-EPVS and SVD burden including white matter hyperintensities, cerebral microbleeds and lacunar lesions was rated by an experienced neurologist (C.S.) on axial T2-weighted images. Baseline NMS burden was established using validated NMS total score with Non-Motor Symptoms Scale (NMSS), Parkinson's Disease Sleep Scale (PDSS)

and Hospital Anxiety and Depression Scale (HADS), together with a first-level cognitive battery (Mini Mental State Examination) and Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS III). Data analyses were performed using Spearman's rank coefficient and non-parametric partial correlations.

Results: Baseline BG/CSO/H-EPVS were significantly positively associated with older patients age ($p<0.01$). BG-EPVS burden negatively correlated with the sleep/fatigue NMSS domain (rho=-0.321; p=0.011) whilst controlling for age (r=-0. 412, $p<0.001$); BG-EPVS burden was positively associated with PDSS scale (rho=0.263; p = 0.04) also when age was included as covariate (r=0.329, p=0.01). EPVS burden was not associated with baseline cognitive or motor impairment.

Discussion: It has been observed that EPVS number, a part of SVD burden, increases with age [1] and has been linked to glymphatic system impairment [2]. Glymphatic pathway dysfunction may lead to PVS enlargement suggesting a possible link with protein misfolding diseases. However, it has also been suggested that increased EPVS burden might represent a compensatory mechanism against accumulation of waste products in brain but, as PD progresses, adaptation may become decompensatory: α-synuclein aggregation might obstruct the PVS drainage system, leading to lower MRI-visible EPVS burden [3]. Similarly, our findings showed that increased sleep disfunction appears to be negatively correlated to BG-EPVS burden.

Conclusion: Despite being related with ageing, lower EPVS burden associated with PD-related sleep dysfunction may reflect a decompensated drainage mechanism, potentially due to underlying α-synuclein misfolding and aggregation.

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## AN INFECTIOUS TRIGGER IN A CASE OF PRIMARY FAMILIAL BRAIN CALCIFICATION

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Objective: To describe a case of PFBC with atypical clinical onset.

Materials and Method: The patient underwent neurological clinical examination, CSF analysis, brain CT scan, brain MRI and genetic tests.

Results: A 33-year-old man with no relevant medical history presented at the emergency department with fever, altered mental status and agitation. Neurological examination revealed generalized choreoathetoid movements. A brain CT scan showed bilateral calcification in cerebellum, thalami and basal ganglia. Blood tests showed elevated WBC and CRP. A brain MRI showed a DWI and Gad+ hyper-intense area in the left parieto-occipital cortical region. Glucose levels, proteins and WBC were normal on CSF and microbiological analyses turned out to be negative; no oligoclonal bands were detected. Extensive blood screening for neuronal auto-antibodies was also negative. To rule out an infectious etiology an echocardiography was performed, revealing an aortic valve vegetation which required cardiac surgery. Despite negative cultural exams, a diagnosis of possible endocarditis was made. After the surgical procedure and antibiotic therapy the choreiform movements disappeared. At a nine month follow-up visit, he presented with mild chorea in the lower limbs and mild postural tremor in the upper limbs. Genetic tests for PFBC resulted negative.

Discussion: Primary Familial Brain Calcification (PFBC), also known as Fahr's Disease, is a rare neurological disorder characterized by abnormal calcified brain deposits, particularly in the basal ganglia and cerebellum, which are best detected by a brain CT-scan. It is a genetic condition most commonly inherited as an autosomal dominant trait. A negative genetic test does not rule out PFBC diagnosis as 50% of patients do not present with mutation in any of the six known causative genes. PFBC must be differentiated by secondary forms of brain calcification (i.e. metabolic, infectious, toxic) and from other inherited diseases. The acute onset of chorea with altered mental status in the context of an infectious state pointed to an autoimmune or parainfectious etiology; however, CSF analysis did not reveal alterations. After heart surgery and antibiotics, the movement disorder subsided.

Conclusion: We speculate that clinical onset of the disease was facilitated by the infection acting as a trigger, representing an atypical presentation of PFBC.

Reference:

– Carecchio M., Mainardi M., Bonato G. The clinical and genetic spectrum of primary familial brain calcification. Journal of Neurology (2023);270:3270-77

## NEURAL CORRELATES OF MOTOR IMAGERY VERSUS ACTION OBSERVATION OF GAIT TASKS IN PATIENTS WITH PARKINSON'S DISEASE AND FREEZING OF GAIT: A FMRI STUDY

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Objectives: We previously demonstrated that patients with Parkinson's disease (PD) and freezing of gait (PD-FoG) showed an altered recruitment of the mirror neuron system (MNS) during action observation and motor imagery relative to healthy controls. The aim of this study was to compare the neural correlates of motor imagery and action observation of gait tasks in PD-FoG patients relative to healthy controls.

Materials: Twenty-four PD-FoG patients and 19 age- and sex-matched healthy controls were included.

Methods: All the subjects underwent brain magnetic resonance imaging (MRI) including a motor imagery/action observation task: during motor imagery, subjects were asked to imagine themselves performing three gait tasks exacerbating FoG (starting/stopping walking in a narrow hallway; turning around 360° in a small radius; going through a doorway) while navigating first-person videos of realistic environments. Participants were instructed to focus their attention on their body and to imagine moving the body parts involved in the task. During the action observation, subjects were asked to observe third-person

videos representing a person performing the same three actions, in the same environments, presented during the motor imagery period.

Results: During motor imagery relative to action observation, both PD-FoG patients and healthy controls showed higher activity of lingual gyrus and cerebellum lobule VI. Healthy controls also showed increased recruitment of fusiform and middle occipital gyri, while PD-FoG patients showed a higher activity in the calcarine sulcus. Healthy controls also had an increased activity of middle/superior frontal and middle occipital gyri, precuneus and caudate during action observation relative to motor imagery. PD-FoG patients relative to healthy controls showed a reduced activity of lingual gyrus and a higher recruitment of insula during motor imagery relative to action observation.

Discussion: Both healthy controls and PD-FoG subjects showed an activation of areas belonging to the MNS during both motor imagery and action observation. Motor imagery relative to action observation required higher recruitment of lingual gyrus that is involved in visual memory and motion perception, and of cerebellum VI that is implicated in body representation, motor processing and attentive-executive functions. Only in healthy subjects, action observation compared to motor imagery activated more the fronto-parietal MNS that plays a role in action understanding and imitation learning of complex actions.

Conclusions: Motor imagery and action observation might represent complementary approaches in PD-FoG patients to stimulate the activity of sensorimotor and MNS brain areas in a specific way.

## GAA-FGF14 ATAXIA (SCA27B): CLINICAL PHENOTYPE OF AN ITALIAN MULTICENTER COHORT

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Objective: Autosomal dominant spinocerebellar ataxia due to intronic GAA repeat expansion (RE) in the FGF14 gene (GAA-FGF14 ataxia; SCA27B) is a recently identified, relatively common, potentially treatable form of late onset ataxia. Here, we aimed to characterize the clinical phenotype in Italian GAA-FGF14 patients collected in a multicenter study.

Materials: We analyzed the clinical, genetic and neuroradiological features of 25 index cases carrying a heterozygous GAA-FGF14 RE. We also focused on 4-aminopyridine (4-AP) treatment response. Methods: Longitudinal clinical records were systematically assessed according to a comprehensive eCRF data form. We assessed disease severity and progression by using the Scale for the Assessment and Rating of Ataxia (SARA), the Friedreich Ataxia Rating Scale functional disability stage (FARS-DS) and functional impairment in terms of mobility aids. Finally, we analyzed longitudinal SARA scores by linear regression over disease duration.

Results: Twenty-four out of 25 GAA-FGF14 patients consistently presented as late-onset (57.5 years ± 14.4) cerebellar syndrome, partly combined with afferent sensory deficits (30%). A single case, age 17 years, was asymptomatic at the time of our study, though his examination was significant for mild intellectual disability and slight pyramidal signs in lower limbs. All symptomatic individuals showed evidence of impaired balance and gait; cerebellar oculomotor signs (saccadic intrusion, nystagmus, slowing saccades) were also frequent (78%). Episodic manifestations at onset occurred in 39% of patients; episodes were characterized mostly by dysarthria (44%) and vertigo (55%). Dysautonomia and cognitive impairment were infrequent. Peripheral neuropathy was reported in 26% of patients. Brain magnetic resonance imaging showed cerebellar atrophy in most cases (18/21). Longitudinal assessments indicated slow progression of ataxia (0.33 SARA points/year) and minimal functional impairment (11 patients are still fully ambulant after 8 years of disease duration). We found no correlation between RE, age at onset, longitudinal SARA scores or disease duration. Series of N-of-1 trials with 4-AP are ongoing.

Discussion: Consistent with previous reports, Italian GAA-FGF14 patients present an adult-onset, slowly progressive cerebellar ataxia with predominant impairment of balance and gait and frequent cerebellar oculomotor signs.

Conclusion: Combined with multisite international efforts, our study paves the way towards large-scale natural history studies in this newly discovered late-onset ataxia.

Reference:

– Pellerin D, Danzi MC, Wilke C, Renaud M, et al. Deep Intronic FGF14 GAA Repeat Expansion in Late-Onset Cerebellar Ataxia. N Engl J Med. (2023);388(2):128-41

## SUBSTANCE P IS OVEREXPRESSED IN OLFACTORY NEURONS FROM PARKINSON DISEASE PATIENTS REFLECTING GASTROINTESTINAL DYSFUNCTION

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Objective: To clarify the role of Substance P (SP) in Parkinson disease (PD) using a molecular characterization of patients' olfactory neurons (ONs).

Materials: ONs were withdrawn from 30 PD patients and 20 sex/age-matched healthy controls through mucosa brushing.

Methods: Gene expression levels of SP and the NK1 receptor were comparatively assessed by the Real Time-PCR. The immunofluorescence staining was also performed to measure SP. In patients, the biochemical data were correlated with main clinical scores (MDS-UPDRS III, MoCA, NMSS, LEDD calculation), the Gastrointestinal Dysfunction Scale for PD (GIDS-PD), and the presence of constipation.

Results: SP mRNA expression was significantly higher in PD patients' ONs (PD: 5.1±7.4 fold increase vs controls:1.6±1.6; U=139, p=0.04). In PD, the SP mRNA levels directly correlated with GIDS-PD total score (R Spearman = 0.47, p=0.02) and was significantly higher in patients with constipation than those without (7.9±9.3 vs 1.9±1.6; U=44, p<0.05). NK1 receptor mRNA levels, instead, were similar between patients and controls. Also the SP protein levels were increased in the ONs of PD patients compared to controls, as demonstrated by immunofluorescence staining.

Discussion: SP and its cognate receptor NK1R are expressed in the CNS, the PNS, the enteric nervous system, and the immune cells, operating as neuroinflammatory mediators. In particular, SP expression is abundant in the gastrointestinal-nervous ascending pathway in response to various triggers. Preclinical evidence indicates that SP might be involved in PD pathogenesis through inflammatory mechanisms. However, no direct proof exists yet. ONs are now emerging as a reliable model to analyse molecular events underlying PD in vivo. Here, we thus used the ONs to explore the role and relevance of the SP/NK1R pathway in PD.

Conclusions: ONs SP overexpression in association with gastrointestinal dysfunction suggests a main role of the tachykinergic system within the clinical-pathological dynamics of PD. SP might represent a mediator of the "body-first" trajectory, serving either as a specific biomarker or a novel therapeutic target.

Reference:

– Schirinzi T et al. Olfactory Neuron Prokineticin-2 as a Potential Target in Parkinson's Disease. Annals of Neurology (2023);93(1):196-204

## REMOTE PHYSICAL ACTIVITY IN PATIENTS WITH PARKINSON DISEASE DURING SARS-COV-2 PANDEMIC: EXPERIENCE OF AN ITALIAN CENTER

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Background: The Sars-Cov-2 pandemic decreased people's participation in many social activities. This consequence has been deleterious for patients with chronic disease, such as Parkinson's disease (PD), who often discontinued follow-up visits and neuromotor treatments. Therefore, during the Sars-Cov-2 pandemic, the interest in telemedicine and remote patient monitoring increased. Different experiences of physical exercise via digital platforms on small numbers of patients with neurological disorders has been reported (1).

Aims: To asses efficacy of remote physical activity on some motor and not motor parameters of patients with PD.

Methods: Remote physical activity was proposed to patients during visits at our hospital. At baseline (T0), and at the end of the intervention (T1), after 11 weeks in a period between December 2021 and February 2022, patients were evaluated via UPDRS I, UPDRS II, UPDRS III for motor and non motor evaluation of PD; Beck depression inventory (BDI) to investigate depression; Epworth sleepiness scale (ESS) to assess the probability of falling asleep; King's Parkinson's disease Pain Scale (KPPS) to assess pain; abnormal involuntary movement scale (AIMS) to detect dyskinesia, Parkinson's Disease Fatigue Scale (PFS-16) to explore fatigue perception; and Non-Motor Symptoms Scale for Parkinson's Disease (NMSS) for non-motor symptoms.

Results: 13 participants underwent physical exercise three times a week. Each meeting lasted 90 minutes. Only one patient has dropped-out. The evaluations before and after physical exercise showed an improvement in fatigue perceptions as evaluated by PFS-16 (mean and SD, 6.7 ± 5.2 vs 5.4 ± 4.4, p= 0.004), and a reduction in depression score as evaluated by BDI (mean and SD, 10.7 ± 9.01 vs 8.2 ± 6.7, p= 0.065), although statistical significance was not reached in the latter case. Other evaluations showed no significant results. No adverse effects occurred during physical activity.

Discussion and Conclusions: Our experience demonstrated that remote exercise can be safe and effective in improve fatigue of patients with PD and could be used in case of physical impediment to the attendance of rehabilitation programs in site.

Reference:

– Brown EG, Chahine LM, Goldman SM, Korell M, Mann E, Kinel DR, Arnedo V, Marek KL, Tanner CM. The Effect of the COVID-19 Pandemic on People with Parkinson's Disease. J Parkinsons Dis (2020)

## ANODAL TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) ON SENSORIMOTOR CORTEX IN PATIENTS WITH EARLY-ONSET PARKINSON'S DISEASE: A PILOT STUDY

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Objective: To evaluate the clinical effects of anodal Transcranial Direct Current Stimulation (tDCS) application on sensorimotor cortex in a group of early-onset Parkinson's Disease (EOPD) patients.

Materials and Methods: We recruited 11 idiopathic EOPD patients. tDCS was administered by a transcranial direct current stimulator (Model BrainSTIM, EMS) with the anode placed over the left sensorimotor cortical area (C3) and the cathode over the contralateral supraorbital ridge (Fp2). The protocol consisted of 10 sessions of stimulation of 20 minutes each, administered in two weeks, with a current intensity of 2mA. Participants were assessed at baseline and at the end of the stimulation cycle with MDS-Unified Parkinson's Disease Ranking Scale (MDS-UPDRS) part III, Non-motor symptoms scale (NMSS), PD-cognitive rating scale (PD-CRS), and PD Quality of Life Questionnaire-39 (PDQ-39). Paired T-test was used to compare changes in clinical scores.

Results: At the end of the protocol significant score reduction resulted in NMSS (M 32,36± DS 29,07 vs 17,45±20,92, p=0.001); score improvement was also found in PD-CRS (M 100,82±13,95 vs 106,55±13,97, p=0. 040). Total UPDRSIII score did not change pre and post treatment. However, by grouping the items of the scale into rigidity, bradykinesia and tremor subscores, a significant amelioration of the rigidity subscore emerged (M 0,67±0,78 vs 0,42±0,70, p=0.05). PDQ-39 score was unmodified. No relevant side effects were recorded.

Discussion: Early-onset PD (EOPD) labels PD patients with an age at onset < 50 years. EOPD seems to have a slower progression and lesser number of comorbidities when compared to the late-onset PD (LOPD). However, EOPD affects people in the full of the employment and fertility, with a severe impact on the quality of life. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation

technique used for therapeutic modulation of cortical excitability in various neurological diseases [1], including Parkinson's Disease (PD) [2]. To date, tDCS has never been specifically applied to EOPD patients. This pilot study showed that a 10 session-long protocol of anodal sensorimotor tDCS might exert beneficial clinical effects in EOPD patients in non-motor symptoms and cognitive performances, consistently with a direct effect of the stimulation on cortical cognitive network. Motor symptoms did not significantly improve, albeit some amelioration was noticed in rigidity. Further confirmation in larger samples and with sham-controlled subjects is now needed.

Conclusions: Anodal tDCS on sensorimotor cortex emerges as a promising therapeutic option for non-motor symptoms in EOPD patients.

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## CREATION AND PRELIMINARY VALIDATION OF THE ITALIAN VERSION OF THE DBS IMPAIRMENT SCALE

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Objectives: The present study aim was to create and provide a preliminary validation of the Italian version of the Deep Brain Stimulation-Impairment Scale (DBS-IS) [1] and to investigate its relationships with functional status and quality of life (QoL) in Parkinson's disease (PD) patients who underwent subthalamic nucleus deep brain stimulation (STN-DBS) [2].

Materials: Thirteen patients (6 males, 7 females) with PD were included in the study. The participants had a mean age of 69 ± 5.4 years and an average disease duration of 20 ± 5.1 years. Various assessment tools were utilized, including the Hoehn and Yahr (H&Y) scale, Unified Parkinson's Disease Rating Scale (UPDRS), Apathy Evaluation Scale (AES), Beck Depression Inventory-II (BDI-II), Self-Report Manic Inventory (SRMI), Parkinson's Disease Questionnaire (PDQ-39), and the Italian version of the DBS-IS (DBS-IS-IV). Statistical analyses were conducted using R Studio.

Methods: The Italian version of the DBS-IS scale was translated [3] and preliminarily validated. The participants completed the assessment scales, which were administered either directly or to their caregivers, ensuring confidentiality. The Mann-Whitney U Test was employed to compare scores between subgroups, and Pearson correlation coefficients were calculated to examine relationships between variables.

Results: The participants had moderate PD severity (mean H&Y score of 2.9) and a mean UPDRS score of 33.3. Apathy was observed in 62% of the patients, while 31% exhibited symptoms of depression. No clinically significant scores for mania or psychotic symptoms were detected. The PDQ-39 and DBS-IS-IV scales demonstrated a significant correlation, indicating the validity of the DBS-IS-IV scale. Correlations were also observed between different variables, such as DBS-IS x PDQ-39, Age x UPDRS, H&Y x UPDRS, H&Y x SRMI, and AES x PDQ-39.

Discussion: Although the study was conducted on a limited number of patients, the results support a preliminary validation of the DBS-IS-IV scale as a measurement tool for assessing various aspects related to DBS treatment. Apathy, postural instability and gait difficulties (PIGD), and language disorders were commonly reported symptoms. The absence of statistically significant differences in subgroups suggests that age, sex, and disease duration may not strongly influence functional impairment in this context.

Conclusion: The Italian version of the DBS-IS scale was successfully translated and a preliminary validation was provided. Further studies with larger sample sizes are warranted to complete the validation process and enhance the robustness of the scale.

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## THE USE OF AN INSTAGRAM FILTER FOR POSTURAL TREMOR ASSESSMENT

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Objective: The aim of this study is to evaluate an Instagram filter as a complementary tool for postural tremor assessment.

Materials: We recruited 34 patients with the most common tremor syndromes: Essential Tremor, Essential Tremor plus and Dystonic Tremor according to the new classification of tremor1.

Methods: We asked patients to take a video of a printed Archimedes' spiral using an Instagram filter (i.e., Slit-scan), which overlaps the single video frames into one picture. The photographed spirals (p-spirals) were then scored by a blinded rater using the identical system used to score the classic Archimedes' spirals drawn by the patients themselves (d-spirals) according to the TETRAS. The Spearman test was used to correlate p-spiral scores with d-spiral scores, with a measure of postural severity for single arm calculated as the mean of the items assessing arm tremor in the outstretched, wing-beating positions and dot approximation, with a measure of kinetic severity for single arm calculated as the mean of the items assessing arm tremor with Archimedes' spiral, index-index proof and glasses proof and finally with the mean score of p-spirals and total TETRAS score.

Results: The Spearman test disclosed a significant correlation between p-spirals and d-spirals scores ($\rho$=0.316, $p<0.009$), between p-spirals scores and the mean of the items assessing postural tremor ($\rho$=0.306, $p<0.011$) and between the mean score of p-spirals and total TETRAS severity ($\rho$=0.441, $p<0.009$). While severity of kinetic tremor did not correlate with p-spirals scores.

Discussion: The assessment of tremor is currently performed by means of validated scales which require patients to be evaluated in person, but there is the need for remote tremor telemonitoring, so the use of slit-scan could represent a useful tool for measuring postural tremor in addition the classic Archimedes' spirals drawing.

Conclusions: The use of this filter might be useful in distinguishing the various components of action tremor and their response to therapeutic treatment. Larger studies are needed to validate this Instagram filter as a tool to be used in clinical practice.

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## STEPWISE FUNCTIONAL BRAIN ARCHITECTURE FROM DISEASE EPICENTER CORRELATES WITH ATROPHY IN PROGRESSIVE SUPRANUCLEAR PALSY

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Objectives: MRI connectomics is an ideal tool to test the model of network-based spread of pathological protein aggregates in neurodegenerative disorders. Stepwise functional connectivity (SFC) is a graph-theory-based neuroimaging method, which detects whole-brain functional couplings of a selected region of interest, at increasing link-step topological distances. This study applied SFC to test the hypothesis that topological stepwise architecture propagating from the disease epicenter would shape patterns of grey matter (GM) atrophy in a cohort of patients with progressive supranuclear palsy (PSP).

Materials: Thirty-nine patients with PSP and 44 healthy controls underwent brain magnetic resonance imaging (MRI) on a 3T scanner, including 3D-T1 weighted and resting-state functional MRI sequences. Methods: The disease epicenter was defined as the peak of atrophy observed in an independent cohort of 13 cases with post mortem confirmation of PSP pathology, and used as seed region for an SFC analysis. GM was parcellated into 90 regions using the Automated Anatomical Labeling (AAL) atlas. First, SFC modifications in PSP patients were assessed. Then, correlations between SFC architecture in controls and atrophy patterns in PSP patients were tested.

Results: The disease epicenter was identified in the left midbrain tegmental region. In PSP patients, a pattern of mostly increased functional connectivity of the midbrain within direct connections was mirrored by a progressively widespread decreased connectivity through indirect connections with sensorimotor cortical regions. Compared with controls, PSP patients showed prevalent atrophy in the subcortical GM (mostly, in the thalami and caudate nuclei), but also in frontal, parietal and cerebellar cortical regions. For each region of the AAL atlas, a correlation was found between average link-step distance from the left midbrain in controls and mean normalized GM volume in PSP patients ($r=0.38$, $p<0.001$).

Discussion: We demonstrate that the brain architectural topology, as described by SFC propagating from the disease epicenter, shapes the pattern of atrophic changes in PSP. The present findings support the view of a network-based pathology propagation in this primary tauopathy.

Conclusions: The results of this study open fundamental insights supporting the notion of PSP and other neurodegenerative diseases as "disconnection syndromes", providing promising perspectives to understand the physiopathological underpinnings and to model disease evolution in future longitudinal studies.

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## HYPOTENSIVE EPISODES AT AMBULATORY BLOOD PRESSURE MONITORING PREDICT DISABILITY MILESTONES IN PARKINSON'S DISEASE: A LONG-TERM RETROSPECTIVE STUDY

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Objectives: Neurogenic orthostatic hypotension (nOH) is a frequent non-motor feature of Parkinson's disease (PD), associated with severe complications and shorter survival. [1,2] Due to the important circadian variability of blood pressure (BP) in PD, bedside evaluation could misestimate the actual prevalence of nOH. Recently, 24-hour ambulatory BP monitoring (ABPM) has been proposed as a useful tool to detect nOH [3]; in particular, the presence of at least 2 episodes of systolic BP drop $\geq$15 mmHg demonstrated a high level of accuracy. This study aims at evaluating the prognostic role of ABPM-hypotensive episodes in predicting PD disability milestones and mortality and comparing it to the prognostic role of bedside nOH on the same outcomes.

Materials and Methods: PD patients who underwent ABPM from January 2012 to December 2014 were retrospectively enrolled and assessed for age, disease duration, motor disability (H&Y stage), and Charlson Comorbidity Index (CCI) at baseline, and for the development of the following complications, during an up-to-10-year follow-up: falls, fractures, dementia, bed/wheelchair confinement, hospitalization, mortality. Unadjusted Kaplan-Meyer analysis and Cox regression analysis (corrected for age, disease duration, CCI, and H&Y stage at baseline) evaluated the association between ABPM-hypotensive episodes or bedside nOH and disability milestones/mortality.

Results: Ninety-nine patients (men: 73.7%; age: 64.2±10.1 years; PD duration: 6.4±4.2 years) satisfied inclusion criteria. The mean follow-up was 5.9±2.7 years (range 1-10). At baseline, 38.4% of patients had at least two ABPM-hypotensive episodes, while 46.4% had nOH at bedside evaluation. The Kaplan-Meier analysis showed that patients with ABPM-hypotensive episodes had an earlier onset of falls (4.9 vs. 7.9 years; $p<0.001$), fractures (6.4 vs. 9.0 years; $p=0.004$), hospitalizations (5.3 vs. 8.2 years; $p=0.009$), bed/wheelchair confinement (7.1 vs. 9.4 years; $p=0.032$), and dementia (5.0 vs. 8.1 years; $p<0.001$). The mortality rate was 13.1%, and patients with hypotensive episodes showed a shorter survival (8.0 vs. 9.5 years; $p=0.009$); however, adjusted Cox regression analysis did not confirm a significant association ($p=0.655$). Cox-Regression analysis showed significant association between ABPM-hypotensive episodes and falls (OR:3.626; $p<0.001$), hospitalizations (OR:2.016; $p=0.038$), and dementia (OR:2.926; $p=0.008$), while bedside nOH was only associated with dementia (OR:2.100; $p=0.025$).

Discussion and Conclusion: ABPM represent a widely available and reliable assessment. The presence of at least two ABPM-hypotensive episodes independently predicted the development of falls, dementia

and hospitalization, showing a stronger prognostic value than the simple bedside assessment. Although larger and prospective confirmatory studies are needed, our observations support the usefulness of ABPM in PD clinical practice.

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## SALIVARY EXTRACELLULAR VESICLE A-SYNUCLEIN AS A NOVEL POTENTIAL BIOMARKER OF PARKINSON'S DISEASE ONSET AND PROGRESSION

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Objective: Extracellular vesicles (EVs) are small vesicles released by many cells, including neurons and can be isolated from body fluids, like saliva[1]. α-Synuclein (α-syn) has recently been detected in EVs and may contribute to the spreading of disease pathology in α-synuclein-related neurodegeneration[2]. The detection of α-syn in salivary EVs may contribute to find potential biomarker for Parkinson disease (PD) onset and progression. So, the main objectives of this work are: 1) to establish the methodology to isolate EVs from saliva; 2) to examine both oligomeric (α-synOlig) and total α-Syn (α-synTotal) contained in the EVs to validate their potential diagnostic and 3) to evaluate their possible role as progression biomarkers in PD.

Materials and Methods: Saliva samples were obtained from 48 PD patients (PDs) and 31 healthy controls (HCs). The EVs were isolated by differential ultracentrifugation[3]; western blot (WB) and Nanosight (NTA) were used to validate the protocol and to analyze EVs size and concentration. The transmission electron microscopy (TEM) was used to assess EVs morphology4. The concentration of α-synTotal, α-synOlig was determined by ELISA technique. Diagnostic value and clinical relevance of salivary EVs α-syn were assessed by Receiver Operator Characteristic (ROC) curve and Pearson correlation6. We are now recalling patients, after one year from the first collection, to evaluate if the two forms of α-Syn should be considered as progression biomarkers for PD.

Results: We first characterized the EVs by WB and TEM, the NTA showed that the concentration of EVs is higher in HCs than PDs, while the dimensions do not change. The ELISA test revealed that the level of both α-synTotal and α-synOlig are higher in PDs compared to the HCs (α-synTotal: sensitivity = 66%, specificity = 76%; α-synOlig sensitivity = 83%, specificity = 60%). We found correlations of α-synOlig with the duration of the disease and the mini mental state examination (MMSE).

Conclusions: These findings support the role of salivary EVs cargoes as a promising biomarker for PD and purpose to further investigate the possible correlation of α-Syn with disease severity, which could reveal α-Syn as a predictor of PD progression.

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## CLINICAL AND AUTONOMIC PROFILE OF MULTIPLE SYSTEM ATROPHY WITH POSTGANGLIONIC CARDIOVASCULAR DYSFUNCTION

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Introduction: Cardiovascular autonomic dysfunction in Multiple System Atrophy (MSA) clinically manifests with orthostatic hypotension and in most of patients is related to preganglionic abnormalities. In fact, cardiac imaging using iodine-123-metaiodobenzylguanidine(123I-MIBG), which examines the sympathetic innervation of the heart and thereby enables the quantification of the postganglionic cardiac sympathetic innervation, is typically normal in MSA [1][2]. However, reduced cardiac tracer uptake has been reported in one third of patients with MSA. Whether cardiac postganglionic denervation in MSA is associated to a different and/or more severe clinical phenotype is still unclear.
Objectives: To compare clinical and cardiovascular autonomic tests findings of patients affected by MSA with normal (N) and reduced (R) cardiac postganglionic sympathetic innervation.

Materials and Methods: Clinical records, plasma cathecolamine dosages and cardiovascular autonomic tests findings of patients affected by MSA, who underwent cardiac 123I-MIBG scintigraphy, referring to our clinic from 2018 to 2023, were retrospectively revised.

Results: Data from 60 patients diagnosed with clinically established or probable MSA according to the Movement Disorders Society 2022 diagnostic criteria [3], 46 with normal and 14 with reduced sympathetic innervation on cardiac 123I-MIBG scintigraphy were collected. Mean age of disease onset (57.4-N vs 59.1-R), disease duration (3.6vs4 yrs), Levodopa Equivalent Daily Dose (527.1vs513.5), Unified MSA Rating Scale scores in part I (18.5vs19.4) and part II (20.7vs22.6) showed no significative difference. Parkinsonian and cerebellar phenotypes were equally represented in both groups. Self-rated composite autonomic system scale total score (35.3vs33) and subscores, were similar. Patients with reduced cardiac innervation had lower supine noradrenaline plasmatic concentration, while no difference was found in the orthostatic condition. Moreover, such patients had significantly lower blood systolic (-23vs-7 mmHg) and diastolic (-11vs-2) pressure values reduction around the 7th minute of tilt test. No difference was found in the incidence of orthostatic hypotension within 3 minutes of standing, as well as in other indexes of sympathetic dysfunction on autonomic testing, such as mean blood pressure (BP) fall in early phase II, mean BP rise in late phase II, pressure recovery time and presence of BP overshoot during Valsalva maneuver. We also analysed cardiac vagal indexes, which were similar in both groups.

Discussions and Conclusions: Patients with MSA and postganglionic cardiovascular dysfunction show similar clinical features and

disease severity scales scores compared to those with preganglionic, while they had lower supine plasma noradrenaline levels. Cardiovascular autonomic testing showed similar results in both groups, except for a more marked tardive BP decrease on tilt test in postganglonic patients.

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## QUANTITATIVE EEG IN PD-RBD: WHEN RBD ONSET REALLY MATTERS

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Introduction and Aim: Intraneuronal a-synuclein aggregates are the pathologic hallmark of Parkinson's disease (PD). According to a recently proposed hypothesis, alpha-synuclein pathology may originate and spread in two different directions: either downward from the brain to the enteric or peripheral autonomic nervous system or upward in the opposite direction. The temporal relationship between RBD and motor symptoms onset has been considered as the key factor in differentiating these two subtypes. The aim of this study was to investigate electrocortical differences between patients with PD and different RBD onset timing.

Methods: PD patients were retrospectively selected and according to the presence of probable RBD, were divided into: N = 38 patients without RBD (NRBD), N = 14 patients with RBD onset before motor symptoms onset (PRERBD) and N = 31 patients with RBD onset after motor symptoms onset (POSTRBD). Spectral analysis was performed in resting state EEG and the absolute power spectral density was calculated for the common frequency bands. Kruskal-Wallis H test was used to assess between-group differences.

Results: Comparing global PSD absolute values, significantly lower beta band values were obtained in patients with RBD onset before motor symptoms (60,25 ± 30,52) as compared to both NRBD (116,13 ± 90,39; p = 0.02) and POSTRBD (112,79 ± 101,57; p = 0,06). Site specific lower beta values were also found PRERBD in frontal, temporal, and parietal regions. The post-hoc comparison showed highest differences between NRBD and PRERBD patients. On the contrary, no differences were found between NRBD and POSTRBD patients. In addition, no significant differences were obtained comparing delta, theta and alpha absolute powers across all the investigated sites.

Discussion: PRERBD patients have lower fast-frequencies representation in resting-state EEG and they show different electrocortical features as compared to both patients with later RBD onset and without RBD.

Conclusion: RBD onset as compared to motor symptoms is a crucial determinant in PD: PRERBD represent a different subgroup of patients with unique quantitative EEG features.

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## UNSUPERVISED MACHINE LEARNING STRATEGY AND SHAPLEY ADDITIVE EXPLANATION TO DISTINGUISH GAIT ABNORMALITIES THROUGH IMU-BASED GAIT ANALYSIS IN SUBJECTS WITH MOVEMENT DISORDERS

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Objectives: When paired with gait analysis using magneto-inertial measurement units (mIMUs), automated classification of gait disorders using Machine Learning algorithms can enable fast and clinically significant assessment of gait abnormalities in persons with gait disorders [1]. Unsupervised methods can be used to classify gait patterns of people suffering from various neurological illnesses [2-3]. In this study, the ability of clustering algorithms to detect differences in gait patterns between subjects with movement disorders and healthy subjects (HS) using mIMUs-derived gait data was investigated.

Materials: In this study, 59 subjects with Parkinson's disease (swPD) at moderate disease stage, 39 subjects with hereditary cerebellar ataxia (swCA), and 35 age and gait speed-matched HS were included. Spatiotemporal and kinematic gait parameters, and trunk acceleration-derived gait indexes were calculated using a mIMU.

Methods: Unsupervised machine learning methods such as partitioned clustering (K-Means), hierarchical clustering, and density clustering (DBSCAN) were implemented to observe their ability to distinguish subjects based on diagnosis on the initial dataset and on a second dimensionality-reduced dataset obtained through feature extraction. Finally, supervised statistical analysis and Shapley Additive Explanations (SHAP) analysis were performed to identify the most impactful set of features for differentiating between movement disorders and healthy subjects.

Results: Partitioned clustering performed better than the other algorithms in differentiating movement disorders in both internal cluster metrics and external metrics. Feature extraction by Principal Component Analysis (PCA) improved internal cluster metrics making them more recognizable and homogeneous while slightly worsening external metrics. On the K-Means cluster with the best external metric results (Accuracy = 0.91, F1-Score = 0.91), SHAP analysis revealed how several gait features mostly weighted for differentiating subjects with movement disorders from each other and from healthy subjects.

Discussions: ML algorithms may generate excellent classification metrics when considering gait data from single lumbar-mounted IMUs in CA and PD populations at moderate disease stage. To improve classification performances and obtain reliable results, initial data exploration and pre-processing is mandatory, particularly to avoid multicollinearity and overfitting.

Conclusions: The results of this study demonstrated that, when considering gait data from single IMUs mounted at the lumbar level in moderate disease-stage pwCA and pwPD populations, the unsupervised K-Means and hierarchical clustering algorithms can generate excellent insights and classification metrics, and that pelvic rotation plays a key role in differentiating extrapyramidal and cerebellar gait disorders.

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## A CASE OF HEMICHOREA ASSOCIATED WITH NON KETOTIC HYPERGLYCAEMIA: A NEW MAGNETIC RESONANCE SPECTROSCOPY (MRS) FINDING AND POSSIBLE FUTURE IMPLICATIONS

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Background: Diabetic Striatopathy (DS) is a rare complication of a poor-controlled Diabetes Mellitus consisting of sudden onset of movement disorders. To date, there is still poor knowledge about the pathogenesis.

Case: We describe a 79 y.o men affected by sudden onset hemichoreic movements whose cause was a nonketotic hyperglycaemia diagnosed despite the normal blood glucose levels thanks to brain CT and MRI. Then, we introduce a new MR-spectroscopy (MRS) finding never described until today which allowed us to produce a new pathogenetic theory of a phenomenon still without definitive explanations.

Conclusions: Thanks to our MRS we show new imaging findings never described until today, with a new pathogenetic explanation, since all the causative hypotheses produced during the past years have never found evidence.

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## OROMANDIBULAR DYSTONIA: CLINICAL PHENOMENOLOGY AND NATURAL HISTORY

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Introduction: Oromandibular dystonia (OMD) is a cranial dystonia affecting the lower face. It can be isolated, or combined if other sites are affected. To date, association between OMD and other kinds of dystonia has been poorly investigated.

Objectives: To define the clinical and demographic features of the Italian population affected by OMD and to search for possible variables which could predict its spread to other body regions.

Methods: Data were obtained from the Italian Dystonia Registry (IDR), a multicenter Italian dataset of patients with adult-onset dystonia. We extracted and analysed the main features of those patients who presented an OM dystonia.

Results: Study population included 313 patients with OMD. Most of them presented a primary dystonia – mainly idiopathic - while among the secondary forms, the majority had a drug-induced one. 53 patients (17%) presented an OMD onset; 109 (34.8%) a combined onset (OM plus another site); 151 (48.2%) manifested the onset of dystonia in a non-OM site. Spread occurred with a significant lower prevalence in the following groups: patients with combined onset when taken from the entire sample (P=0.001) and when analysing just the idiopathic forms (P=0.001), and in patients with acquired dystonia (P=0.04). Those populations presented also a significantly llow prevalence of sensory trick. Patients presenting sensory trick, regardless of the site of onset, presented a significantly higher rate of spread. Finally, spread of dystonia in those patients with idiopathic syndrome and OM onset resulted to occur within 10 years from the onset (mainly in 4 years).

Discussion and Conclusion: Data from IRD show that OMD is prevalently idiopathic and associated with dystonia in other sites. When the onset is combined and in acquired dystonia, the spread of dystonia in other body regions has a very low prevalence whereas sensory trick seems to increase the rate of spread in overall OMD patients. Results of the study confirm evidence of previous research and point out the possibility of pathogenetic mechanisms of dystonia depending on the increase of neurons' activation threshold and the cortical neural plasticity.

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## NETWORK-BASED ANALYSIS OF MOVEMENT PATTERNS: ENHANCING MOTOR EVALUATION IN PARKINSON'S DISEASE

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Aims: Motor assessment of Parkinson's disease is highly valuable in evaluating the severity of the disease and its progression over time [1]. Typically, quantitative outcomes such as step length, stance time, etc., are considered. However, these measures do not capture higher-level functions such as coordination and fail to account for the fact that movement arises from the finely regulated synergy of different body parts. Therefore, we applied network theory [2] to human movement to capture these aspects and assess the coordination characteristics of patients with Parkinson's disease (PD).

Materials: We recruited twenty-three PD patients (in OFF condition) and twenty-three healthy age, education and gender matched subjects (HS). Using a stereophotogrammetric system, we conducted 3D gait analysis to capture the three-dimensional position of 21 anatomical markers.

Methods: From this data, we calculated acceleration time series and, by applying Pearson's correlation, we obtained a movement connectivity matrix, referred to as the kinectome. Each kinectome presented body landmarks on the rows and the columns, while the elements in the matrix represented the level of coordination between each couple of body landmarks. Then, through a permutation test, we analyzed the characteristics of each kinectome to perform topological analysis.

Results: Topological analysis revealed that individuals with PD displayed higher values of nodal strength at the level of the 10th thoracic vertebra. Furthermore, the nodal strength was significantly correlated with the UPDRS motor score of the patients and was able to predict the test through a cross-validated multilinear regression model.

Discussion: Our results might be capturing the trunk rigidity typical of PD, causing hyper-synchronization of the movement between the trunk and the limbs [3]. Moreover, the prediction based on the multilinear model highlighted that such a hyper-synchronization shown that the topological characteristics of movement network were related to the subject-specific clinical condition.

Conclusions: The application of network theory to human movement presents a novel technique for studying motor function both in health and disease such as in PD. This approach has the potential to provide valuable insights for rehabilitation protocols and therapeutic follow-up.

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## ATYPICAL SONOGRAPHIC FINDINGS IN A YOUNG MAN WITH PARKINSONISM IN MACHADO-JOSEPH DISEASE

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Introduction: Machado-Joseph disease (MJD), also known as spinocerebellar ataxia type 3 (SCA3), is an autosomal dominantly inherited cerebellar ataxia caused by CAG trinucleotide repeat expansions in the coding regions of ATXN3 gene [1]. Few studies have performed transcranial sonography (TSC) in SCA 3 patients and found hyperechogenicity of Substantia Nigra (SN) associated with a larger width of third ventricle and lenticular nucleus hyperechogenicity compared to healthy controls [2]. The disease is characterized by phenotype variability and several subtypes have been defined that could be related to the atypical echofeatures found in our young patient.

Objective: Case report.

Methods: We studied the case of a 27 years old African man with a 3-years history of gradually progressive slowness of movements and balance difficulty, with referred negative family history for neurological diseases. He underwent full neurological examination and genetic analysis on peripheral blood sample using PCR and capillary electrophoresis.

Results: Neurological examination revealed marked bradykinesia (mainly on the left) and gait ataxia, moderate gaze-evoked horizontal nystagmus and generalized hyperreflexia, without tremor, hypertonia or rigidity. Poor response to L-dopa therapy. Brain MRI showed cerebellar vermian atrophy with ventricular enlargement. 123I-FP-CIT SPECT (DaTscan) revealed a moderate bilateral reduction of dopamine presynaptic transporter levels. TCS showed third ventricular enlargement and right lenticular nucleus hyperechogenicity. There was no evidence of SN hyperechogenicity. Genetic analysis demonstrated pathogenetic CAG repeat expansion (67 repeats) in the coding region of ATXN3 gene.

Conclusion: In agreement with previous studies, MJD should be considered in the differential diagnosis of PD-like symptoms. The enlargement of third ventricle but the absence of SN hyperechogenicity found in our patient may suggest the presence of different pathophysiologic substrates correlated to a possible distinctive phenotype, that deserves to be investigated. Furthermore, given the fact that lenticular nucleus hyperechogenicity is associated with dystonia [3], follow-up is indicated regarding a possible development of this symptom.

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## THERMAL QUANTITATIVE SENSORY TESTING AND ENDOGENOUS MECHANISMS OF PAIN CONTROL ASSESSED BY THE OFFSET ANALGESIA PARADIGM IN PATIENTS WITH PARKINSON'S DISEASE

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Objective: Pain represents a major, though poorly understood aspect of non-motor symptoms of Parkinson's disease (PD). The etiology of pain in PD has not been completely clarified and can be multifactorial. Alterations in emotional-motivational and sensory-discriminative pain processing have been supposed. Our aim was to assess in a group of PD patients both in on- and off-medication state the thermal sensory thresholds (TST), the heat pain threshold (HPT) and the response to a offset analgesia (OA) paradigm, that evaluates the function of the endogenous pain modulation system.

Material and Methods: Nine PD patients (mean age 62 yrs, 3 F) and 8 age- and sex-matched healthy subjects underwent an experimental paradigm including assessment of warm and cold detection thresholds (using the levels method), HPT, 3 stimulus offset trials and 3 constant temperature trials based on the individual HPT. Both the forearm and the dorsal foot were assessed on the most affected side of PD patients (the right side in the healthy subjects) when on- and off-medication state (two different sessions) when assessing the TST. The constant and offset trials were applied only at the forearm.

Results: Compared to healthy subjects, patients with Parkinson's disease in off-state had a reduced threshold for perception of the cold (less discriminative ability) stimulus at the forearm. The offset analgesia phenomenon was similarly observed in both off and on-therapy patients, with no difference vs. healthy subjects, albeit in off-therapy patients the visual analogue scale (VAS) score reduction was observed with a delayed latency.

Discussion: The altered perception threshold of the cold stimulus seems due to disease-related brain network abnormalities rather than to the loss of small fibers, in consideration of both the non-length-dependent pattern of the alteration and the normalization in the on-state. Findings form the OA paradigm are not compatible with alterations in the endogenous mechanisms of pain modulation in off-state patients. Noteworthy, only a delay of a few seconds in the VAS reduction recording during the OA paradigm was observed in the off-state patients, that was probably linked to bradykinesia.

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## GENDER DIFFERENCES IN IDIOPATHIC ADULT-ONSET DYSTONIA

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Background: Sex is thought to be a significant factor in the phenotypic expression of idiopathic adult-onset dystonia (IAOD). Earlier observations suggested a women preponderance in most forms but task-specific upper limb dystonia, and an earlier age at dystonia onset in men. Since most information was from relatively small clinical series recruited in one or a few centers, a referral bias could not be excluded.

Objective: To analyse sex differences in the phenotype of IAOD in a large multicentre cohort from the Italian Adult-onset Dystonia Registry (IADR).

Materials and Methods: On May 2023, the IADR included 1698 IAOD patients from 42 centers. Age at dystonia onset, anatomical localization of dystonia, spread of focal dystonia, family history of

dystonia and dystonia associated sensorimotor features were compared between men and women.

Results: We observed that: (i) age at dystonia onset was similar in men and women (mean age 52.2 ± 14.7 vs 52.7 ± 14.4 years, p = 0.5); (ii) women predominate over men in cranial dystonia; (iii) the sex ratio was reversed in upper limb and lower limb dystonia; (iv) no clear sex difference emerged in cervical and trunk dystonia; (v) neck tremor predominates in women, while no sex difference emerged in terms of spread and family history of dystonia, sensory trick and sensory symptoms.

Discussion and Conclusions: Information from this large multicentre cohort indicated that the influence of sex on the phenotypic expression of IAOD is limited to some forms and features. It is possible that certain sex differences result from sociocultural rather than biological factors.

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## GAIT PARAMETERS DIFFERENTIATE PHENOTYPES IN AN APPARENTLY HOMOGENEOUS COHORT PATIENTS AFFECTED BY PARKINSON'S DISEASE

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Background: Parkinson Disease (PD) subtypes have been generally based on motor symptoms such as the tremor-dominant versus postural instability and gait disorder or akinetic/rigid form. Non-motor symptoms in PD represent a significant burden of disease with high impact on quality of life. Non-motor symptoms phenotyping in PD is relevant to identify subtype-directed treatment strategy [1]. Cluster analysis is a method of unsupervised Machine Learning (ML) algorithms, which do not require labelled dataset [2].

Objectives: The aim is to identify different phenotypes of PD through a clustering method implemented with subclinical gait changes detected by gait analysis.

Materials and Methods: Ninety-four PD Patients were consecutively enrolled according to inclusion and exclusion criteria reported elsewhere [3]. All subjects were clinically assessed by total MDS-UPDRS scale and were evaluated by Gait Analysis, using an optoelectronic system supplied by BTS Bioengineering. An unsupervised approach to ML was performed through MATLAB (v.2020b). A k-means clustering algorithm was implemented to evaluate if different phenotypes could be distinguished in PD patients based on spatial-temporal parameters. After obtaining the clustered data, a univariate statistical analysis with IBM SPSS (v.28) was performed to find any other demographic and clinical difference between the clusters.

Results: K-means algorithm clustered the data into two groups: Cluster 1 and Cluster 2 with a sample size of 67 and 27, respectively. When comparing the two clusters on gait parameters, Cluster 2 in comparison with Cluster 1 patients showed reduction in single support phase, mean velocity, step, cadence and mean cycle length (p-value=0,001). In addition, Cluster 2 versus Cluster 1 exhibited increase in double support phase, stance phase and stance duration (p-value=0,001). Regarding demographical and clinical variables, Cluster 2 versus Cluster 1 showed worse scores on the Part I, Part II and Part III of the MDS-UPDRS scale and on H&Y scale (p-value=0.012, 0.004, 0.026, 0.016 respectively). Thus, Cluster 2 as compares to Cluster 1 patients showed more severe non motor symptoms, despite comparable disease duration and age.

Discussions and Conclusions: The present study shows that a cluster analysis was able to identify two discrete PD phenotypes based on a data-driven approach implemented with gait parameters. Therefore subclinical gait impairment could identify a worse PD phenotype characterized by more severe non-motor symptoms and more disability, as displayed by worse scores on MDS-UPDRS Part I and II.

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## MUSCLE SYNERGIES DURING GAIT IN PARKINSON'S DISEASE

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Rationale/Objectives: Gait disorders are a major cause of morbidity and mortality in Parkinson's disease (PD), involving continuous and episodic disturbances associated with abnormal activation of individual muscles [1]. Still, it is unclear whether muscle synergies (i.e., groups of synchronously-activated muscles, variably combined to produce complex movements) are impaired during gait and affected by dopaminergic therapy [2,3]. This study aims to investigate muscle synergies during gait and their relationship with L-Dopa in PD.

Material/Methods: Fifteen PD patients (OFF and ON state of therapy) and 10 healthy subjects (HS) were monitored through inertial and electromyography (EMG) wearable systems while walking on a 20-m straight path. Eight IMUs, placed on the trunk, pelvis and lower limbs, were used to reconstruct joint angles and the gait cycle of at least ten consecutive strides. Muscle synergies were extracted from the surface EMG of 11 muscles of the dominant lower limb by a non-negative matrix factorization method. The "Variance Accounted For" (VAF) (i.e., the correlation coefficient between measured and reconstructed EMG signals) was analysed to examine the variability amount of recorded data explained by extracted synergies.

Results: PD patients showed a comparable number and composition of muscle synergies to HS, regardless of their therapeutic status. Moreover, the temporal activation profile of muscle synergies was similar between patients and HS. In both subgroups, four muscle synergies were associated with a VAF greater than 90% in reconstructing muscle activity during gait. Despite the similar composition and activation

profiles of synergies, PD patients exhibited higher amplitude peaks of involved muscles compared to HS. L-Dopa did not significantly impact the number, composition and amplitude peaks of muscle synergies in PD but partially enhanced the VAF, in line with improved gait kinematics in patients ON compared to OFF therapy.

Discussion/Conclusions: The number, internal structure and temporal activation profiles of muscle synergies during gait are normal in PD, suggesting preserved lower-level central generators. Dysfunctional higher-level centres, including basal ganglia and cortical motor areas, may be responsible for abnormal modulation of muscle synergies leading to co-contraction and increased amplitude peaks of involved muscles. The limited effects of L-Dopa on muscle synergies support the contribution of non-dopaminergic pathways in the pathophysiology of gait disorders in PD. However, the low sensitivity of sEMG to changes associated with dopaminergic therapy can not be excluded.

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## GAIT PARAMETERS DEPICTING PARKINSON'S DISEASE PROGRESSION: FROM THE PRODROMAL PHASE TO THE CLINICALLY EVIDENT STAGE

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Objectives: Gait alterations are a prominent feature of Parkinson's disease (PD), whereas their progression and differences between stages is still theme of debate. Idiopathic REM sleep behavioral Disorder (iRBD) is the condition with the highest conversion to PD and other alpha-synucleinopathies, thus it is studied as a prodromal phase of PD. Aim of the study was to analyze gait temporal and spatial parameters in PD spectrum from the prodromal phase to the overt phase and to compare these parameters to Healthy controls and treated PD.

Methods: The prospective study included consecutively individuals with PSG- confirmed iRBD, drug-naïve PD patients, middle-stage treated PD patients and healthy controls. Each individual underwent a multidimensional assessment including evaluation of motor and non-motor symptoms, cognitive status and comorbidity. All individuals underwent a gait assessment using mobile health technology (MHT) in supervised condition at normal and fast pace and during dual-task performance.

Results: The study included 23 individuals with iRBDs, 60 drug-naïve PD patients (nPD), 60 middle-stage treated PD patients (tPD) and 65 controls (HC). MHT showed an increased step time in normal gait in nPD and in iRBD in comparison to controls, whereas tPD showed values similar to HC. Conversely, in fast gait MHT showed increased step time in untreated and treated PD in comparison to HC and iRBD. In dual task gait, iRBD, nPD and tPD showed increased step time in comparison to HC. Persons with PD, Naïve or not, exhibited shorter step length compared to HC in all tests ($p<0.001$), while iRBD showed values similar to HC and significantly greater than PD.

Conclusion: This multicenter study using MHT showed that step temporal parameters are more sensitive to change in prodromal phases of the disease, while step length seemed to be preserved in this phase. The dopaminergic treatment in PD appear to reduce the temporal gait differences to control in normal gait but exhibited no impact on dual-task and fast gait. Further ongoing longitudinal studies are warranted to evaluate the value of MHT in defining the risk of conversion and track the subtle motor progression in prodromal phases and early response to treatment in PD.

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## SEED-BASED FUNCTIONAL CONNECTIVITY CHANGES AND CERVICAL MOTION ANALYSIS ALTERATIONS IN PATIENTS WITH CERVICAL DYSTONIA

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Objectives: Evaluating neck movement quality and studying the brain mechanisms underlying cervical dystonia (CD) are fundamental to plan the best treatment strategy. This study aimed at assessing kinematic and resting-state functional connectivity (FC) characteristics in patients with CD relative to healthy controls.

Materials: Seventeen CD patients and 14 age- and sex-matched healthy controls were recruited.

Methods: Electromagnetic sensors were used to obtain spatio-temporal parameters of neck movements in CD patients and healthy controls during three tasks: repeated cervical movements, target reaching and joint position error. Mean and maximal cervical movements amplitude was measured, both with eyes open and closed. Movement quality parameters during target reaching were obtained. Joint position error parameters were registered with both eyes open and closed. The precise dystonic position was also calculated. All participants underwent resting-state functional MRI (RS-fMRI). A seed-based FC analysis with supplementary motor area (SMA) as region of interest was performed. Correlations between motion analysis parameters and FC data were assessed.

Results: CD patients relative to controls showed reduced mean and maximal range of motion (ROM) in rotation both towards and against

dystonia pattern and reduced total ROM in rotation both with eyes open and closed. Moreover, CD patients had less severe dystonia pattern with eyes open relative to eyes closed. The RS-fMRI analysis showed reduced FC in CD patients between SMA and bilateral occipital and cerebellar areas compared to controls. A reduced FC within the visuo-motor network correlated with a lower cervical ROM in rotation both with eyes open and closed and with a worse cervical movement quality during target reaching.

Discussion: Our results highlighted specific motor deficits of CD patients: movement amplitude resulted compromised not only against dystonia, but also towards. Moreover, visual input could play an important role in movement control in CD patients as shown by the results of the comparison between movement with eyes closed and open. Functional changes of the visuo-motor network correlated with a worse cervical motor control.

Conclusions: FC alterations in the visuo-motor network may represent the neural basis of cervical motor control deficits in CD patients. Electromagnetic sensors and RS-fMRI might be promising tools to monitor CD and to assess the efficacy of rehabilitative interventions.

## CLINICAL UTILITY AND REPRODUCIBILITY OF VISUAL RATING SCALE FOR CINGULATE ISLAND SIGN IN A REAL-WORLD MEMORY CLINIC: A FDG-PET/MRI STUDY

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Purpose: Brain [18F]FDG-PET is a supportive biomarker for dementia with Lewy bodies (DLB) showing occipital hypometabolism and presence of the cingulate island sign (CIS), a relative preservation of the posterior cingulate cortex (PCC) metabolism compared with that of precuneus and cuneus. We assess the clinical utility and reproducibility of a visual qualitative CIS scale in differentiating DLB from Alzheimer's disease (AD) in the memory clinic setting.

Methods: Patients with a diagnosis of Lewy bodies disease (DLB and MCI-LB) and with AD with available FDG-PET/MRI were recruited and followed for at least 24 months. data were retrospectively collected. Visual rating scale was applied independently by a nuclear medicine and neurologist physician. Validation of qualitative CIS scores was made with ROI-based semiquantitative analysis of FDG uptake ratio of PCC, cuneus and precuneus.

Results: 77 patients were recruited: 36 with LBD (30 DLB and 6 MCI-LBD) and 31 patients with AD (20 typical and 11 atypical presentations). Mean CIS score was 1.84±1.69 for DLB and 0.9±1.24 for AD patients (p=0.001). With a cut-off CIS score ≥ 2, sensitivity and specificity were 0.56 and 0.81, respectively (accuracy 0,67). Positive CIS in patients with a biological diagnosis of AD was mainly due to atypical presentations. Negative CIS in LBD were due to (a) normal FDG-PET or (b) marked hypometabolism of both PCC and cuneus. Scores of CIS rating scale correlated with uptake of FDG tracer ($r = 0.45$; $p < 0.001$) and showed high concordance among different specialists (K 0.62, p<0.001).

Conclusion: A visual CIS scale can be a surrogate for a quantitative CIS ratio and can be successfully applied by different specialists. Lower sensitivity is expected for cases of MCI-LB or dementia due to mixed DLB/AD changes. Specificity may be influenced by inclusion of atypical AD cases, mostly young-onset cases posterior variant of AD.

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## MULTIPLE SCLEROSIS

## OPTIMAL RESPONDERS TO PLATFORM DISEASE MODIFYING THERAPIES FOR RELAPSING MULTIPLE SCLEROSIS: A REAL-WORD STUDY

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Objective: The objective of the present study is to identify the proportion and characteristics of relapsing MS patients who can obtain greater benefits from a less effective but safer, platform DMT.

Methods and Materials: relapsing MS patients starting a platform DMT (interferons, glatiramer acetate, teriflunomide, dymethilfumarate, azathioprine), with follow-up ≥ 10 years (n=7852) were extracted from the Italian MS Registry. Confirmed disability accrual (CDA) was defined as an increase in Expanded Disability Status Scale (EDSS) score confirmed at 6 months. Optimal responders to platform DMT (patients remaining on platform DMT and without any CDA during the follow-up) were compared with patients remaining on platform DMT experiencing a CDA and patients switching to high efficacy DMT using multinomial regression models.

Results: Over a follow-up of 14.7+3.8 years, 2112 (26.9%) patients were considered optimal responders to platform DMT, while 2238 (28.5%) experienced a CDA and 3502 (44.6%) switched to a high efficacy DMT. As compared with patients still on platform DMT and those experiencing a CDA, optimal responders had younger age (OR=0.96,95%CI 0.95-0.97, p<0.001) and shorter disease duration at baseline (OR=0.97,95%CI 0.96-0.98, p<0.001). As compared with switchers, optimal responders had older age (OR=1.03,95%CI 1.02-1.04, p<0.001), shorter disease duration (OR=0.98,95%CI 0.97-0.99, p<0.001), lower EDSS at baseline (OR=0.76,95%CI 0.72-0.80, p<0.001) and monofocal onset (OR=1.26,95%CI 1.05-1.51, p=0.011). These findings were confirmed in the subgroup of 4500 patients with baseline magnetic resonance imaging (MRI) data available. In addition, as compared with patients still on platform DMT and CDA, a greater proportion of optimal responders had an active baseline MRI (OR=1.28,95%CI 1.09-1.51, p=0.003).

Discussion: The superiority of early introduction of high efficacy disease modifying therapies (DMT) in relapsing Multiple Sclerosis (MS) is being increasingly recognized, although long-term safety

data are largely missing and some patients may still obtain benefits from a safer DMT.

Conclusion: In this real-world population, the majority (two thirds) of patients initially treated with platform DMT had poor outcomes or switched to high efficacy DMT in the long term. Platform DMT might be considered in young adults with monofocal onset, active MRI, short disease duration and low disability levels.

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## THE POSITIVE EFFECTS OF AEROBIC CAPACITY ON FATIGUE ARE MEDIATED BY THALAMIC NUCLEI IN PEOPLE WITH MULTIPLE SCLEROSIS

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Aims: Fatigue is a common symptom in people with multiple sclerosis (pwMS) affecting mental and physical domains. Aerobic capacity (AC), disability and cognitive impairments contribute to fatigue perception. The thalamus has been consistently involved in fatigue pathogenesis. Aims of this study were to identify associations between thalamic nuclei volumes and fatigue and explore whether the effect of AC on this symptom is mediated by the volume of thalamic nuclei in pwMS.

Materials and Methods: In this cross-sectional study, Modified Fatigue Impact Scale (MFIS), Expanded Disability Status Scale (EDSS), Symbol Digit Modalities Test (SDMT), maximal oxygen uptake (VO2max) and brain MRI data of thalamic volumes were collected from 74 pwMS. 47 sex- and age-matched healthy controls (HC) were included for MRI comparison. Thalamic nuclei volumes were obtained using Freesurfer 7.1.1 on 3D T1-weighted lesion-filled images. PwMS and HC were compared using the $\chi 2$ Pearson, Mann-Whitney or t-test. Correlations between thalamic nuclei and MFIS scores were performed using Pearson's or Spearman's partial correlations. A mediation model was applied in pwMS to assess the existence of an indirect pathway of AC acting through thalamic nuclei on fatigue.

Results: Patients and HC did not differ for age and sex ($p>0.557$). Compared to HC, pwMS were characterized by global atrophy and lower thalamic nuclei volumes ($p\leq0.001$). In pwMS, fatigue was associated with atrophy of left latero-dorsal nucleus (left-Dor) (r-value=-0.278; $p\leq0.018$), with a stronger association with cognitive rather than physical fatigue. More severe disability (r-value=0.355; p=0.004) and worse processing speed (r-value=-0.353; p=0.003) were associated with more severe fatigue and diffuse thalamic atrophy. In contrast, higher AC was associated with less severe fatigue (r-value=-0.263; p=0.027) and atrophy of the left-Dor (r-value=-0.288; p=0.015). The mediation model showed that in pwMS there was a significant indirect effect of VO2max on fatigue through the volume of the left-Dor nuclei (b =-0.305, CI [-0.678;-0.005]).

Discussion: The aim of this study was to better understand fatigue in pwMS, taking in consideration the multifactorial nature of this symptom and with a special focus on the role of AC and thalamic nuclei. Our results confirmed the positive effects of AC on fatigue, which seems to be partially mediated by the integrity of a specific thalamic nucleus.

Conclusions: Aerobic capacity exerts a positive effect on fatigue in pwMS, which is indirectly mediated by a preserved volume of the left-Dor thalamic nucleus.

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## INEBILIZUMAB FOR NEUROMYELITIS OPTICA SPECTRUM DISORDER: THE FIRST ITALIAN PATIENT

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Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is an antibody-mediated disease of CNS where autoantibodies directed against aquaporin-4, a water channel, destroy astrocytes. Transverse myelitis, optic neuritis and area postrema syndrome are typical presentations of this disease. If untreated, patients will experience a severe illness which may bring to wheelchair or even to death. Relapses must be treated aggressively to prevent disability. A relapse prevention is crucial and needs long-term immunosuppression. In 2022 the Italian regulatory agency for drug prescription approved two new drugs for NMOSD: eculizumab and satralizumab; both of them must be prescribed to those patients with an EDSS $\leq$ 6.5. With an higher EDSS score there have been no chance until march 2023 when inebilizumab have been approved. Actually this drug may be administered to those NMODS patients with an EDSS score $\leq$ 8. We present our experience with the first Italian patient treated with inebilizumab.

Case report: A 40 years old male patient was referred to our institution with a diagnosis of CIDP to continue IVIg treatment. The patient was on wheelchair and he was able to walk just for few steps. Deep tendon reflexes were brisk with clonus; Babinski sign and ankle clonus were recorded. Diagnosis of CIDP was reconsidered. Patient underwent to brain and spine MRI revealing a transverse myelitis. Cerebrospinal fluid tests showed and albumin-cytological dissociation. Nerve conduction studies were consistent with CIDP. Anti-AQP4 antibodies were present: patient was diagnosed with CIDP and NMOSD and began rituximab, with no benefits: he experienced one relapse per year requiring plasma-exchange. So rituximab was discontinued and mycophenolate was began. In 2022 his clinical status worsened with a marked spasticity and he reached an EDSS score of 7.5. As eculizumab and satralizumab could not be prescribed, when inebilizumab was available it was suggested. The patient accepted; a wide viral screening did not show any contraindications. The day of the administration, patient was pre-treated with a steroid pulse and an antihistamine; then inebilizumab was reconstituted in 250 cc of saline solution in the fume hood of our hospital pharmacy. Inebilizumab was administrated in one hour and a half and no side effects were recorded. The day after first administration patient referred an improvement of spasticity, noticeable during the clinical evaluation before the second administration.

Conclusions: In our experience inebilizumab seems a promising drugs and may be indicate for those patients who suffer from a severe form a NMOSD.

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## BALANCE DISORDERS IN MULTIPLE SCLEROSIS: ASSESSMENT AND ROBOTIC REHABILITATION TREATMENT


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Balance impairment is present in 50-80% of people with multiple sclerosis (PwMS), significantly impairing patients' quality of life and autonomy. Robotic rehabilitation has been shown to be a promising modality of intervention to improve balance in orthopedic, geriatric, and neurological settings, with applications in post-stroke rehabilitation, Parkinson's disease, and MS. This study evaluated the use of Hunova robotic footplate rehabilitation treatment in PwMS. The study involved 35 PwMS, who each performed ten sessions of 30 minutes on a biweekly schedule with Hunova. In order to identify the patients' achieved progress, clinical and robotic assessments were performed at the beginning and end of the rehabilitation course. Results revealed a significant improvement in balance assessed with the Berg balance scale (BBS, p value=0.0081). In the robotic assessment, positive changes in parameters related to elastic, passive, reactive balance and Five Times Sit to Stand tests were significant. The improvement in these specific parameters is mainly related to an optimization of the vestibular component of balance and trunk control. The effects on BBS are similar to those found in other pathologies, like in the Parkinson's disease. Results in the PwMS subgroups differed from the trend in the total population, identifying a different response depending on the age (under and over 50 years old) and the degree of disability (EDSS 0-3.5 and 4-6.5). In conclusion, we were able to show that robotic rehabilitation with Hunova effectively improved balance in patients with mild to moderate MS. Improvements mainly regarded trunk control and the vestibular component of balance. We therefore assume that PwMS suffering from balance impairment can benefit from Hunova treatment. However, additional studies are needed to further assess efficacy and to define the optimal therapeutic dose of robotic rehabilitation in the setting of PwMS and in specific subgroups, differentiating, for example, between patients with main spinal or cerebellar involvement.

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## DIMETHYL FUMARATE-ASSOCIATED LYMPHOPENIA FOLLOWING BARIATRIC SURGERY: TWO CASE REPORTS


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Introduction: Lymphopenia is a common side effect of treatment with dimethyl fumarate (DMF) in patients with multiple sclerosis (PwMS) [1]. Higher baseline absolute lymphocyte count (ALC) and a body mass index (BMI) $\geq$ 30 kg/m2 has been identified as protective factors for lymphopenia [2]. Although there are data about higher BMI, no data are available on ALC changes in pwMS undergoing to weight loss due to diet modification or to bariatric surgery.

Objective: We herein report two cases of lymphopenia in female pwMS treated with DMF and history of bariatric surgery.

Methods: Patients underwent a multidimensional assessment including neurological and hematological evaluation, with a longitudinal follow up.

Results: Patient 1 is a 25-year-old woman with history of obesity treated with gastric bypass in 2016. She started DMF due to intolerance to DMTs injection in 2021. Since DMF beginning, ALC showed a downward trend until a grade 3 lymphopenia persisting for more than 6 months. Patient 2 is a 50-year-old woman with history of obesity treated with bariatric surgery in 2006. Due to injection site reaction she underwent to DMF in December 2020. Four months after blood examination showed lymphopenia that worsened and persisted for more than 6 months. Both patients discontinued DMF treatment due to persistent lymphopenia with rapid normalization of ALC and switched to another oral platform therapy that was well tolerated.

Discussion: After bariatric surgery, several mechanisms can affect drug bioavailability. After oral intake, DMF is hydrolyzed to monomethyl-fumarate (MMF), its main bioactive metabolite, mostly in the small intestine, where there is an alkaline environment that promote the transformation [3]. The exposure to stomach higher pH levels and the faster transfer of this drug to the bowel due to increased gastric emptying rate, but also changes in body compositions, alterations of molecular pathways and changes in gut microbiota could lead to an increased absorption rate, hypothetically enhancing some side effects.

Conclusions: To improve the care provided to bariatric surgery pwMS, additional clinical studies are necessary to explore the impact of this surgery on DMT.

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## DORSOLATERAL PONTO-MEDULLARY SYNDROME WITH IPSILATERAL HEMIPARESIS AFTER HERPES ZOSTER OPHTALMICUS

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Objectives: To underline the value of MRI in diagnosis and early detection of Central nervous system (CNS) involvement after Herpes Zoster infection.

Methods - Case presentation: A 71-year-old woman affected with Relapsing Remitting Multiple Sclerosis (RRMS) treated with dimethyl fumarate (DMF) complained itch/tingling and pain followed by a skin maculopapular and vesicular rash in the V1 distribution of the left trigeminal nerve, six days after the administration of the first dose of COVID-19 vaccine. A diagnosis of herpes zoster opthalmicus was done and oral antiviral treatment was started. Despite treatment, vesicular rash worsened and the patient complained dizziness and paraesthesia/hypoesthesia involving right arm and leg. Neurological examination revealed cranial multineuropathy involving left facial and trigeminal nerves, a mild ipsilateral limb ataxia, decreased pain and temperature sensation in controlateral limbs, and a mild ipsilateral hemiparesis with Babinski sign. Intravenous therapy with acyclovir was started.

Results: A brain and cervical spinal cord MRI showed a T2 hyperintensity of the left trigeminal nerve, in the dorsolateral regions of the pons and medulla, extending to the upper cervical cord (C2), with T1 hypointensity and diffuse contrast enhancement after gadolinium administration in the same regions, findings that confirmed the suspicion of herpetic encephalomyelitis. Cerebrospinal fluid (CSF) examination showed a slightly elevated total protein level of 0.48 g/L, CSF/serum glucose ratio of 55% and 7 leukocytes/microL. Polymerase chain reaction (PCR) analysis was negative for Varicella-Zoster DNA. Intravenous acyclovir was continued for 21 days with symptomatic improvement. A brain MRI performed 4 months after showed a reduction of lesion extension and contrast enhancement was no longer seen.

Discussion: CNS involvement after Herpes Zoster infection is a rare complication that can lead to permanent neurological damage or even death [1]. In our case report, Varicella-Zoster DNA was not detected in the CSF. However, the analysis was performed 14 days after the onset of antiviral treatment and in the majority of treated cases there is a substantial decline of PCR-positivity [2]. Brain MRI provided a sort of "in-vivo tracing" of trigeminal nerve and nuclei, following the diffusion of herpes zoster reactivation from Gasser ganglion to the pontine, and medullary-spinal nuclei and neighboring areas. In our patient, the involvement of CNS led to the complex and unusual clinical picture of a dorsolateral ponto-medullary syndrome with ipsilateral hemiparesis.

Conclusion: Although rare, potential CSN involvement should be considered, since prompt diagnosis and consequent early treatment are essential to favorable outcome [3].

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## IMPACT OF COVID-19 ON PREGNANCY AND FETAL OUTCOMES IN WOMEN WITH MULTIPLE SCLEROSIS

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Objectives: To assess maternal and fetal outcomes and their predictors in pregnant women with Multiple Sclerosis (MS) and COVID-19 infection selected from two large national registries and compared with matched control pregnancies extracted from a historical Italian cohort.
Methods: We recruited pregnant patients with MS who contracted COVID-19 after conception and were followed-up in Italian and Turkish Centers, in the period 2020-2022. A control group was extracted from a previous Italian multicenter cohort. The primary outcome measures were maternal complications, fetal malformations and spontaneous abortion. Associations between group (COVID-19 or healthy patients) and clinical outcomes were investigated with a weighted logistic regression where propensity score-based inverse probability of treatment weighting (IPTW) approach was applied for adjusting for difference in baseline confounders. Variables considered possibly associated with the outcome in univariate analysis ($p<0.10$) were tested for multivariable analysis.

Results: Data on pregnancy outcome are available for 61 out of 67 pregnant MS women with COVID-19 after conception. In the

multivariable analysis, COVID-19 during pregnancy was associated with a higher risk of maternal complications (OR 2.00, CI 1.25 – 3.24; p = 0.005). The infection was not associated with higher risk of spontaneous abortion and fetal malformations (respectively 0.53, CI 0.23 – 1.17; p = 0.13 and 1.40, CI 0.53 – 3.87, p = 0.50). The sole independent predictor of spontaneous abortion and fetal malformations was a previous spontaneous abortion (respectively 5.06, CI 1.93 – 12.17, p < 0.001 and 12.26, CI 4.23 – 34.47, p <0.001).

Discussion: Data in the general population have shown an increased risk for adverse maternal and fetal outcomes in infected women [1]. So far, only one small study [2] and a larger international study [3] have assessed COVID-19 clinical outcomes in pregnant women with MS, showing no significant increase of severe COVID-19 outcomes, but there is total lack of information about maternal and fetal outcomes. This is the first study assessing the impact of COVID-19 on pregnancy and fetal outcomes in women with Multiple Sclerosis, showing that COVID-19 during pregnancy was associated with higher risk of maternal complication, in line with data from the general population. As concerning spontaneous abortion and fetal malformations, our findings seem to be in contrast with data from the obstetric literature, as we found no significant correlation between COVID-19 and adverse fetal outcomes.

Conclusion: Our data indicate that SARS-CoV-2 infection during pregnancy increases the risk of maternal complications, while it seems to have no significant impact on fetal outcomes.

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## OCRELIZUMAB-INDUCED NUMMULAR ECZEMA IN A PATIENT WITH RELAPSING MULTIPLE SCLEROSIS

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Aims: Anti-CD20 monoclonal antibodies are among the drugs that showed the greatest efficacy in controlling disease activity and in preventing long-term disability in patients with multiple sclerosis (MS). Main adverse reactions of these therapies are hypogammaglobulinaemia, infections, infusion-related skin reactions. We describe a case of an ocrelizumab-induced nummular eczema in a female patient with relapsing MS.

Material: In 2008, at the age of 25, diagnosis of relapsing-remitting MS. In the medical history: contact/atopic dermatitis. She was first treated with interferon and then with natalizumab, both suspended due to ineffectiveness, without any dermatological adverse effects. Ocrelizumab was started in May 2020, without any infusion-related hypersensitivity reaction.

Method: About 3 months after the third infusion, onset of hands dermatitis with subsequent appearance of exuding and itchy vesicles; initially, these symptoms were associated with the known atopic/contact dermatitis, so corticosteroids, antihistamics and antibiotics were performed with partial benefit. Then, Ocrelizumab was repeated. At the same time, the patient was vaccinated for Sars-CoV-2. In the next moths, skin lesions got worse again and diagnosis of nummular eczema was done but, since vaccinations or infections may worsen pre-existing dermatological lesions, it was uncertain if the responsible was the vaccine or the drug. So, Ocrelizumab was re-infused, with further worsening of the skin lesions and a biopsy was performed.

Results: Histological examination revealed chronic inflammatory skin lesions with superficial spongiotic dermathosis: these features confirmed nummular eczema. Due to the severity of the clinical picture, Ocrelizumab was definitely stopped.

Discussion: The correlation between anti CD-20 therapies and the onset of skin manifestations is well known. Reports of induced or worsened psoriasis by Rituximab[1] and palmoplantar or oral pustulosis and lichen planus following Ocrelizumab infusion are described[2]. The mechanism below could be the disruption of the balance between T and B cells, with hyperfunctioning of T cells and consequent increase in susceptibility to viral and bacterial infections, or the alteration of the skin barrier, with hypersensitivity to common environmental factors. As a result, these features can lead to various types of skin lesions. In medical literature, only another case of nummular eczema following Ocrelizumab infusion is reported[3].

Conclusions: In this case, the temporal connection between Ocrelizumab and the skin lesions and the lack of any other causative factor support their causal connection. It's important for the clinicians to consider this relationship, in order to early recognize these manifestations, and to promptly reevaluate the therapy.

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## PEDIATRIC ONSET OF MULTIPLE SCLEROSIS FOLLOWING EBV INFECTION AND COVID-19 VACCINATION

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Background: Epstein Barr Virus (EBV) infection has recently received attention as a potential environmental trigger that may contribute to the development and progression of multiple sclerosis (MS). Several lines of evidence suggest a link between EBV and MS, including the observation that individuals who were infected with EBV at a younger age have more risk of developing MS. During the vaccination campaign against SARS-CoV-2, there have been reports of autoimmune CNS demyelinating diseases, including cases where MS was the first manifestation. We present a case involving a young patient who experienced the clinical onset of pediatric MS (POMS) following EBV infection and COVID-19 vaccination.

Case description: A 16-year-old girl referred to our center for onset of symptoms including numbness and weakness on the right side of her face, as well as tingling sensations in her right hand. Approximately three weeks prior to the neurological symptoms, she received

the third dose of the Pfizer-Cominarty COVID-19 vaccine, which was well-tolerated. About a year and a half before the onset of her current symptoms, the patient was hospitalized with fever and severe occipital headache due to EBV infection. In that occasion, a brain CT scan was normal. At presentation (one week after symptom onset), the patient showed tingling in right side of face and in the right hand (EDSS 2.0). Brain magnetic resonance imaging (MRI) revealed multiple voluminous white matter (WM) lesions that resembled Acute Disseminated Encephalomyelitis (ADEM), with most of the lesions located in the periventricular region and showed enhancement after the administration of gadolinium. The patient underwent a diagnostic workup, including basic metabolic panel and autoimmune tests, which all came back within the normal range. Oligoclonal bands were detected in the cerebrospinal fluid analysis. Screening for antibodies associated with CNS demyelinating disorders, including MOG and AQP4, yielded negative results. A follow-up brain MRI performed four months later showed an increase in the size of previously enhancing lesions and presence of new WM lesions. Based on the evidence of spatial-temporal dissemination on MRI, in accordance with the 2017 McDonald criteria, a diagnosis of pediatric multiple sclerosis (POMS) was made.

Discussion and Conclusion: This case highlights a potential association between EBV infection, possibly complicated by COVID-19 vaccination, and the development of pediatric MS. It supports the existing evidence suggesting a link between EBV and MS and emphasizes the importance of monitoring potential neurological complications in individuals with EBV infection.

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## SPONTANEOUSLY RESOLVING BRAIN RING-ENHANCING LESIONS DUE TO IMMUNODEFICIENCY-ASSOCIATED CENTRAL NERVOUS SYSTEM LYMPHOMA: A CASE OF "VANISHING LYMPHOMA"


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Background: The differential diagnosis of brain ring-enhancing lesions is broad, especially in patients with systemic autoimmune diseases undergoing immunosuppression, and includes infections, inflammatory lesions and treatment-related malignancies. We present the case of a patient with several ring-enhancing lesions, some of which resolved without treatment at a follow-up MRI, due to immunodeficiency-associated central nervous system (CNS) lymphoma secondary to immunosuppression for systemic lupus erythematosus (SLE).

Description: A 57-years old woman was evaluated at emergency department after tonic-clonic seizure. Her past medical history included SLE, diagnosed 34 years before, with renal and hematologic involvement. She was treated with mycophenolate mofetil (MMF) for 20 years (initially 2000 mg daily, then 1000 mg daily for 6 years), hydroxychloroquine for 6 years and prednisone from disease onset. She underwent brain MRI, which showed 7 ring-enhancing lesions located both at the grey/white matter junction and in the basal ganglia. The largest lesion measured 13x13x13 mm, was located in the parieto-occipital lobe and showed MRI signs of central necrosis. Cerebrospinal fluid (CSF) proteins, glucose level and cell count was within normal limits; microbiological analyses, comprehensive of Cryptococcus, Toxoplasma, Aspergillus, Mycobacterium tuberculosis and EBV, were negative. Isoelectric focusing showed the presence of CSF-restricted oligoclonal bands. Full-body computed tomography and [18F]-fluorodeoxyglucose positron emission tomography showed no evidence of systemic disease and hypermetabolism of the known brain lesions. A follow-up MRI scan, performed one month after presentation, showed increase of the size of the largest brain lesion and substantial resolution of contrast-enhancement in the other lesions. She underwent brain biopsy: histological analysis showed large lymphoid elements with irregular nuclei, positive for CD20, BCL2 and EBV-related markers. A diagnosis of immunodeficiency-associated CNS lymphoma was made.

Discussion: Immunodeficiency-associated CNS lymphoma is a known adverse effect of MMF treatment for SLE [1]; its pathogenesis is related to EBV-sustained replication, transformation and immortalization of B-lymphocytes [2]. Immunodeficiency-associated CNS lymphoma is more often multifocal than primary CNS lymphomas occurring in immunocompetent patients; however, presentation with seven different contrast-enhancing foci is unusual. Moreover, in our patients some of the lesions resolved without treatment while other progressed, a rare pattern known as "vanishing lymphoma" [3].

Conclusions: Our case highlights the importance of brain biopsy, even in the context of spontaneously resolving lesions, in the diagnostic workup of brain ring-enhancing lesions.

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## ALL IS WELL THAT ENDS WELL: A CASE OF PREGNANCY DURING SC NATALIZUMAB


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Objectives: Natalizumab (NTZ) is a humanized monoclonal IgG4 antibody directed against the a4-ß1 integrin (VLA-4). In 2021 the subcutaneous (SC) injection of natalizumab, dosed 300 mg every 4 weeks (Q4W), received marketing authorization in Europe to treat Relapsing-Remitting Multiple Sclerosis (RMS), building on the similar efficacy, pharmacokinetic and pharmacodynamic profiles of the intravenous formulation. In recent years, several studies have shown that continuation of intravenous infusion of NTZ during gestation protects from relapses during pregnancy and post-partum, without major risks for newborns. No data is yet available for the new SC route. To describe efficacy and safety of the use of sc NTZ during pregnancy we report the case of a patient followed up at the Pregnancy Clinic of MS center of Tor Vergata University Hospital who found out being pregnant during SC Natalizumab treatment.

Materials and Methods: We report on a 33-years-old, nulliparous Italian woman, 40 kg body-weight at conception, treated with i.v. Natalizumab for 10 years, Q4W, which was switched to the SC formulation due to difficult venous access. She was found out being pregnant after the first injection and she accepted to continue therapy throughout pregnancy with extended interval dose (EID) Q6W.

Results: No relapses or other relevant side effects during pregnancy and postpartum were recorded. She delivered a healthy baby through cesarean section (weight 2500 g and length 46cm). No major congenital nor hematological anomalies were reported after birth and at 6 months follow-up.

Conclusion and Discussion: This case confirms the good maternal-fetal safety profile of NTZ administered during pregnancy. Indeed, it shows that extending the interval doses during pregnancy does not affect the risk of MS relapses also in the case of subcutaneous formulation. Further research on larger case series is needed to confirm present results.

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## ANTI-JCV ANTIBODY INDEX KINETICS DURING PREGNANCY AND POST-PARTUM IN WOMEN WITH MULTIPLE SCLEROSIS TREATED WITH NATALIZUMAB


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Background and Objectives: During pregnancy maternal immune system undergoes major reorganizations in order to establish fetal immunotolerance. Such immunological changes may impair immunosurveillance against pathogens. The John Cunningham virus (JCV) is a latent pathogen occasionally causing progressive multifocal leukoencephalitis (PML) in patients with Multiple Sclerosis (MS) treated with natalizumab (NTZ). Although there is a general consensus upon continuation of NTZ during pregnancy, it is not yet known whether the interaction between pregnancy immunology and NTZ pharmacodynamic may alter the immunosurveillance for JCV. This retrospective study aims to describe the kinetic of humoral response to JCV before, during and after pregnancy in women with MS exposed to NTZ during pregnancy and post-partum.

Materials and Methods: Serum levels of anti JCV antibodies index (JCV-Index) assessed before conception (baseline), at each pregnancy trimester, and 3 months after delivery were collected in women with MS treated with NTZ during pregnancy and post-partum. JCV-index was analysed by a two-step second-generation enzyme-linked immunosorbent assay provided by STRATIFY Unilabs. For risk stratification three risk categories were considered: low (≤0.9), intermediate (0.9 < JCV index > 1.5), and high (>1.5). Results: Data from 26 pregnant MS women were analyzed (mean age 32 ±4.3 years, median infusions number during pregnancy 4 (1-6). 15/26 (58%) women had a negative JCV-index at baseline. Among these, 13/15 (87%) remained negative throughout pregnancy and at 3-months post-partum (PP); 2 women seroconverted to the low risk category, respectively during 2 trimester and at 3 months-PP. Among positive (n=11), 6/11 (54%, high risk category) showed no changes in JCV Index during pregnancy and at 3-months PP; in 4/11 (36%) JCV-index shifted from a higher to a lower risk category during pregnancy returning to the higher category after delivery (2/4 cases), and in 1/11 from a lower to intermediate. Looking at mean values, positive women overall showed a trend toward a reduction of JCVindex title from the first to the third pregnancy trimester.

Discussion and Conclusions: Our results show that continuing NTZ during pregnancy does not impact JCV serostatus; therefore, this approach does not expose pregnant women with MS to increased risk of PML. Conversely, the decrease of JCV index in the third trimester, although it has to be confirmed by larger samples, is possibly explained by increasing plasma volumes along with pregnancy advancement or to physiological rearrangement of B cells compartments.

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## THE EFFECT OF NATALIZUMAB ON THE RETINA OF PATIENTS WITH MULTIPLE SCLEROSIS: A LONGITUDINAL OCT STUDY


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Objectives: This study enrolled patients with the indication to undergo Natalizumab treatment, aiming to: 1) characterize variations in retinal volumes and thickness in patients affected by Relapsing-Remitting MS (RRMS), 2) examine the origin and significance of retinal hyper-reflective foci (HRF).

Materials and Methods: Retina of RRMS patients was studied by performing several OCT: the first one within one month from the initial Natalizumab infusion (baseline, T1), the second one 2-3 months later (T2), and the last one 5-6 months after the first infusion (T3). OCT parameters were investigated together with HRF behaviour during the recruitment

period. The HRF number in each layer and timepoint was analyzed with Wilcoxon test. The mixed effects model (adjusted for age, sex and previous treatments) with random intercept for subject and eye within subject was performed to see how the HRF modified during the study.

Results: 29 patients with a diagnosis of RRMS were recruited and a total of 58 eyes were analyzed. The results did not show significant changes in peripapillary RNFL and macular volumes and thickness, while an early increase of INL HRF between T1 and T2 was detected (p=0.041), further confirmed by the mixed effect model (β=2.72, p=0.019, between T1 and T2, p = 0.053 for the whole timespan).

Discussion: Retina and the optic pathway may represent an ideal model to assess both neurodegeneration and inflammation in multiple sclerosis (MS) by using Optical Coherence Tomography (OCT) to investigate changes in volumes and thickness of macular and peripapillary retina. In addition, through OCT, it is possible to evaluate the presence and number of HRF, presumably consisting of aggregates of activated and proliferating microglia. All the variations of these OCT parameters can be considered as a further means to describe the Natalizumab effect.

Conclusions: This study evidences substantial stability in terms of thickness and volumes of the peripapillary and macular retina in RRMS patients undergoing Natalizumab treatment, while a significant increase in INL HRF number has been found. The latter result needs to be clarified in order to establish whether the activation/proliferation of retinal microglia is due to a pro- or anti-inflammatory process.

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## BLURRED LINES: BILATERAL OPTIC PERINEURITIS MIMICKING IDIOPATHIC INTRACRANIAL HYPERTENSION


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Case report: A 62-years-old overweight woman, with a history of well-controlled type 2 diabetes and hypertension, was admitted to our department for subacute bilateral vision loss accompanied by severe, dull, non-throbbing headache. An ophthalmological examination performed three days after the onset of symptoms revealed bilateral papilledema, visual acuity of 5/10 in the right eye and 9/10 in the left eye, and normal eye pressure. Head CT scan showed no intracranial masses nor hydrocephalus. A contrast-enhanced brain MRI showed two non-specific deep white matter hyperintensities. Brain MRI, with angiography and venography were normal. Neurological and general examination, aside visual loss and bilateral pupillary light reflex impairment were unremarkable. A lumbar puncture was performed: intracranial pressure was only slightly increased (37 cm H2O, sitting position); CSF testing including biochemical analysis, cytology, microbiological evaluation and immunoelectrophoresis were negative. For suspected idiopathic intracranial hypertension (IIH), acetazolamide therapy was initiated. The patient's condition worsened: two weeks after symptoms onset, visual acuity was "count fingers" at 30 cm bilaterally, with severe papilledema, flame-shaped haemorrhages and persistent headache. Optical coherence tomography (OCT) confirmed marked optic discs swelling. Visual evoked potentials (VEPs) were undetectable bilaterally. Blood count, erythrocyte sedimentation rate, and C-reactive protein were normal. Bilateral optic neuritis was suspected. Infectious serum screening was negative for herpes viruses, HIV, Mycoplasma pneumoniae, Borrelia burgdorferi and Treponema pallidum. Serum and CSF anti-aquaporin-4 (AQP4) and anti-myelin oligodendrocyte glycoprotein (MOG) were undetectable. Blood autoimmune autoantibody screening was negative. Orbit MRI scan revealed bilateral optic nerve T2 hyperintensity and peripheral enhancement compatible with bilateral optic perineuritis; spinal cord MRI was normal. A 5-days course of high-dose intravenous methylprednisolone (ivMP) was initiated and visual acuity slightly improved. A second course of 3 days ivMP was administered, followed by every-other-day 7 plasma exchange sessions and oral prednisone tapering. Following this therapy, we observed a significant clinical response with headache improvement and substantial recovery of visual acuity (7/10 bilaterally). Funduscopic examination showed resolution of papilledema and hemorrhages, with residual optic discs pallor. VEPs were evocable, with prolongation of P100 latency and amplitude reduction, suggestive of residual optic nerve damage.

Discussion: Optic perineuritis is an uncommon inflammatory disorder of the optic nerve sheath. Simultaneous bilateral involvement is extremely rare and can mimic IIH. Although some cases are associated with MOGAD, systemic autoimmunity, vasculitis or infections, most are idiopathic. Clinical suspicion in the setting of atypical features for IIH should be raised to ensure prompt antinflammatory treatment.

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## GENE-ENVIRONMENT INTERACTOME ANALYSIS SUPPORTS CAUSALITY OF EBV IN MULTIPLE SCLEROSIS


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Objectives: Growing evidence supports Epstein Barr virus (EBV) as a causal factor in Multiple Sclerosis (MS). However, we still do not completely understand how the complex interaction between the virus and human predisposing genetic variability leads to MS, whether this is a disease-specific process, how it mechanistically translates to pathological processes and whether it is therapeutically actionable. Here, we aimed to address these issues exploiting human genetic information to assess non-genetic influences in MS and other complex diseases, analyzing gene modules whose products physically interact with environmental exposures ("interactomes").

Materials: Genome-wide association studies (GWAS) data of autoimmune diseases (MS, Crohn disease, celiac disease, rheumathoid arthritis, type 1 diabetes mellitus) and other complex diseases (Type 2 diabetes; Hypertension; bipolar disorder; coronary artery diseases). Interactomes of viral exposures and biological processes derived from public databases or were manually curated. Spontaneously-outgrowing lymphoblastoid cell lines (spLCLs), carrying the endogenous EBV strain, were generated from 13 subjects with relapsing remitting MS and 8 healthy donors (HD); PBMC infected with laboratory EBV B95.8 strain (B95.8-LCLs) were generated from 5 MS subjects and 4 HD.

Methods: Enrichment analysis of nominally significant SNPs from GWAS, and SNP-to-gene mapping, was performed through ALIGATOR. Definition of proteins binding MS-associated-interactome SNPs was assessed in RegulomeDB and through colocalization analysis. Frequency of MS-associated interactome genes (MSAIG) was evaluated in blood and brain gene expression data from MS patients. In vitro validation of bioinformatic results was performed by flow cytometry of lymphoblastoid cell lines from MS subjects and healthy controls. Network-based drug repurposing was implemented through NEDrex algorithm and leveraging the Priority Index resource.

Results: Modules of Herpesviruses- and, prominently, EBV-interacting genes are specifically associated with MS. Viral (EBNA2) and human (POLR2A, CTCF) factors cooperate in regulating MSAIGs. Analyses of MS blood and brain transcriptomes confirmed a dysregulation of MS-associated EBV interactors. The CD40 pathway emerged as the convergence of pathogenic interactions. EBV-interacting MS-associated genes are endowed with a high therapeutic potential and could be readily targeted by repurposable drugs.

Discussion: Our results strengthen a causal interpretation of sero-epidemiological associations between viruses and MS, highlighting widespread, MS-specific pathogenic interactions between the host's genetic background and EBV. Multi-omics analysis revealed functional implications of such interactions, pinpointing candidate therapeutic targets and drugs.

Conclusions: EBV-host interactions contain the causal structures of MS and hold promise for etiology-based therapeutic strategies.

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## NEED FOR AQP4 AND MOG ANTIBODY TESTING IN THE WORKUP OF INFLAMMATORY CNS DISEASES: TO TEST OR NOT TO TEST?

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Aim: The 2015 criteria for Neuromyelitis Optica Spectrum Disorders (NMOSDs) improved diagnostic accuracy for anti-aquaporin4 (AQP4) antibodies (Ab) associated NMOSDs. Recently, Myelin oligodendrocyte glycoprotein (MOG) Ab Associated Diseases (MOGAD) criteria have been proposed [1]. In most Multiple Sclerosis (MS) Centers, the workup for inflammatory diseases of the Central Nervous System (CNS) includes AQP4 and MOG Ab. Given the accuracy of criteria for MS, NMOSD, and those proposed for MOGAD, Ab testing could be considered only in cases with clinical and magnetic resonance imaging (MRI) features typical for NMOSD/MOGAD or atypical for MS. The study aim is to investigate the need for routine AQP4/MOG Ab testing in the workup of inflammatory CNS disease.

Materials: We selected subjects evaluated for an inflammatory CNS disease and tested for serum AQP4/MOG Ab (fixed cell-based assay) at Foundation IRCCS Neurological Institute Carlo Besta, Milan, from 2019 to 2023. Clinical and MRI data at first evaluation were collected.

Methods: We selected clinical, MRI and laboratory data suggesting MS [monolateral anterior optic neuritis (ON); spinal cord syndrome with multifocal posterior lesions; brain focal/polyfocal deficits with periventricular/corpus callosum/infratentorial/cortical ovoidal brain lesions; presence of oligoclonal bands (OCB) in cerebrospinal fluid (CSF)] or NMOSD/MOGAD (bilateral or longitudinal ON or with chiasm or optic nerve stealth involvement; transverse or longitudinally extensive myelitis or conus lesions or nerve roots involvement; encephalic/diencephalic/area postrema symptoms with deep grey matter or area postrema or periependimal involvement) [1]. All subjects were grouped as MS (at least one clinical and one MRI MS feature, none of NMOSD/MOGAD, presence of CSF OCB); NMO (at least one clinical or MRI feature of NMOSD/MOGAD) and OTHER (no MS or NMOSD/MOGAD features).

Results: We included 216 subjects, 66,7% female, mean age 41.6±12.7 years. 3,2% (7/216) were AQP4 Ab positive, 1.9% (4/216) were MOG Ab positive. We found a significant association between group assignment and positivity for AQP4/MOG Ab (Fisher's exact test, $p<.001$). There was no Ab positivity in the MS group, 11,7% in the NMO group, 2% in the group OTHER.

Discussion: Initial stratification based on typical disease characteristics could guide the need to test for AQP4/MOG Ab. Identification of key clinical and MRI features may properly differentiate MS from NMOSD/MOGAD or atypical cases, without the support of serological tests.

Conclusions: We suggest that AQP4/MOG Ab testing should be performed according to clinical/MRI presentation, in the presence of features typical for NMOSD/MOGAD or atypical for MS.

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## TOPOGRAPHICAL DISTRIBUTION OF BRAIN WHITE MATTER LESIONS VISUALIZED BY MRI IN PATIENTS WITH MULTIPLE SCLEROSIS AND MARKERS OF BETTER EXPLANATION OF THE DIAGNOSIS

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Objective: The specificity of the diagnostic criteria for Multiple Sclerosis (MS) is suboptimal [1], especially in patients carrying a least one red flag for better explanation without fulfilling criteria of other diseases (MS plus). Frequency of brain white matter lesion lesion (WML) in typical location (juxtacortical, juxtaventricular, infratentorial), a MRi marker easily detectable by routine conventional MRi, is not included in the diagnostic criteria and its association with MS is unknown. In this study this marker will be evaluated in MS and MS plus patients versus a reference standard of MS as the "central vein sign" (CVS) a MRi marker currently detectable mainly in research setting.

Materials: Monocentric retrospective study in MS and in MS-plus patients stratified according to the CVS perivenular lesions frequency(>50%threshold), evaluating the frequency of WMLs in location typical for MS.

Methods: Each patient underwent a standardized MRi examination, including FLAIR* sequences. In each patient stratified according to presence of the CVS, frequency of WML lesions in typical MS sites was classified.

Results: Definite MS patients (n=28; 100% CVS+) and MS plus (n = 59), were included. Out these 32 (53%) had >50% PVL (CVS+). The proportion of WMLs in the typical MS sites was similar in MS and in MS-plus patients fulfilling the CVS (59% and 57%, respectively). In the CVS negative MS plus patients, the proportion of WMLs in the typical MS sites was significantly lower (22%) compared to the other two groups ($p < 0.0001$). This marker predicted CVS positivity with 89% specificity and 85.7% positive predictive value (PPV). On the contrary sensitivity and negative predictive value of this marker for detecting MS seems low (64% and 71.4% respectively).

Discussion: Frequency of WMLs in typical MS lesion sites segregates with the CVS ad therefore with MS with remarkably good specificity and PPV.

Conclusions: These data shows that WML lesion frequency in typical MS site is helpful for increasing MS diagnostic criteria specificity and confirm also that in the MS-plus cases with low WML frequency in MS typical sites, MS diagnosis should postponed and confirmed by CVS analysis. In CVS negative cases a "better explanation" of the diagnosis should be further searched.

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## AGE DEPENDENT EFFICACY OF MULTIPLE SCLEROSIS TREATMENTS: A STUDY FROM THE ITALIAN MULTIPLE SCLEROSIS REGISTER

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Objectives: A meta-analysis of 38 clinical trials published in 2017 showed that disease-modifying therapies (DMTs) efficacy decreased with age and that after age of 53 there was no predicted benefit. On the other side, peak-age prevalence of people with Multiple Sclerosis (pwMS) is shifting towards 55-59 years and nation-wide registry data show that DMTs continue to be commonly prescribed in pwMS >60 years. In our study we evaluated age-dependent efficacy of DMTs in a real-world population of Relapsing Remitting Multiple Sclerosis (RRMS) patients.

Materials: We studied a real-world population of RRMS patients extracted from the Italian Multiple Sclerosis Register.

Methods: In this multicentric, retrospective, cohort study based on prospectively acquired data from the Italian Multiple Sclerosis Register, 22196 pwMS were extracted with the following inclusion criteria: diagnosis of Clinically Isolated Syndrome (CIS) or RRMS, at least four Expanded Dysability Status Scale (EDSS) evaluations, at least 2 years follow up. We evaluated confirmed disability accumulation (CDA), defined as 24 weeks confirmed EDSS increase from study baseline (1.5 points if baseline EDSS=0; 1.0 point if EDSS>1.0 and <5.5; 0.5 point if EDSS>6.0), and determinants of CDA performing a logistic regression analysis with the following covariates: age, sex, disease course, disease duration, EDSS, number of relapses at baseline and class of efficacy of DMT (platform vs high efficacy).

Results: After 2 years follow up 3178 pwMS had CDA; these patients, at baseline, were older (39,8+11,3 vs 36,5+10,9; p<0,001), had greater EDSS (2,2+1,5 vs 2+1,3; p<0,001), had longer disease

duration (7,2+7,7 vs 6+7; p<0,001) and were less frequently treated with a high-efficacy DMT as first DMT (4,5% vs 5,9%;p=0,002). In the logistic regression analysis older age at baseline (OR 1,29, CI 1,25-1,35, p<0,001), a multifocal onset (OR1,24, CI1,1-1,39, p<0,001), a greater number of relapses before baseline (OR1,07, CI1,06-1,09, p<0,001), and platform therapies (OR1,26, CI1,04-1,51, p=0,016), resulted as predictors of CDA in the first 2 years of follow up.

Discussion: In this real-world population of CIS and RRMS patients older age at DMT start was associated with decreased efficacy in terms of disability worsening prevention. However, independently of age, early treatment with high efficacy DMTs reduced the risk of disability accrual.

Conclusion: This study adds evidence that DMT efficacy could be age-related; early high efficacy treatment confirms to be the best treatment strategy.

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## CGRP BEYOND MIGRAINE: EXPLORING ITS SERUM AND CSF LEVELS IN MULTIPLE SCLEROSIS

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Background: Multiple Sclerosis (MS) is a disease of the central nervous system (CNS) characterized by progressive demyelination and inflammatory process. While the exact etiology of MS remains unknown, it relies on an autoimmune process that includes the activation of microglia and localizes at the perivenular site. Calcitonin Gene Related Peptide (CGRP) is a neuropeptide ubiquitous in the peripheral and CNS, mostly known for the role in vasodilation and pain signal transmission during migraine attacks. Recent studies have been unraveling its immunomodulatory properties, showing both anti and pro-inflammatory effects.

Objective: In this study we evaluated soluble CGRP, determined at MS diagnosis in cerebrospinal fluid (CSF) and serum, and correlated its levels with progression and short-term disease severity.

Patients and Methods: We enrolled for a retrospective cohort study 59 patients (39 females, mean age at diagnosis 38.79 years ± standard deviation or SD 9.89) with Radiological Isolated Syndrome (RIS), Clinical Isolated Syndrome (CIS) and Relapsing-Remitting (RR) MS. During the diagnostic work-up were collected clinic-demographic data, serum and CSF. Patients were followed with clinical visits in which clinical data were collected. CGRP levels were determined through an ELISA commercial kit (MyBioSource Inc, MBS267126, San Diego, CA, USA). None had a history of migraine attack at diagnosis. Statistical analyses were conducted with STATA software to determine Mann–Whitney, Kruskal-Wallis test and Spearman's rank correlation coefficient significance.

Results: CGRP levels were significantly higher in MS patients if compared to healthy controls published by Papiri et Al. [1] and Han et Al. [2]. Mean values resulted 73.10 pg/ml in serum (±9.42 vs 29.50 ± 8.91, p<0.05 t-test) and 64.01 in CSF (± 10.39 vs 52.05 ± 5.70, p<0.05 t-test). CGRP levels did not relate to clinical variables at diagnosis: age, gender, Expanded Disability Status Scale (EDSS), number of T2, gadolinium enhancing and spinal cord lesions. However, there was a positive correlation between serum CGRP and the Multiple Sclerosis Severity Score (MSSS) at the last follow up (r^2 = 0.27, p<0.05 Spearman's rank correlation).

Discussion: We observed an increased CGRP level in the CSF and serum of MS patients at diagnosis. Our study firstly evaluated this biomarker both in CSF and serum and subsequently confirmed and expanded on its possible role in identifying cases with poor prognosis, as suggested by the work of Al-Keilani et Al. [3]. However further research is needed to better understand the potentials of this neuropeptide in MS.

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## MICROCHIMERISM AND MULTIPLE SCLEROSIS: THE IMPACT OF FETAL MICROCHIMERIC CELLS ON MATERNAL CLINICAL AND OPHTHALMOLOGICAL FEATURES

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Introduction and Aims: Multiple sclerosis (MS) is a chronic disorder characterised by inflammation and neurodegeneration. Pregnancy is considered a protective factor in MS in the short-term, while evidence on its long-term effects remain inconclusive. During pregnancy, fetal microchimeric cells (fMCs) migrate to maternal blood and tissues, where they can survive for decades. A role for fMCs as a possible long-term factor influencing MS course could be hypothesised, although the available data are still limited. The aim of this study was to investigate the effect of fMCs on MS features.

Methods and Materials: We enrolled 14 female MS patients, including 7 nulliparous patients and 7 parous patients. Each patients underwent (1) blood test analysis using real-time qPCR to amplify Y chromosome-specific sequences and identify XY fMCs, (2) a clinical assessment, including Neurostatus, Multiple Sclerosis Functional Composite (MSFC), and Brief International Cognitive Assessment for MS (BICAMS), and an optical coherence tomography (OCT) scan using Toccon DRI OCT Triton machine to obtain data on retinal nerve fibre layer (RNFL) and ganglion cell-inner plexiform layer (GCIPL) of the optic nerve. Multiple regression models and mixed regression models with adjustments were performed to evaluate the relationship between

fMCs and disease features testing the possible effects of confounding factors.

Results: We found that 3 nulliparous patients and 5 parous patients were positive for fMCs (fMCs+), while no fMCs were detected in the remaining 6 patients (fMCs-). The prevalence of fMCs was non-significantly higher in parous patients (71.4% vs 42.9%, p=0.280) and fMCs- had a longer interval from last pregnancy (174.8±131.1 vs 478.5±72.8, p=0.031). At onset, the involvement of brainstem was more frequent in fMCs+ (62.5% vs 0.0%, p=0.004). At diagnosis, the same group reported more gadolinium-enhancing lesions (0.7±0.8 vs 0.4±0.5, p=0.018), although a trend towards a difference for higher number of T1-weighted lesions in fMCs- was detected (0.7±0.8 vs 2.0±0.0, p=0.059). fMCs- also reported higher frequencies of previous optic neuritis (0.1±0.3 vs 0.8±0.8, p=0.046), although no differences were detected in RNFL and GCIPL thickness (p>0.050). Finally, although an unbalance was detected comparing z-scores from cognitive tests, the differences were not significant (p>0.050).

Discussion: Our findings showed different trends in the involvement of brainstem and optic pathway and in lesion load between patients with and without fMCs, letting hypothesise that the disease features could be influenced by fMCs.

Conclusion: These preliminary results support the hypothesis of a possible role for fMCs in the biological processes underlying MS.

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## A CASE OF VERY LATE-ONSET NEUROMYELITIS OPTICA SPECTRUM DISORDER MIMICKING ANTERIOR ISCHEMIC OPTIC NEUROPATHY


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Introduction: The most common cause of isolate acute optic nerve damage in the elderly is acute ischemic optic neuropathy (AION); while the typical age of onset of optic neuropathy (ON), in particular neuromyelitis optica spectrum disorder (NMOSD), is between 30-40 years. Nevertheless, there is growing evidence about the possibility of a late or of a very late onset (VLO) NMOSD, i.e. respectively over 50 and over 70 years old at onset.

Case description: An 82-year-old male presented to hospital with a sudden-onset painless loss of vision in both eyes. Neurological examination revealed loss of the inferior region of the right visual field and of the superior region of the left visual field. A CT scan of the brain and an angiography of the cranial vessels excluded an ischemic attack. Hence, he was initially suspected of AION, however coherence tomography (OCT) and fluroangiography were negative. In the following days, the patient's condition worsened: he was almost blind from both eyes. Unexpectedly, a brain magnetic resonance imaging (MRI) showed a T2-hyperintensity and a gadolinium-enhancing lesion in T1 in the left optic nerve. In consideration of a serum positivity for anti-AQP4 antibody (titer 0.68), a diagnosis of VLO-NMOSD was made. The patients received high-dose glucocorticoid treatment and successive rescue therapy with plasmapheresis with slowly and partial recovery. He was discharged whit a chronic immunosuppressive treatment with azathioprine. At the last follow-up, he showed clinical stability; azathioprine was well tolerated in absence of adverse events (AEs).

Discussion: The acute-onset, the altitudinal vision loss, the patient's vascular risk factor (hypertension) and in particular the age of the patient were all strongly suggestive of AION. NMOSD has been rarely described in elderly patients (onset over 70 years); however, VLO-NMOSD in patients over the age of 80 is even rarer. According to the current data, it is characterised with a poor prognosis because of high disability and mortality rate. Therefore, an early diagnosis and prompt treatment is crucial, even if in these patients the use of high steroids treatment and, in particular, of strong immunosuppressive agents is not always possible for the higher risk of AEs.

Conclusions: Even in the elderly, a diagnosis of NMOSD should be considered for patients with the with acute painless vision loss. Despite the importance of early treatment, close monitoring for drug-related side effects throughout the disease course is vital in elderly individuals.

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## SIPONIMOD FROM FINGOLIMOD DIRECT SWITCH IN PATIENTS TRANSITIONING IN SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS: A CASE SERIES


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Introduction: Fingolimod (Gilenya® - FIN) and siponimod (Mayzent® - SIP) are both sphingosine-1-phosphate (S1P) receptor modulators approved for relapsing form of multiple sclerosis (RMS). The concept of RMS applied by the European Medicines Agency (EMA) for regulatory purposes includes both relapsing remitting MS and secondary progressive MS with relapses. Nevertheless, solely SIP showed a documented reduction in disability progression in an active secondary progressive multiple sclerosis (SPMS) cohort of patients. Therefore, in patients transitioning to SP course, an early switch from FIN to SIP could determine a better prognosis in the long term.

Objectives: The main objectives of this charts review were to evaluate the efficacy, in terms of annualized relapse rate (ARR) and radiological activity, and safety in the patients who switched to SIP.

Methods: The study population included all the patients who switched directly from FIN to SIP due to transitioning to SP course at the Multiple Sclerosis (MS) Center of the University Hospital Policlinico of Bari. The patients were extracted from Italian MS Registry

Results: In April 2023, we extracted data of nine MS patients who had switched directly from FIN to SIP. The mean time of FIN washout was of 10 ±6.17 weeks, during which four patients assumed steroid

therapy to reduce rebound risk4 after FIN withdrawal. The mean age at first administration of SIP was 50.22±9.76 years. During SIP exposure the patients presented clinical stability, in particular, we found a significative reduction of the ARR during FIN (0.56%) and SIP (0%). Only one patients presented radiological activity during SIP. In regard to safety, we registered only one adverse event during SIP, a grade 4 lymphopenia for which the treatment was interrupted. The incidence of grade 3 and 4 lymphopenia resulted higher during SIP than during FIN exposure.

Conclusions: Our data showed that the direct switch from FIN to SIP in patients transitioning in SP course is associated with clinical and disability progression stability. There were no safety concerns to declare.

Further research with larger populations is needed to confirm these results.

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## LESION PHENOTYPING USING QSM IN PEDIATRIC AND ADULT MULTIPLE SCLEROSIS

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Objectives: To compare different multiple sclerosis (MS) lesion phenotypes distribution in pediatric and adult MS.

Materials: A sample of pediatric and disease duration matched-adult MS patients underwent a 3T-MRI brain exam including T2-FLAIR, T1-MPRAGE and 3D echo-planar imaging (EPI) sequences. EPI was used to obtain Susceptibility Weighted Imaging (SWI) and Quantitative Susceptibility Mapping (QSM) with an isotropic resolution of 0.65 mm.

Methods: White Matter Lesions (WMLs) were classified as Paramagnetic Rim Lesions (PRLs), Hyper-intense lesions (HILs) or iso-hypo intense lesions on the basis of QSM appearance by two independent raters. SWI was used to support WMLs classification by identifying QSM hyperintensities ascribable to veins.

Results: Fourteen pediatric- and fifteen adult-RRMS patients were included in the analysis with a mean (SD) age of 16.1 (2.1) and 22.8 (10.6) respectively. Mean (SD) disease duration was 2.2 (1.9) years [Pediatric MS: 2.5 (2.1); Adult MS 2.0 (1.8)]. No differences in EDSS score ($p = 0.49$), total lesion burden ($p = 0.66$) and total brain volumes ($p = 0.70$) were found. 577 lesions were analyzed; 123/577 lesions were excluded due to infratentorial position, confluent shape or movement artifacts. PRLs were found in 6/14 (43%) of pediatric and 8/15 (53%) of adult MS patients. PRLs represented 6% of WMLs in pediatric (0.86 per subject) and 10% (1.73 per subject) in adult MS ($p =0.27$), with 1/14 pediatric and 2/15 adult patients exhibiting ≥4 PRLs. A trend toward a higher number of HILs both expressed as number per subject [mean (SD): 3.6 (3.1) in pediatric MS and 1.6 (2.1) in adult MS; $p = 0.05$] and as a percentage with respect to total lesion (20% in pediatric MS and 9.9% in adult MS; $p = 0.03$) was noted in pediatric MS patients. No differences were found in iso-hypointense lesion number ($p= 0.45$) and percentage ($p= 0.41$).

Discussion: PRLs are considered a biomarker of chronic inflammation in MS. Although PRLs seem to be associated with an older age and a longer disease duration they have been detected since the early phases of the disease. PRLs distribution largely overlapped between pediatric and adult MS in our sample. Pediatric patients showed a slightly higher prevalence of HILs which have been associated with chronic inactive lesions with potential for remyelination.

Conclusions: Although older age may favour PRLs formation, chronic inflammation seems to arise in a similar fashion in pediatric MS as compared to adult patients with a similar disease duration.

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## OPTIC NERVE IMAGING WITH OPTICAL COHERENCE TOMOGRAPHY IS ABLE TO PREDICT DISEASE PROGRESSION AND TO MONITOR CEREBRAL AND SPINAL CORD ATROPHY IN PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS (PPMS)

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Background: A previous international study using optical coherence tomography (OCT) in MS patients (mostly with a relapsing phenotype), found that a lower retinal nerve fiber layer (pRNFL) (≤87µm) was linked to a higher risk of confirmed disability progression (CDP). Our study aimed to [1] compare disease characteristics based on this pRNFL threshold, and [2] assess the predictive value of this threshold in primary progressive MS (PPMS) patients.

Materials and Methods: Retrospective study including PPMS patients with OCT; demographic, clinical, and MRI data were collected. Brain volumetric measures and spinal cord cross-sectional area (SCA) were obtained from a filled brain 3D MPRAGE sequence using Statistical Parametric Mapping and Spinal Cord Toolbox. Group comparison (pRNFL ≤87µm and >87µm) was done as appropriate. Partial Pearson (rp) correlation analysis (adjusted for age and MRI machine) was used to evaluate OCT and MRI association. A univariate survival analysis and a multivariate Cox regression analysis were done to evaluate the ability of pRNFL≤87µm to predict CDP (defined as a confirmed ≥1 point increase in the EDSS score or ≥0.5-point increase for patients with a baseline score of ≥5.5), adjusting for age, disease duration, sex, and baseline disability.

Results: 69 PPMS patients were analysed, 21(31%) with pRNFL≤87µm, mean follow-up: 2.3 years (SD 1.3). Compared to pRNFL>87um, in the pRNFL≤87um group a higher proportion of patients presented a higher number of spinal cord lesions (≥3 lesions:

89% vs 68%, p=0.001) and lesions at the bulbomedullary junction (75% vs 43%, p=0.001). pRNFL showed a positive correlation with grey matter (rp=0.332, p=0.048), white matter (rp=0.457, p=0.005), brain parenchymal (rp=0.463, p=0.005) fractions, and SCA (rp=0.441, p=0.007). 17/58 patients (29%) presented CDP after a mean time of 1.4 years (SD 0.92). Patients with pRNFL≤87µm had a significantly higher probability of experiencing CDP (47% vs 21%, p=0.001), and the progression occurred at a faster rate: at 2 and 4 years, 83% of patients with pRNFL≤87µm experienced CDP, while 25% and 45% with pRNFL>87µm did so (p=0.027). In multivariate Cox regression analysis, pRNFL≤87µm was the only measure that predicted CDP (aHR 3.44, 95%CI 1.21-11.30).

Conclusions: PPMS patients with pRNFL thickness ≤87µm had a higher risk for disability worsening adjusting for disease duration, sex, and baseline disability. This supports pRNFL thickness as a biomarker for predicting disability worsening in PPMS, aiding treatment decision-making.

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## PHARMACOGENOMICS OF CLINICAL RESPONSE TO FIRST-LINE TREATMENTS IN MULTIPLE SCLEROSIS: A MULTI-CENTRIC STUDY

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Aims: To conduct a multi-centric unbiased genome-wide screen to identify genetic predictors of response to first-line treatments (dimethyl fumarate, interferon and glatiramer acetate) in multiple sclerosis (MS) patients.

Material and Methods: We included MS patients from different centers using a harmonized protocol to standardize clinico-demographic variables. Inclusion criteria comprised relapsing-remitting MS at drug start and follow-up for 4 years. Imputation yielded ~4.7M autosomal common variants after quality control for downstream analyses. Association analyses with the number of relapses occurring in 2 years of follow-up were carried out by fitting negative binomial regression models, adjusting for gender, age, disease duration, number of relapses 1 and 2 years before drug start and principal components to control population sub-structure, using duration of treatment exposure as an offset in the models. Rate ratios were meta-analyzed across centers with an inverse-variance weighted meta-analysis, under a fixed effect model.

Results:1802 patients were included for Interferons, 962 for dimethyl fumarate and 705 for glatiramer acetate from different European countries including Italy, Belgium, Denmark, Germany, Norway and Sweden. Strongest signals of associations were rs10835054, located at the 3'UTR of a gene named SLC5A12 (p=2.68*10-8) for Interferons, rs34140003 in the intronic region of an uncharacterized non coding RNA named LOC107984282 (p=4.91*10-8) for dimethyl fumarate and rs150307803 (p=2.68*10-8) in an intergenic region between LINC00659 and MRGBP and rs78852235 (p=4.08*10-8) in an intronic region of MAP3K1 gene for Glatiramer Acetate.

Discussion: Inter-individual differences in treatment response are marked in Multiple Sclerosis (MS), with only a paucity of body-fluid biomarkers aiding clinicians to individualize optimal drug choice. This includes first-line treatments, where a subset of patients displays suboptimal treatment response.

Conclusion: This large, unbiased genome screen of response to first-line treatments suggests potential variant candidates which are deemed for further investigations.

## THE RELATIONSHIP BETWEEN COGNITIVE IMPAIRMENT, RETINAL DAMAGE AND BRAIN ATROPHY IN MULTIPLE SCLEROSIS: AN OCT-MRI STUDY

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Introduction: Multiple sclerosis (MS) is one of the most common chronic, inflammatory, demyelinating and neurodegenerative diseases involving the central nervous system. Cognitive impairment (CI) is a common and debilitating feature of MS, occurring in 40-65% of patients. MRI showed how brain atrophy in many cortical and subcortical structures is highly correlated to such cognitive impairment in MS patients. Optical Coherence Tomography (OCT), with the measure of retinal layers thickness, represents a rapid, low-cost, noninvasive and well-tolerated alternative to MRI in the evaluation of neurodegeneration in MS.

Objective: In order to understand whether retinal damage could be a good marker, as well as brain atrophy, of cognitive impairment in people with MS (pwMS), our objective was to identify the relationship between cognitive performance, retinal damage, and brain atrophy in pwMS.

Materials and Methods: One hundred pwMS were consecutively enrolled at our MS Center. For each patient we performed: (i) Neurological examination; (ii) Cognitive assessment by means of the Brief Repeatable Battery of Neuropsychological Tests and STROOP Test;

(iii) 3T-MRI scan for the evaluation of the brain lesion load and brain volumetric measures using SIENAx software on 3DT1 refilled images; (iv) OCT for the evaluation of the peripheral retinal nerve fiber layer (pRNFL) thickness. Analyses were performed by means of SPSS, version 25. Pearson's r coefficients were calculated to assess the possible association between cognitive performance, pRNFL mean thickness and brain volumes. A p-value ≤0.05 was considered the threshold of statistical significance.

Results: We found a significant correlation between pRNFL thinning and worse cognitive performance measured by SDMT, and STROOP tests, showing a relationship between retinal thickness and information processing speed (IPS) and executive functions in pwMS. Moreover, white matter (WM) involvement, measured by T2 lesion volume (T2LV) and normalized white matter volume (nWMV), also showed a relationship with cognitive performance in the same cognitive domains (IPS and executive functions). As expected, normalized gray matter volume (nGMV) and normalized brain volume (nBV) showed a significant correlation with cognitive performance in many cognitive domains: IPS, memory, executive functions.

Conclusions: Our results showed a relationship between retinal damage and cognitive performance in the same cognitive domains (IPS and executive functions) related with WM damage. Our study showed that retinal damage (measured by OCT) is a good marker for cognitive decline in pwMS, further highlighting the role of OCT as a rapid, low-cost, well-tolerated and noninvasive tool for pwMS evaluation.

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## BREAKTHROUGH PRIMARY VARICELLA PNEUMONIA IN A PATIENT WITH SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS TREATED WITH SIPONIMOD: A CASE REPORT


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Introduction: Varicella (chickenpox) is a common contagious infection caused by Varicella Zoster Virus (VZV), affecting mostly childhood, but with increasing incidence in adults. Varicella pneumonia, although rare, is a serious complication of VZV infection in adults. S1PR modulators, such as recently approved siponimod, are associated with increased rates of herpesvirus infections, both primary and secondary.

Objectives: To describe a case of breakthrough primary varicella pneumonia despite varicella vaccination and seroconversion, in a patient with active secondary progressive multiple sclerosis (SPMS) under treatment with siponimod.

Methods: Case report.

Results: We report the case of a 48-year-old woman who came to our attention in 2021 complaining of recent balance disorder, bladder dysfunction and progressive bilateral lower limb motor deficit; the clinical onset had probably been in 1999 with right leg motor deficit. On the basis of clinical history, MRI (multiple demielinating lesions of brain and spine), and CSF analysis (oligoclonal bands with a type II pattern), a diagnosis of active SPMS was made and treatment with siponimod was proposed; however, since the basement serological assessment showed the absence of neutralizing antibodies against VZV, the patient started beta-IFN1b and received two doses of vaccination against VZV in the meanwhile. Once immunized (VZV IgG 427 mUI/mL), she started siponimod in December 2021. At the end of March 2023, 15 days after coming into contact with a person with herpes zoster, the patient started having fever, cough, headache and diffuse skin rash. She was hospitalized in isolation and started on intravenous acyclovir, while treatment with siponimod was interrupted. The CT scan showed signs of bilateral interstitial pneumonia. VZV DNA was detected in skin lesions. Five days after siponimod discontinuation, the patient started having diplopia. In order to exclude neurological complications of VZV, a contrast enhanced brain MRI + MRA and a lumbar puncture to detect VZV DNA and meningitis/encephalitis pathogens, were performed: all negative. After two weeks of acyclovir treatment, the neurological symptoms were improving, the skin rash had resolved and the patient was asymptomatic for pneumonia.

Conclusion: To our knowledge, this is the first described case of breakthrough primary varicella in a MS patient treated with siponimod. Is is important to suspect VZV infection even in immunized patients, as early identification and treatment can improve the outcome.

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## UNUSUAL REBOUND AFTER FINGOLIMOD DISCONTINUATION MIMICKING STROKE IN A MULTIPLE SCLEROSIS PATIENT


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Objectives: We report the case of a multiple sclerosis female patient, 42 years old, who presented an acute neurological deterioration with a challenging radiological finding, following a therapeutical shift.

Methods and Results: The patient was diagnosed with Multiple Sclerosis in 2004, with a highly active disease during the first years. In 2012 treatment with fingolimod was started, with clinical and radiological stability until August 2022, when MRI showed two new demyelinating lesions, in the frontal lobe and in the cervical medulla. A therapeutic shift was planned. Fingolimod was interrupted; fifteen days after stopping fingolimod the patient reported a mild facial-brachial sensitive impairment, resolved with oral prednisone for few days. MRI didn't show any new lesion. Therapy with ofatumumab was started

after a wash out period of 40 days. After three months of ofatumumab treatment, the patient complained about sensitive impairment on the right side and gait imbalance; she underwent MRI scan that revealed a new small left thalamus-capsular lesion, hyperintense inT2-weighted and DWI images, without contrast enhancement. Radiological report was of an acute vascular ischemic lesion and diagnosis was confirmed by a different neuroradiologist on a new MRI scan. Antiplatelet therapy was started and vascular screening exams were performed. After initial fluctuation in the severity of neurological deficit, without substantial changes of radiological finding, between day 21 and 28 from the onset, neurological deficits got worse progressing to right hemiplegia, severe visual impairment, dysarthria and dysphagia. A fourth MRI scan showed an evolution of the left thalamus-capsular lesion to a pseudotumoral lesion with mass effect involving left optic nerve and brainstem, without contrast enhancement. Lumbar puncture was performed: CSF analysis was negative for JCV DNA and cytochemical parameters were in the normal range. High dose i.v. methylprednisolone treatment was started and antiplatelet therapy stopped, with a subsequent gradual clinical and radiological improvement.

Discussion: The presented case was challenging because of the atypical radiological finding, initially mimicking a stroke, then evolving into a pseudotumoral inflammatory lesion without contrast enhancement. This particular disease activity should be considered a rebound after fingolimod discontinuation (even if atypical for its timing of onset), that anti CD20 treatment didn't prevent, possibly because of its latency in being effective.

Conclusions: Because of the various therapeutic options now available, sequencing therapies in MS is frequent and still more experience is needed to manage the delicate phase of shifting.

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## AN ATYPICAL WERNICKE'S ENCEPHALOPATHY PRESENTATION WITH PAPILLEDEMA AFTER SLEEVE GASTRECTOMY


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To raise awareness of Wernicke's encephalopathy diagnostic challenge outside the alcohol-related, classic triad of symptoms. We present the case of a 19 years old woman who started to vomit a month after she underwent a sleeve gastrectomy for obesity with no obvious complications. On admission she had a negative abdominal exam, increased bilirubin and transaminases. A biliary tree stenosis was ruled out. A gastroscopy showed gastritis. She was treated with antiemetics and parenteral nutrition and stopped vomiting. A few days after she complained of reduced sensation in the lower limbs from the knees up to the umbilical line. She had a painful sensation in the perineal region without saddle anaesthesia or sphynteric disfunction and referred of pain in the right shoulder. Her neurological examination was unremarkable. A thoracic and lumbo-sacral mri of the spine was normal. A functional disorder was suspected and she was referred to the bariatric surgery psychologist. The day after she complained of blurred vision and she couldn't walk or stand. The ophthalmologist found her to have a severe vision loss with bilateral papilledema and retinal haemorrhages, bilateral VIth cranial nerve palsy with nystagmus both horizontal and vertical in primary position and all gaze directions. A further neurological examination showed also reduced tendon reflexes in the lower limbs with ataxia. She underwent brain and cervical MRI which demonstrated increased signal both on DWI and FLAIR sequences in the paramedian thalamic nuclei, mammillary bodies and periaqueductal area. A diagnosis of Wernicke encefalopathy was made and she was treated with thyamine 200 mg im three times a day for a week, then switched to oral. B1 vitamin level after the first dose were normal. 24 hours later she started to gradually improve. Visual acuity and eye movements were restored, sensation in the lower limbs subjectively improved. She had gait ataxia but could walk. Somatosensory and visual evoked potentials were normal as well as nerve conductions study. Eventually she was transferred to a rehabilitation facility. Wernicke's Encephalopathy (WE) presents with the classic triad in less than a third of cases [1]. The association with papilledema has been rarely described in previous case series [2]. Bariatric surgery, including sleeve gastrectomy, can lead to thyamin deficit especially in young women with vomiting; atypical neurological features are common [3]. Neurologists should be aware of the risk of WE in this clinical setting.

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## IL-1 RS1143634 SNP INFLUENCES CSF INFLAMMATION AND CLINICAL PRESENTATION IN MULTIPLE SCLEROSIS


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Objectives: The clinical course of multiple sclerosis (MS) is critically influenced by interplay between proinflammatory and anti-inflammatory cytokines [1]. Interleukin 1 (IL-1) has been reported as a factor capable of influencing clinical presentation of relapsing remitting MS (RR-MS) [2]. However, only few studies focused on its single-nucleotide polymorphisms (SNPs) in MS.

Materials: We explored in a cohort of 188 RR-MS patients at the time of diagnosis the associations between four IL-1 SNPs (rs315952, rs1143623, rs1143634 and rs1143627). Clinical and biochemical parameters at the diagnosis including age, sex, disease duration, oligoclonal band presence Bayesian Risk Estimate for Multiple Sclerosis (BREMS) score. Clinical disability was also evaluated after three years of follow up in a sub-group of 66 patients treated with low efficacy disease modifying therapy. We also performed a comprehensive neuropsychological assessment including Beck's Depression Inventory (BDI), State-Trait Anxiety Inventory, and Brief Visuospatial Memory Test - Revised (BVMT-R), Symbol digit modality test (SDMT). Finally, we

dosed the concentrations of lactate and group of 14 pro-inflammatory and anti-inflammatory cytokines in the cerebrospinal fluid (CSF).

Methods: Shapiro–Wilk test was used to evaluate normality distribution of continuous variables. Data were shown as mean (standard deviation, SD) or median (interquartile range, IQR). Categorical variables were presented as absolute (n) and relative frequency (%). Chi-square or, when necessary, Fisher exact test, were applied to explore the association between categorical variables. Difference in continuous variables between RR-MS patients and controls was evaluated using nonparametric Mann–Whitney test, considering the high number of variables, we corrected for multiple comparisons using Benjamini-Hochberg (B-H) procedure.

Results: Using Mann-Whitney test we identified an association between rs1143634 A minor allele carriers, TNF-α (p= 0.04) and IL-17 (p=0.09). Investigating clinical characteristic at the diagnosis we found that A minor allele carriers presented also a higher EDSS score at the diagnosis (p= 0.04) and after three years (p=0.05). We also found an association between A minor allele carriers and worse BVMT-R score at the diagnosis (p= 0. 04). No association were found between other SNPs and clinical or inflammatory parameters.

Conclusions: Our results suggest that rs1143634 polymorphism minor allele carriers present a distinct neuroinflammatory phenotype associated with worse disability and visuospatial memory at diagnosis. We also associated the presence of the A allele with worse disability after three years of follow-up.

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## FACTORS INFLUENCING LONGITUDINAL MRI STRUCTU RAL AND COGNITIVE MEASURES IN MOGAD AND MS

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Objectives: In contrast to multiple sclerosis (MS), progression independent from relapses does not occur in Myelin-Oligodendrocyte-Glycoprotein antibody disease (MOGAD) with only rare exceptions. Longitudinal volumetric MRI measures can detect subtle neurological decline before it becomes clinically relevant. In this prospective study, we aimed to compare longitudinal brain MRI measures across MS, MOGAD and healthy controls (HC) and to identify factors influencing these markers of neurodegeneration in MS versus MOGAD.

Materials and Methods: At the Oxford National NMO Service and the Verona MS Centre, 32 MS, 21 MOGAD and 22 HC clinically stable patients were prospectively studied with 3T brain MRIs and cognitive tests (Rao-Battery using modified z-scores) at least 12 months apart. FSL and Freesurfer tools were used to derive annual: % brain volume change (PBVC/y), % cortical thickness change (CThc/y), % deep grey matter structures volume change (DGMVc/y), white matter lesions volumes (WMLV) variation, baseline cross-sectional brain volumetrics, cortical lesions number (CLs), normal-appearing white matter fractional anisotropy (NAWM-FA). ANCOVA and mixed effects models were used.

Results: Baseline demographics were matched as were the EDSS and SDMT scores in the disease groups. Change over time was only significantly different for the mean percentage change of thalamus volume per year (ThalVc/y) in MS group compared to the other two groups (p=0.013). In both MS and MOGAD, PBVC/y was associated with WMLV variation and ThalVc/y while in only the MS group it was associated with CLs and hippocampus volume change per year (HypVc/y). In MOGAD, CThc/y was associated to DGMVc/y (p=0.040) and WMLV variation (p<0.001). In both MS and MOGAD, DGMVc/y was related to corpus callosum volume change per year (p=0.01 and p=0.002 respectively). In MOGAD, delta SDMT z-score was associated to PBVC/y (p=0.034) and DGMVc/y (p=0.021) while in MS delta SDMT z-score was found associated with CLs (p=0.006).

Conclusions: Our prospective study shows that 1) thalamus volume change could distinguish MS from MOGAD, 2) white matter lesions and subcortical structures volume variation influence the longitudinal brain volumetrics and cognitive measures in both MOGAD and MS and, 3) CLs influence the longitudinal brain volumetrics and cognitive measures in MS.

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## MULTICENTRE PROSPECTIVE REAL-WORD STUDY ON THE SHORT-TERM EFFICACY AND TOLERABILITY OF OFATUMUMAB IN PATIENTS WITH RRMS: A PRELIMINARY STUDY

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Objectives: Ofatumumab is the first fully human anti-CD20 monoclonal antibodies (mAb) for the treatment of MS. Ofatumumab has similar clinical efficacy to, and more favorable safety and tolerability profiles than other highly efficacious mAb disease modifying drugs (DMDs)

due to its subcutaneous administration. However, real-world data on efficacy, safety, tolerability, patient's reported outcomes (PROs), and relationships with previous therapies and serum immune profiles have been not described yet. In this preliminary multicentre prospective study we aimed to verify the real-world efficacy of ofatumumab on clinical, MRI activity, PROs scores measures and to explore its effect on lymphocytes subpopulations, serum cytokines, and chemokines levels measured before and after the ofatumumab treatment initiation.

Materials and Methods: 47 MS patients (72.3% female, mean age 37.3 ± 9.7, median EDSS 2 (range:0-7)) were enrolled at the time of Ofatumumab initiation (T0) due to inefficacy, intolerance, and safety using another disease-modifying treatment or due to highly active disease at the time of diagnosis. Expanded disability status scale (EDSS), reports of adverse reactions, Symbol-Digit-Modalities tests (SDMT), Modified Fatigue Impact Scale (MFIS), Depression, Anxiety and Stress Scale-21 (DASS-21), Multiple Sclerosis Impact Scale-29 (MSIS-29), Multiple Sclerosis Neuropsychological Questionnaire (MSNQ), Treatment Satisfaction Questionnaire Medication (TSQM) were recorded at T0, after 1 month (T1), 3 months (T3), 6 months (T6). Serum samples were collected at T0 and T6 and bioplex-multiplex analysis was performed. 3T MRI with contrast data was collected before starting the therapy and at the T3 timepoint.

Results: Of the 47 RRMS patients, naïve patients were 25.5%, patients switching from a first-line therapy (teriflunomide, glatiramer acetate, IFN-beta, dimethyl fumarate) were 25.5% while those switching from a second-line therapy (S1PR-inhibitors and natalizumab) were 49%. At 6-months of follow-up, no patients relapsed. Two patients (6.6%), presenting gad-enhancing lesions during natalizumab treatment, showed persistent gadolinium-enhancing lesions at MRI performed at 3 months from ofatumumab initiation. Injection-related adverse reactions were more frequent during the first months of therapy ($p<0.001$), while infections were mild and occurred randomly during the follow-up. CD 19+ B cells were completely suppressed within one month from the ofatumumab initiation independently of the proceeding therapy ($p<0.001$). Interestingly, the treatment appeared to improve MS related quality of life measured by MSIS-29 when comparing T0 and T3 timepoints ($p=0.039$).

Conclusions: Ofatumumab treatment appears to be effective and safe either in naïve patients or in switching from other highly effective treatments and seems to improve the impact of MS-related quality of life.

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## SUBACUTE ONSET HEMIPARESIS IN A PATIENT AFFECTED BY MULTIPLE SCLEROSIS UNDER NATALIZUMAB THERAPY: LOOKING FOR AN ANSWER IN OCCAM'S RAZOR


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The subacute onset of a focal neurological deficit in a Patient affected by Multiple Sclerosis under Natalizumab therapy for more than two years and with a high JCV index, always leads the clinicians' suspect they are facing a Progressive Multifocal Leukoencephalopathy (PML). However, when the clinical, laboratory and radiological findings are not completely suggestive of such diagnosis, other possible conditions as Multiple Sclerosis relapse, other infectious diseases of the Central Nervous System (CNS) and haematological disorders, should be taken into consideration [1]. We present a case of subacute onset of right facial-brachial-crural paresis and dysarthria in a patient with the aforementioned characteristics whose diagnostic workup was complicated and still full of unsolved questions. Three lumbar punctures were performed and high sensitivity PCR for JCV was always negative. On the other hand, both the clinical evolution and brain MRI features were strongly consistent with a possible PML [2,3]. Sometimes the final diagnosis cannot be made on the basis of the commonly accepted diagnostic criteria, but it is a result of the clinician's interpretation of the clinical and paraclinical elements and the evolution of the course of the disease. Occam's razor, the principle according to which the simplest explanation is the best one, fits perfectly with our case.

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## LONGITUDINAL CHANGES IN HIPPOCAMPAL SUBFIELD VOLUMES OF RELAPSING REMITTING MULTIPLE SCLEROSIS PATIENTS


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Background: Neuronal loss has been considered irreversible in the adult human brain for a long time. However, recent evidence demonstrated that neurogenesis occurs in adult human brain in the dentate gyrus of hippocampus and in the subventricular zone. A few studies suggested neurogenesis can follow a damaging stimulus, such as lesion formation in multiple sclerosis (MS). Due to the coexistence of neurogenesis and neurodegeneration, the hippocampus represents an interesting structure to analyze the interplay between these two processes in MS patients.
Objectives: To identify longitudinal trajectories of hippocampal subfield volume loss and the contribution of its progression in determining clinical disability and cognitive impairment.

Methods: Using a 3T scanner, 3DT1- and T2-weighted images were obtained from 62 early relapsing remitting MS patients at baseline and yearly for a maximum of 5 years, together with clinical and cognitive evaluation. Hippocampal subfields were segmented by using Freesurfer version 7.2.0. Algorithms of growth models by alternating conditional expectation were used to assess long term trajectories of hippocampal subfield volume changes, and linear regression models were used to assess the relationship of a progression index of thalamic damage with clinical disability and cognitive decline.

Results: Most hippocampal subfields showed progressive volume loss over disease course. Instead, dentate gyrus and cornus ammonis 1 (CA1) – related to neurogenesis – showed a bimodal pattern: early volume stability, then rapid volume decrease, and finally again stability. By using algorithms of growth models by alternating conditional expectation, we were able to identify an index of relative progression $\gamma$, considering the shared variance among hippocampal subfields.

Significant associations were observed between γ and performance at visuo-spatial memory (β=-1.94, p<0.001) and verbal fluency tests (β =-0.94, p<0.001). No significant associations were observed with clinical disability or cognitive decline in other domains.

Conclusions: The different pattern of progression of hippocampal subfield volume loss suggests an initial resilience of hippocampal regions related to neurogenesis, which then experience volume exhaustion after few years of disease. The association observed between γ and cognitive functions makes this index relevant for monitoring specific cognitive abilities.

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## COMPARISON BETWEEN OPTIC NERVE MRI AND OPTICAL COHERENCE TOMOGRAPHY (OCT) IN DETECTING PREVIOUS OPTIC NEURITIS IN PWMS

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Objectives: Few data are available on comparison between optic nerve MRI (ON-MRI) and optical coherence tomography (OCT) efficacy in identifying previous ON neuritis (ONIS) in pwMS. Paraclinical diagnostic criteria for ONIS include: i) abnormal (increased) ON signal on ON-MRI, or ii) inter-eye asimmetry in OCT-derived measures. On this background we aimed to assess diagnostic efficacy of MRI vs OCT criteria in a group of pwMS with and without previous ONIS.

Material and Methods: 101 pwMS were included in the study. MRI signal abnormality of the ON (ON-MRI-A) was detected through review of axial and coronal STIR sequences of the ON. OCT was defined as abnormal if was detected an inter eye difference >4μm for macular ganglion cell+inner plexiform layers (mGCIPL-A) or >5 μm in the peripapillary retinal nerve fiber layer (pRNFL-A).

Results: Eighty pwMS did not have clinical history of ONIS (ON-wo-ONIS), 21 had suffered of monolateral previous (more than 3 months) ONIS (ON-w-ONIS) (11 in the right ON and 10 in the left). No clinical-demographic differences were observed in pwMS with and without ONIS. We observed: pRNFL-A in 90.5% of ON-w-ONIS and in 15.4% of ON-wo-ONIS; mGCIPL-A in 90.5% of ON-w-ONIS and in 20.5% of ON-wo-ONIS; ON-MRI-A in 33.3% of ON-w-ONIS and in 25.6% of ON-wo-ONIS. OCT-A and ON-MRI-A was observed in 33.3% of ON-w-ONIS and 12.5% of ON-wo-ONIS. ROC analysis showed 100% sensitivity and 73.7% specificity in identifying previous ONIS when using OCT-A (area under ROC curve (AUC) = 0.93) criteria; 33.3% sensitivity and 74.4% specificity when using ON-MRI-A (AUC=0.54) criteria; 33% sensitivity and 87.5% specificity when combining OCT-A and ON-MRI-A (AUC=0.6).

Discussion and Conclusions: OCT-A criteria performed better than both ON-MRI-A criteria and the combination of OCT-A and ON-MRI-A criteria in ONIS diagnosis.

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## THE NEW PADOVA EMOTIONAL DATASET OF FACIAL EXPRESSIONS (PEDFE) DETECTS EARLY IMPAIRMENT OF SOCIAL COGNITION IN ACTIVE RELAPSING-MULTIPLE SCLEROSIS: A COMBINED NEUROPSYCHOLOGICAL AND MRI STUDY

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Background: Social cognition is frequently impaired in patients with multiple sclerosis (MS), even from the early stages of the disease [1]. The Padova Emotional Dataset of Facial Expressions (PEDFE) is a new social cognition test for facial emotion recognition (FER) in which subjects are asked to recognize the type and genuineness of different genuine or posed emotions [2].

Aims: Our aim was to test the PEDFE in a group of recently-diagnosed (<2 years from diagnosis) relapsing-MS and controls and to evaluate association with neuropsychological scores and MRI measures of grey matter (GM) atrophy and white matter (WM) macro- and micro-structural damage.

Methods: PEDFE was acquired in 36 relapsing-MS (15 highly-active [HA]-MS and 21 not-HA-MS) and 32 controls, by calculating emotion-type (ET) and emotion-genuineness (EG) scores. Patients also underwent neuropsychological and brain-MRI. Segmentation with FreeSurfer of regional GM-atrophy and WM-lesion probability map were obtained. WM fibre density and cross-section measures were extracted from 72 WM-tracts, using fixel-based analysis (MRtrix and TractSeg software). Spearman correlations with FER-scores and regression analyses were conducted, setting p<0.05.

Results: HA-MS showed reduced EG-scores, but not ET-scores, compared to both not-HA-MS and controls (one-way-ANOVA p=0.008). ET correlated with executive performance at SDMT (p=0.02) and SRT (p=0.006) and with GM thickness in many cortical frontal, parietal and temporal areas. Conversely, EG correlated with GM thickness in cingulum-isthmus and different subcortical GM-volumes. Despite significant correlations between axonal damage within different WM-tracts and PASAT scores (p<0.001) were found, no associations with PDFE were observed. Similarly, WM-lesion load did not affect our PEDFE results.

Discussion and Conclusions: This study tested for the first time the new PEDFE in MS. Our results suggest that PEDFE may represent a valid tool to assess FER in MS, possibly distinguishing different anatomical structures involved in FER, with ET scores that are mostly linked to executive and memory functions, while EG scores that are more related to the limbic system functioning. EG-scores are impaired earlier in active relapsing-MS, possibly detecting early alteration in social cognition. Notably, impairment of social cognition as measured by PEDFE is not linked to WM-damage.

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## VALIDATION OF THE ROAD SCORE IN AN ITALIAN COHORT OF PEOPLE WITH RELAPSING MULTIPLE SCLEROSIS

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Objectives: Scoring the risk of future disability in Multiple Sclerosis (MS) is a big challenge of today's clinical practice. Recently, the Risk of Ambulatory Disability (RoAD) Score was proposed as an useful tool to predict individual prognosis and optimize treatment strategy for MS patients. The score includes both baseline factors and one-year outcomes on platform treatment with a score of >= 4 as the best cut-off score for the risk of reaching EDSS score >= 6. In this study, we evaluated the performance of RoAD score in our cohort of long-term RMS patients.

Materials: We analysed a dataset of RMS patient from our MS centre.

Methods: the cohort included in the study had to be made up of patients who had started platform injectable disease modifying therapies (DMTs) with at least 10 years of follow-up. EDSS at the time of initiation of therapy had to be less than 4.

Results: 255 patients met all inclusion criteria and were included in the analysis. Median RoAD score was 2 with 61(24%) patients having a RoAD score >= 4. At 10-year follow-up, 42(16.5%) patients reached a confirmed EDSS score >= 6. The best RoAD score cut-off for estimating the risk of EDSS score >= 6 was 4 with an AUC of 0.77 (IC 0.70-0.85, p<0.01).

Discussion: In our study we confirmed a RoAD score >= 4 as the best cut-off score for discriminating patients at higher risk of reaching the disability milestone of EDSS score >= 6.

Conclusion: This study confirmed that RoAD score could represent a valuable tool to help the clinician in the assessment of long-term prognosis in patients treated with platform injectable DMTs as first-line treatment.

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## ATYPICAL PRESENTATION OF ALZHEIMER'S DISEASE AND MULTIPLE SCLEROSIS IN A 54-YEAR-OLD PATIENT

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Introduction: Multiple Sclerosis (MS) and Alzheimer's disease (AD) are two neurological conditions that have a significant impact on patients, families, and society. It could be challenging to diagnose AD in a patient with MS, because MS itself can cause cognitive decline, dementia, and brain atrophy. However, little research has been conducted into the coexistence of MS and AD.

Objectives: To describe a 54-year-old female patient that was admitted to our MS centre in June 2022 due to demyelinating lesions on a brain magnetic resonance imaging (MRI) which was indicated due to visual difficulties. The husband reports progressive cognitive difficulties beginning in September 2021 and affecting daily activities such as manipulating or finding objects, driving, navigating her environment, getting dressed, and behavioural disturbances such as delusions. No other clinical events were referred.

Materials and Methods: The patient underwent screening tests such as neurological examination, evoked potentials, brain and spinal MRI, lumbar puncture and cognitive evaluation.

Results: The neurological examination revealed abnormal tendon hyperreflexia; evoked potentials were normal. The MRI showed posterior cortical regions atrophy, altered signal in supratentoral and infratentorial white matter bilaterally, spinal lesions in C2-C3 and D7-D8. The cerebrospinal fluid (CSF) analysis showed the presence of oligoclonal bands, reduced amyloid-β-42 concentration, and increased phosphorylated-tau-levels, while total-tau-levels were normal. No mutations were detected in APP, PSEN1 and PSEN2, C9orf72, TDP-43 and NOTCH3. The neuropsychological evaluation revealed visuo-spatial and visuo-perceptual deficits, simultanagnosia, environmental agnosia, left-right disorientation, neglect, constructional and limb apraxia, although verbal anterograde memory and executive abilities were mostly unaffected.

Discussion: The patient was diagnosed with Radiologically Isolated Syndrome (RIS) and probable presenile onset AD (non amnestic presentation, according to NINCDS-ADRDA criteria) based on his history, CSF levels, MRI findings, and cognitive profile. She began treatment with memantine and was later administered quetiapine due to the presence of behavioural and psychological symptoms of dementia.

Conclusion: This case report adds to the body of data that AD and MS can coexist in the same patient. The potential that AD and MS may both contribute to cognitive decline, possibly with cumulative consequences, warrants further investigation.

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## BRAINSTEM LESIONS IN ADULTHOOD: THINKING OUTSIDE THE BOX

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Introduction: Differential diagnosis of adult-onset subacute brainstem syndromes is very challenging. We report a rare case of late onset isolated brainstem involvement of Myelin oligodendrocyte glycoprotein (MOG)-immunoglobulin G (IgG)-associated disease (MOGAD).

Clinical case: A 61-year-old female patient was admitted in March 2023 to the Emergency Room of our Hospital for subacute onset of diplopia, followed by dysarthria, dysphagia and gait instability. Her

past medical history was unremarkable except for colorectal polypectomy in 2009. Neurological examination showed: up-beating nystagmus, dysarthria, dysphagia, ataxic gait, dysmetria and adiadochokinesia (L>R). Brain MRI scan showed 3 poorly demarcated hyperintense lesions on T2 sequences: one in the midbrain (10x9 mm in axial diameter and 8 mm in craniocaudal diameter) with margin enhancement (gd+) and perilesional edema, one in the right occipital cortex and one in the left middle cerebellar peduncle, both millimeter and gd-. In the suspicion of secondary brain lesions, blood and instrumental exams were performed: routine, autoimmunity, thyroid screening, antibodies against neuronal intracellular antigens and antibodies against synaptic neuronal antigens, whole-body contrast-enhanced CT were unremarkable. Cerebrospinal fluids (CSF) analysis showed normal biochemical values, without cells or oligoclonal bands. Therefore, in the suspicion of an autoimmune inflammatory disease, 1 gr iv Methilprednisolone for five days was started with improvement of neurological symptoms. Fifteen days after steroid administration MRI showed reduction of brain lesions. Anti-MOG-IgG were analyzed and resulted positive in serum (1:160). A Diagnosis of MOGAD was made and oral prednisolone with long term (across 3 months) tapering was started. Two months follow-up visit showed complete resolution of neurological symptoms and resolution of MRI lesions.

Conclusion and Discussion: This case report highlights two important aspects. Firstly, although brainstem involvement in MOGAD is usually associated with optic neuritis or myelitis, in 1.8% is observed an isolated brainstem involvement specially in adult onset of MOGAD. Secondly, even if MOGAD is typically described in children or young adults (median onset between 20 and 30 years) an onset in older patients is possible.

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## IMPACT OF AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION ON RETINAL ATROPHY IN MULTIPLE SCLEROSIS

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Background: Together with sustained suppression of clinical and MRI inflammatory activity, early accelerated brain volume loss - declining after the first year - is commonly observed following autologous hematopoietic stem cell transplantation (AHSCT) in multiple sclerosis (MS). Possible explanations for this phenomenon include treatment-related "neurotoxicity" as well as reduced inflammation-related "pseudoatrophy". The progressive thinning of peripapillary retinal nerve fiber layer (pRNFL) and of ganglion cell+inner plexifom layer (GCIPL) as assessed with optical coherence tomography (OCT) are considered biomarkers of neurodegeneration, while increased inner nuclear layer (INL) thickness might reflect inflammatory activity in MS, but data regarding the effect of AHSCT on retinal layers' thickness are still lacking.

Aims: To assess how AHSCT affects medium-term evolution of retinal layers' thickness dynamics in MS.

Methods: Spectral-domain OCT scans of 5 MS patients were obtained 3 months before, 12-months after, and at least 18-months following AHSCT. Eyes with previous optic neuritis were excluded. Atrophy rates of pRNFL, GCIPL and INL were assessed at different timepoints.

Results: At the time of inclusion, all patients had a relapsing-remitting disease course and showed MRI activity; mean age and disease duration were 30.8+9.9 and 11.8+8.4 years, respectively; median (range) EDSS: was 4.5 (2-6). Mean follow-up (FU) duration (time between baseline and last OCT performed) was 35 months (range 18-58). None of the patients showed MRI activity, relapses or disease progression following the transplant procedure. We found no pRNFL/GCIPL atrophy throughout FU (BL vs 12-months vs last pRNFL/GCIPL thickness: 95.8±8.8 vs 95.4±9.8 vs 96.4±9.3 μm/85.7±6.3 vs 85.9±7.1 vs 86.2±7.4 μm, respectively). A transient INL thinning during the first 12-moths with return to baseline thickness during the subsequent FU was observed (BL vs 12-months vs last INL thickness: 39.5±4.2 vs 38.9±4.6 vs 39.5±4.1 μm).

Conclusions: We observed an overall stability of neuro-axonal measures (pRNFL and GCIPL thickness) during the 1st and up to 3-years following AHSCT, together with an early transient INL thinning. Although still very limited, our data might be consistent with the notion that AHSCT-induced immunosuppression could reduce retinal inflammation resulting in declining INL volumes.

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## THE EFFECT OF CLADRIBINE AND FINGOLIMOD TREATMENTS ON RETINAL ATROPHY

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Introduction: Data regarding the effect of cladribine and fingolimod treatment on retinal atrophy are still lacking.

Aims: To explore and compare the impact of cladribine (I course) and fingolimod treatments on retinal atrophy in a cohort of relapsing remitting multiple sclerosis (RRMS) patients.

Methods: In this ongoing study, patients starting cladribine or fingolimod at the MS Center of the University of Genoa underwent spectral-domain optical coherence tomography (SD-OCT) scans at baseline and at 12-months FU. Eyes with previous optic neuritis were excluded. Atrophy rates of peripapillary retinal nerve fiber layer (pRNFL) and ganglion cell+inner plexiform layer (GCIPL) at different timepoints and their differences between groups were assessed with repeated measures ANCOVA accounting for age, sex, disease duration.

Results: A total of 35 patients were included in the analysis, [17 cladribine and 18 fingolimod; females: 54%; mean (SD) age, disease duration, and relapses in the previous 2-years: 37.3 (14.6) years, 8.6 (10.1) years, and 0.34 (0.53); median (range) EDSS: 1.5 (0-5)]. No differences in terms of age, gender, disease duration, ARR, EDSS, and baseline pRNFL or GCIPL thickness were found between the two groups. At 1-year FU, no significant differences were observed between baseline and FU pRNFL (99.35±10.39 vs 98.10±10.75 μm respectively: p=0.49) and GCIPL (84.63±8.04 vs 83.53±7.27 μm respectively: p=0.31) thickness. Retinal thinning over FU was similar between patients treated with cladribine (pRNFL: -1.23±2.97 μm; GCIPL: -1.56±3.47 μm) or fingolimod (pRNFL: -1.27±1.26 μm; GCIPL: -0.65±2.61 μm) (p=0.86 and p=0.56, respectively).

Conclusions: We observed an overall stability of pRNFL and GCIPL thickness over 1-year in patients treated with cladribine (I course) and fingolimod, without a clear superiority of either one of the two drugs over the other in terms of retinal thinning prevention. Our findings need to be confirmed by larger analyses, which should also take into account the impact of the second course of cladribine treatment.

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## ANTI-MOG, A PEDIATRIC CASE REPORT


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Acquired demyelinating syndrome is a rare condition in pediatric population. It is important to differentiate from early onset MS and acute disseminated encephalomyelitis (ADEM) associated to anti-AQP4 or anti-MOG because they require a different treatment. A 10-year-old boy previously healthy presented to the hospital with persistent fever responsive to paracetamol, urinary retention and abdominal pain. Symptoms developed in 3 days. His exam revealed a bladder overdistension, pain of the inferior left limb associated with paresthesias, and flaccid paralysis of inferior limbs associated with decreased reflexes. Symptoms were preceded by an upper respiratory tract infection 2 weeks before. WBC count and RCP were normal. Urgent CT scan was not significant. CSF was normal apart from mildly elevated protein levels (87 mg/dl, upper limit 45). Since the examination for the detection of viruses and bacteria was negative, additional studies including anti-MOG, anti-AQP4 and oligoclonal bands were run out. Brain MRI showed T2-weighted hyperintense lesions of thalami, bilaterally in the fronto-parietal and periventricular white matter, corpus callosum and cerebellar peduncles. Spinal cord MRI revealed an extensive longitudinal transverse myelitis from C1 to T1 and from D4 to the conus. Anti-MOG turned out positive only in serum (1: 1280), anti-AQP4 was negative. Nasopharyngeal swab was positive for Adenovirus. The patient's demographic features, exam and laboratory were conclusive for a parainfectious ADEM and myelitis anti-MOG associated. He was treated for five days with high-dose corticosteroids (30 mg/Kg) with partial improvements on the paresis and minimal reduction of T2 alteration on a following MRI, then he underwent IVIg for five days (2g/Kg). Twenty days later from the hospitalization he was discharged, his exam revealed exclusively oscillations of inferior limbs in Mingazzini II and fatigability to walking at the moment of discharge. He continued steroids by oral administration for three months, progressively tapering prednisone up to 15 mg per day. Three months later he underwent a brain and spinal cord MRI, all lesions were healed leaving no apparent gliosis. His neurological exam was completely normal and he did not complain about any other symptoms. Anti-MOG in children has a more benign course compared to adults. 32%-53% of patients suffer of relapses but no MRI features were discriminative to predict relapses. Maintenance therapy with immunosuppressive DMT is indicated only in case of poor recovery with steroids after three months or recurrence of relapses.

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## CHRONIC RELAPSING INFLAMMATORY OPTIC NEUROPATHY REQUIRING PLASMAPHERESIS AND RITUXIMAB TREATMENT


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Introduction: Chronic relapsing inflammatory optic neuropathy (CRION) is a type of recurrent optic neuropathy of idiopathic origin that usually responds to treatment with systemic steroids or immunosuppressant and presents relapses upon withdrawal or tapering dose. This disease affects more women than men and is characterized by unilateral or bilateral optic neuropathy, severe and persistent pain followed by subacute visual loss, with both optic nerves affected and a latency period between attacks of days to years [1,2].

Case report: A 49-year-old woman experienced left optic neuritis in March 2022; she was treated with intravenous methylprendisolone (1 g) for 7 days with transitory improvement; due to new worsening of visual

acuity despite steroid oral tapering, the patient was treated with a new course of steroid in another hospital three weeks later, without recovery. Brain MRI failed to show any demyelinating lesion involving brain or left optical nerve. Reumathological assessment demonstrated ANA positivity and oligoclonal bands were found on CSF isoelectrofocusing. One month later she was admitted to our Neurology Unit for reduction of visual acuity in right eye (7/10); at that time, she was already blind in left eye. She was treated again with intravenous steroid for 5 days with benefit. Brain MRI was unchanged, spinal MRI was negative; visual evoked potentials were consistent with left blindness and right optical neuritis; AQ4 and MOG antibodies tested negative. In the following weeks the patients experienced episodes of transitory scothoma and dyschromatopsia in right eye; control brain MRI showed an extended hyperintensive lesion in left optical nerve and a segmental alteration in right optical nerve. No contrast enhancement was seen. Genetic testing for LHON was negative. A diagnosis of CRION was supposed, and azatioprine was started with maintenance of low dose steroid oral therapy (August 2022). In November, few weeks after steroid withdrawal, she experienced a new optic neuritis (visual acuity 4/10) treated with plasmapheresis due to the partial and unpersistent steroid response in previous attacks. Visual recovery was optimal (8/10 on discharge). She is now treated with intravenous rituximab; brain and spinal MRI is unchanged. AQ4 and MOG antibodies are persistent negative.

Discussion: CRION is a challenging diagnosis; other more common diseases such as Multiple Sclerosis, NMOSD, infectious optic neuropathies, hereditary optic atrophies, metabolic neuropathies must be ruled out. Early treatment with iv steroids or plasmapheresis, followed by chronic immunosuppressant therapy, is required considering the risk of blindness if treated inappropriately. [3]

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## NEUROPSYCHOLOGICAL ASSESSMENT IN MULTIPLE SCLEROSIS PATIENTS: THE POLARIS PROJECT

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Objectives: Cognitive change is common in adults with Multiple Sclerosis (MS), ranging from 34% to 65% [1]; fatigue is one of the most common symptoms of MS [2], and exerts the greatest impact on patients' quality of life. Risk of anxiety and depression varies from 14% to 54% [3]. The aim of this study is to assess the prevalence of cognitive impairment, anxiety, depression and fatigue in a population of MS patients, in order to improve medical treatment and psychological support.

Material and Methods: We selected 23 patients of our MS Center; this population included newly diagnosed patients, patients switching to high efficacy therapies (HET) due to incomplete clinical response or with apparent radiological stability but complaining of cognitive change. We choose RBANS (Repeatable Battery for the Assessment of Neuropsychological Status) for cognitive evaluation, Hospital Anxiety and Depression Scale (HADS) for anxiety and depression, MSQoL-54 for quality of life, Fatigue Scale for Motor and Cognitive Functions (FSMC) for fatigue evaluation.

Results: 23 MS patients were tested (18 females, 5 males), mean age 45 ± 8,5 years, mean age at onset 37,5± 9,4 years. 6 patients (26,6%) were newly diagnosed (disease duration < 24 months), 7 (30%) had a disease duration > 10 years and 10 (43%) a disease duration ranging from 2 to 10 years. Median EDSS was 2,5 (range 1-6); 60% of patients were on treatment with HET; 26% of patients were on antidepressive drugs; antifatigue therapies were proposed in 21% of cases. 13% of patients reported pathological score on RBANS and 48% had scores at the lower limits. On HADS, 17% of patients reported marked anxiety, 13% pathological depression. Regarding MSQoL, 48% of patients reported lack of physical wellness and 44% a lack of mental wellness. Global fatigue was found in 78% of patients; cognitive fatigue was present in 74% of patients, physical fatigue in 83% of cases.

Discussion: Cognitive difficulties were found in more than 50% of patients, despite early HET in most cases. Fatigue has a deep impact on quality of life and is often under-reported. Neuropsychological testing helps us to identify cases at higher risk of cognitive deterioration or with unmet needs (anxiety, fatigue, job troubles) [1]. Patients' awareness of their difficulties improved and acceptance of antifatigue/antidepressive drugs or psychological support improved, too.

Conclusions: Systematic neuropsychological assessment can help in identification of patients with early cognitive impairment, patients needing additional symptomatic therapies or a longitudinal psychological support.

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## EFFECTIVENESS OF OCRELIZUMAB IN PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS: A MULTICENTER, RETROSPECTIVE, REAL-WORLD STUDY (OPPORTUNITY)

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Objectives: Ocrelizumab is a recombinant humanized monoclonal antibody selectively targeting CD20-expressing B cells. The effect of ocrelizumab on primary progressive multiple sclerosis (PPMS) has been evaluated during phase 3 trials that enrolled patients under 55 years with a maximum Expanded Disability Status Scale (EDSS) of 6.5. However, little is known on older disabled patients with longer of disease duration. We aimed to assess clinical effectiveness of ocrelizumab in PPMS patients out of the ORATORIO eligibility criteria.

Materials: This multicenter retrospective study collected data about the effectiveness of ocrelizumab in PPMS patients who received treatment between May 2017 and June 2022 in the Italian MS centers contributing to the Italian MS Registry who adhered to compassionate use program.

Methods: The confirmed EDSS worsening (CEW) (defined as either a ≤1-point or ≥2-points increase in EDSS score from baseline that was confirmed at T12 and T24) was calculated. Results. At the date of data extraction, out of 887 PPMS patients who had received ocrelizumab, 589 (mean age 49.7 +/-10.7 years, 242 [41.1%) females) were enrolled. The mean follow-up period was 41.3 +/-12.3 months. A total of 149 (25.3%) received ocrelizumab according ORATORIO criteria (ORATORIO group) and 440 (74.7%) outside the ORATORIO criteria (non-ORATORIO group). No differences in terms of cumulative probabilities of 12- and 24-months of CEW of 1 point were found between ORATORIO and non-ORATORIO groups. Cox-regression analyses showed that age older than 65 years (HR 2.51, 25%CI 1.07-3.65; p=0.01) was associated with higher risk of CEW at 24 months.

Discussion: Patients not responding to ORATORIO criteria for reimbursability may benefit from ocrelizumab treatment, as disease activity, disease duration and EDSS seem to not impact the disability outcome.

Conclusions: Our results may suggest to extend the possible use of this powerful agent in selected patients under the age of 65 years.

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## REAL-WORLD EVIDENCE FOR OFATUMUMAB IN MULTIPLE SCLEROSIS PATIENTS: A SICILIAN MULTICENTER EXPERIENCE

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Objective: Ofatumumab (OFA) is a human recombinant IgG1 CD20 next-generation monoclonal antibody. Two phase III trials investigated the efficacy and safety of OFA in relapsing-remitting Multiple Sclerosis (RRMS) showing a relative reduction of the relapse rate after 3 and 6 months in the OFA arm (50.5% and 58.5%, respectively) compared to teriflunomide. In addition, the risk for confirmed disability was significantly reduced (34.4% and 32.5%, respectively). Subsequent studies confirmed that OFA is a highly effective treatment option for patients with relapsing forms of MS with a manageable tolerability profile. However, to date, real world data about the effectiveness of OFA are still scarce. We aimed to evaluate efficacy and safety of OFA in a real-world setting.

Materials: This prospective real-world study consecutively screened all RRMS patients from three MS centers in Sicily (Italy), who were treated with OFA for at least 6 months.

Methods: Data about Expanded Disability Status Scale (EDSS), relapses, previous treatments, adverse events (AEs) and magnetic resonance imaging (MRI) were collected. We also compared demographical and clinical data between patients naive to treatment before starting OFA (naïve group) and patients switching from other treatments (switch group).

Results: Out of 78 RRMS patients who started OFA treatment in the period between August 2022 and May 2023, a total of 54 patients (32 [59.3%] women, with mean age of 34.8 ± 5 years and mean disease duration of 110.1 ± 21.9 months), were finally enrolled. Of these, 18 (33.3%) were naïve to treatment and 36 (66.7%) switched from another DMTs. At baseline, naive group showed longer disease duration, higher number of relapses before starting OFA, and higher number of brain/spine contrast-enhanced lesions (CELs) before starting OFA compared to the switch group. After 6 months from OFA initiation, 53 (98.2%) of patients remained relapse-free, 50 (92.6%) were EDSS progression-free, and 47 (87%) were MRI activity-free. No significant differences in terms of efficacy outcomes were found between naive and switch groups. During the observation period, all the AEs were mild to moderate and no serious AEs were reported. In particular, fever was the most frequent AE reported in 70.4% of treated patients.

Discussion: Findings from our study confirmed that OFA is effective in reducing risk of relapse and disease progression in a real –world cohort of RRMS patients, also demonstrating a favorable safety profile.

Conclusions: Longitudinal studies are needed to evaluate the long-term effectiveness of OFA for the treatment of RRMS in patients naïve to treatment and in those who have switched from other DMTs.

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## PREVALENCE OF PSYCHIATRIC DISORDERS AT MULTIPLE SCLEROSIS ONSET

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Psychiatric syndromes (PS) in multiple sclerosis (MS) are common, with a variable prevalence up to 60%. [1]. PS are often underdiagnosed during routine neurological follow up and therefore receive suboptimal treatment. On the other hand, the prevalence of psychiatric manifestations before disease onset and their impact on patient's care has been poorly explored so far [2][3].

Objectives: To assess the prevalence of PS at MS onset and to explore whether patients with a psychiatric comorbidity presented any significant difference in terms of age, sex, EDSS and time to diagnosis compared to those without psychiatric history.

Materials: We collected the records of patients diagnosed with MS according to the 2017 revision of McDonald's criteria from January 2018 to December 2022 and evaluated the presence of psychiatric manifestations at disease onset.

Methods: We classified PS into five categories according to DSM-5 and evaluated their relative frequencies and the specific treatment adopted. We compared demographic and clinical differences between patients presenting psychiatric comorbidity and those who did not, and assessed whether there was a delay in MS diagnosis in the first group.

Results: We enrolled 254 patients and we found that 28 patients (11%) had a PS before MS onset. The most frequent disorder was depression (50%), followed by anxiety disorder (25%), schizophrenia spectrum disorders (10.7%), bipolar disorder (7.1%) and eating disorders (7.1%). 92.9% of patients took a specific therapy, mainly antidepressants (46.2%), and anxiolytics (34,6%). The mean time from the first psychiatric symptom to the first neurological event was 8.1 years (standard deviation 5.8 years). Patients with PS at onset showed a higher median EDSS at diagnosis compared to those without psychiatric history (p=0.054). We found no statistical differences in age, sex and time from MS onset MS diagnosis between the two groups.

Discussion: We found a significant percentage of patients presenting a psychiatric manifestation before MS onset. It is not possible to establish whether psychiatric symptoms might be considered an inaugural manifestation of MS. The group of patients with psychiatric history did not differ significantly from the group without it, with the exception of median EDSS at diagnosis. In our cohort the presence of a psychiatric comorbidity did not lead to diagnostic delay.

Conclusions: Psychiatric symptoms occur frequently in individuals with MS, either prior to a definitive neurological diagnosis or with disease progression. A thorough psychiatric assessment should be performed at diagnosis, so as to identify underrated disorders and offer proper treatment.

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## CENTRAL NERVOUS SYSTEM GLIOMA MASQUERADE AS TUMEFACTIVE DEMYELINATING LESION: A CASE REPORT

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Background and Objectives: Central nervous system (CNS) neoplasm and tumefactive demyelinating lesion (TDL) represent a diagnostic challenge for neurologists because they may look radiologically identical, leading to a diagnostic delay.

Materials and Methods: A 27 year-old man, with no known prior medical illness, was admitted in October 2022 to our Neurology Department for a transient vertigo, lasting two hours. His family history was negative for any neurological disease. Neurological examination on admission was unremarkable.

Results: Brain magnetic resonance imaging (MRI) showed a large lesion in the right cingulate gyrus with subcortical cortical involvement,measuring 2x3cm,suspected for TDL or CNS glioma, with normal N-acetylaspartate/choline ratio at spectroscopy and normal perfusion parameters. There were also other small T2-weighted hyperintensity lesions in the deep white matter of bilateral hemispheres, suspected for demyelinating lesions. All lesions showed neither contrast enhancement nor diffusion restriction. Spinal cord MRI was normal. CSF examinations revealed mild lymphocytic pleocytosis (9/mmc), elevated protein level and oligoclonal bands (OCBs) were detected intrathecally. Visual and sensory-evoked potential were normal. Autoimmune profile and MOG antibodies were negative. A diagnosis of TDL in radiologically isolated syndrome (RIS) was made. Patient received pulse steroid therapy for three days. At 4 months follow-up the patient was negative for new symptoms, however MRI showed a mass effect with surrounding edema in the right cingulate lesion without other new lesions. So, biopsy of this lesion was performed and demonstrated histopathological features of low grade oligodendroglioma. The patient finally underwent neurosurgical excision of this lesion.

Discussions and Conclusions: The tumefactive form of demyelinating disorder is rare, however it can be a diagnostic dilemma especially in young adults. Brain tumors are the most frequent misdiagnosis. In our case, a TDL in RIS was initially suspected for the patient's young age and symptom, CSF profile with OCBs and brain MRI showing white matter lesions and a largest lesion without abnormality in spectroscopy and perfusion techniques. TDL could be easily misdiagnosed both for nonspecific clinical presentation and for imaging findings that may mimic intracranial space-occupying lesions. In this case neuroimaging follow-up was crucial to reconsider the diagnosis of CNS glioma. Sometimes, like our case, brain biopsy is needed to confirm diagnosis although it is an invasive procedure and it can imply significant morbidity. Thus, reporting similar cases will help to increase clinicians awareness about this circumstance and highlight the need for additional markers to differentiate these conditions.

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## OUTCOMES, ADVERSE EFFECTS AND EXIT STRATEGIES IN MULTIPLE SCLEROSIS PATIENTS TREATED WITH ALEMTUZUMAB: A MONOCENTRIC RETROSPECTIVE STUDY

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Objectives: Currently few studies exist concerning a long-term follow-up in multiple sclerosis patients treated with Alemtuzumab. Our study aimed to analize the outcomes, the adverse effects and the exit strategy in multiple sclerosis (MS) patients treated with Alemtuzumab in our center.

Materials: We conducted a single-center retrospective observational study of 51 patients with diagnosis of MS, who underwent a disease-modifying therapy (DMT) with Alemtuzumab at Udine University Hospital from September 2015 to March 2023.

Methods: Patients were followed-up since the first subministration of Alemtuzumab, in order to identify adverse effects, outcomes and exit strategy. The outcomes of interest were relapses, EDSS at 24 months and reactivation or evidence of new lesions reported in MR imaging during the follow-up.

Results: At baseline, 46/51 patients (90.2%) were diagnosed as relapsing-remitting multiple sclerosis (RRMS) and 5/51 (9.8%) as secondary progressive MS with residual inflammatory activity. 46/51 (90.2%) patients had completed the second treatment cycle with Alemtuzumab and their mean follow-up was 57 months. 6/51 (11.8%) patients had disease relapse between the first and the second cycle, while 11/51 (21.6%) patients had disease relapse after the second cycle. 10/51 (19.6%) patients showed reactivation signs on MR during the first and the second cycle, while 15/51 (29.4%) patients had MR reactivation signs after the second cycle. For 37/51 patients (72.5%) the follow-up was at least 24 months: their 24month mean EDSS was 2.76 ± 1.8 and 12 patients were classified as NEDA3. 30/51 patients (58.8%) had adverse events. After Alemtuzumab second cycle, 5/51 patients (9.8%) underwent a third cycle with Alemtuzumab, 2/51 (3.9%) patients were treated with another DMT and 2/51 (3.9%) patients underwent a bone marrow transplant.

Discussion: In our study only 17/51 patients (33.3%) had a clinical disease relapse during the follow-up. Adverse events were mild or resolved spontaneously or with medical therapy in most of the patients analized in our study and they didn't affect the course of Alemtuzumab therapy.

Conclusions: We confirmed a high efficacy of Alemtuzumab, compared to contained adverse effects and we reported the exit strategy used in patients treated in our center. We hope that our study and other evidences in future can help to outline a common therapeutic approach following completion of Alemtuzumab treatment.

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## THE IMPACT OF APATHY ON CAREGIVERS BURDEN AND COPING STRATEGIES IN MULTIPLE SCLEROSIS

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Objective: Our aim was to enhance the current state of knowledge about caregivers of people with MS (pwMS) identifying the impact of apathy on caregivers burden and coping strategies.

Materials: Thirty-four dyads of people with MS and caregivers completed the Apathy-Motivation Index (AMI) [1], tapping apathy in terms of behavioural activation (BA), social motivation (SM), and emotional sensitivity (ES), in self-evaluation (SE) and caregiver (CG) version, respectively. In addition, the caregivers completed the Zarit Burden Interview (ZBI) and the Caregiver Burden Inventory (CBI) tapping the caregiver burden, and the Coping Orientation to Problems Experienced (COPE) tapping coping strategies related to positive reframing, social support, acceptance, denial, and turning to religion.

Methods: To evaluate the differences in the AMI-CG and AMI-SE total and subscales scores the Mann-Whitney test was performed. Moreover, Spearman correlations were performed between AMI-SE and AMI-CG total and subscales scores. Finally, to evaluate the association between apathy, caregiver burden, and coping strategies, Spearman correlations were performed between AMI-CG total and subscale scores with CBI, ZBI, and COPE subscales scores.

Results: No statistically significant differences were found between AMI-CG and AMI-SE total ($U = 519$, $p = 0.469$), SM ($U = 523$, $p = 0.502$), and ES ($U = 504$, $p = 0.362$) subscales scores; however, the BA-CG subscale score was significantly higher than BA-SE subscale score ($U = 396$, $p = 0.025$). Correlation analysis showed a considerable agreement between the AMI-SE and AMI-CG total and subscales scores (rrho >= 0.350 p <= 0.042). Moreover, a significant and negative correlation was found between ES-CG subscale score with COPE total score (rrho = -0.355; $p = 0.039$), and with positive reframing subscale score (rrho = -0.503; $p = 0.002$). No significant correlation was found between AMI-CG total and subscales scores with CBI and ZBI scores.

Discussion: Overall, caregivers rated apathy similarly to pwMS, except for behavioural dimension of apathy, suggesting that reduced individual's self-initiated purposeful behaviour would be a possible anosognosic component in pwMS. Moreover, the negative relation between the emotional dimension of apathy and caregivers' coping strategies, particularly their ability to think about a negative or challenging situation in a more positive way, would underlie the impact of affective blunting of pwMS on caregivers' ability to effectively provide care and lead to positive changes in MS management [2].

Conclusions: These findings suggest that apathy in pwMS involves factors other than the patients' symptoms. Comprehensive care of pwMS should include training on coping strategies of caregivers to provide better support services [3].

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## UNUSUAL CLIPPERS PRESENTATION WITH A PREDOMINANT SPINAL CORD INVOLVEMENT

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Objective: Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a discrete nosological entity characterized by punctate and curvilinear gadolinium enhancement 'peppering' the pons and a strong response to steroids [1]. Despite the extremely rare incident of CLIPPERS hindering the exact characterization of the disease, some authors have tried to assess the most common clinical and radiological features and proposed diagnostic criteria [2]. Among all the proposed features the presence of predominant pontine gadolinium-enhancing nodules has been observed in the total of the described cases, making it the most representative feature of the disease [2]. Herein we present an extremely rare case of CLIPPERS presented with a predominant spinal cord involvement.

Materials and Methods: A 23-years old woman with no past medical history presented to our emergency department with a 1-month history of subacute onset gait disturbance. Neurological examination showed moderate gait ataxia, slight right motor hemiparesis, and bilateral Babinski and Hoffmann signs. Brain and spinal cord MRI showed multiple lesions with punctate and curvilinear gadolinium enhancement with a salt-and-pepper-like appearance involving the midbrain and, predominantly, the spinal cord. CSF and blood examination resulted normal for the exclusion of a "better explanation" [2]. The administration of 5 days of high-dose intravenous methylprednisolone leads to substantial clinical and MRI improvement.

Discussion: Our case describes a rare case of CLIPPERS with prevalent spinal cord involvement. To our knowledge, this MRI pattern has been rarely reported in the literature [3]. It is critical to describe this presentation since must be carefully considered in the diagnostic workup of diffuse spinal cord lesions.

Conclusion: Our case focuses attention on a rare MRI CLIPPERS presentation. Since CLIPPERS has a dramatic response to corticosteroid treatment it is fundamental to promptly recognize its MRI pattern to start treatment as soon as possible.

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## MULTIPLE SCLEROSIS AND HEPATIC COMORBIDITIES: CASE REPORTS AND THERAPEUTIC STRATEGIES

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Objectives: The aim of the study is to investigate hepatic comorbidities in Multiple Sclerosis (MS).

Materials and Methods: We analysed 125 consecutive MS patients, to register any transaminases increase before disease modifying therapies (DMTs).

Results: We found sustained transaminase increase (> 1 upper normal limit) in 5 patients out of 125. The 5 patients underwent a targeted anamnesis, first level blood tests including viral and autoimmune screening and hepatobiliary ultrasound. Three patients were diagnosed as fatty liver disease, while two patients required hepatic biopsy and are described below. Case 1: A 42-years old woman with a new diagnosis of MS and two close relapses had a 20-years story of recurrent transaminase increase. Hepatic biopsy showed a nodular regenerative hyperplasia compatible with porto-sinusoidal vascular disease. Therapy with ofatumumab resulted efficient and safe. Case 2: A 21-years old woman with a new diagnosis of MS had two close relapses, the second one treated with methylprednisolone and followed, one month later, by a severe transaminase increase. Hepatic biopsy showed centrolobular necrosis and inflammatory infiltrates. ANA were positive. A drug induced liver disease was supposed, but the persistence of transaminase elevation lead to start prednisone (with enzyme normalization) and to diagnose a probable autoimmune hepatitis. The patient continued a low dose of prednisone and started natalizumab. Four year later, she developed an MS relapse treated with methylprednisolone followed by a hepatic relapse, recovered increasing the dosage of prednisone.

Discussion and Conclusions: Sustained increase of transaminases in new diagnosed MS patients impose a specific diagnostic work-up to understand the underlying condition, contributing to the choice of the most appropriate DMT. We reported the cases of a porto-sinusoidal vascular disease and of a probable autoimmune hepatitis, respectively, concurrent to MS. In the first case, hepatic biopsy was diagnostic and made theoretically administrable any DMT except Alemtuzumab because of the potential thrombotic risk. In the second case, methylprednisolone was a confounding element and, even after hepatic biopsy, the diagnosis of drug induced versus autoimmune hepatitis was difficult, orientating towards autoimmune hepatitis after follow-up. Literature analysis shows that there is a continuous spectrum between hepatoxicity with immunoallergic mechanism and autoimmune hepatitis due to immune rebound phenomenon, often without a clear line of demarcation between the two conditions. The role of natalizumab and other DMTs in toxic and autoimmune hepatitis is debated, our case suggests that natalizumab is apparently safe while methylprednisolone should be avoided.

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## OFATUMUMAB USE IN A REAL WORLD ITALIAN SETTING


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Objectives: The primary outcome was to offer an overview real world practice with ofatumumab in relapsing Multiple Sclerosis (RMS) patients and to observe the first six months on therapy in terms of disease activity and disability progression.

Methods: Inclusion criteria were patients: 1) aged 18-55; 2) with a confirmed diagnosis of RMS, per the revised 2010 McDonald criteria; 2) who started OFA according to Italian Medicines Agency prescription rules and within 12 months from the RMS diagnosis.
Results: 43 patients were enrolled from 5 Italian MS centers, 67% female, mean age 33,4±8,5 years. All patients had magnetic resonance activity and at least one relapse in the previous 12 months. Out of them, 35 had at least six months of follow up. Median EDSS was 1.5 (interquartile range 1.0-2-00). During the first six months of therapy, no relapses or MRI activity were recorded. No worsening of disability was reported.

Discussion: Ofatumumab stabilizes the disease course in our highly active cohort during the first 6 months of therapy.
Conclusions: The progressive and increasing use of anti-CD20 drugs, imposes the need for larger, prospective, real-world long-term studies to characterize further its use and efficacy in different classes of RMS patients.
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## SIPONIMOD-INDUCED LYMPHOPENIA IN PATIENTS WITH SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS: A REAL-WORLD EXPERIENCE


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Objectives: Siponimod, a sphingosine-1-phosphate receptors modulator (S1Prm), leads to a dose-dependent reduction of the peripheral absolute lymphocytes count (ALC) to 20–30% of baseline. In the pivotal phase III study (EXPAND) in Secondary Progressive Multiple Sclerosis (SPMS), only 1% of treated patients reached a grade 4 lymphopenia (ALC <200/mcL). In real world studies, low baseline ALC and previous treatment with interferon-beta have been identified as risk factors for lymphopenia in patients with Multiple Sclerosis treated with Fingolimod, the first S1Prm available for MS. Real world data regarding ALC reduction rates and predicting factors are lacking for Siponimod. We therefore aimed to evaluate Siponimod-induced lymphopenia in clinical practice.

Material and Methods: 31 patients with SPMS (pwSPMS) were included in the analysis. Clinical-demographical data, biometric values and life habits were collected. ALC was obtained before and 3-6 months after Siponimod introduction. STATA 14 was used for statistical analysis.

Results: Seventy-one percent of patients were female; the mean age was 55.2 (± 8) years, with a mean disease duration of 27 (±12.5) years; median EDSS was 6.5 (IQR25=4, IQR75=7). The mean body mass index (BMI) was 24.6 (±2.8) and 15% were smokers. All pwSPMS had previously been treated with other disease modifying therapies (DMTs): 61.3% with interferon beta. Eighty percent of patients carried the cytochrome P2C9*1*2-(CYP2C9*1*2-) and-*1*1-genotype. Mean baseline (BL) ALC was 1395 (±613)/mcL (median 1380/mcL, IQR25=1005/mcL, IQR75=1940/mcL), while average ALC within 3-6 months was 517 (±378)/mcL (median 400/mcL, IQR25=270/mcL, IQR75=660/mcL); an average reduction of 42.8 (±29.4)% of ALC was therefore measured between the baseline and short-term follow-up. Sixty-four percent of pwSPMS reached a grade 3 lymphopenia (ALC <500/mcL); 9.6% reached a grade 4 (ALC <200/mcL), conducting to Siponimod withdrawal. No differences were observed across different cytochrome P2C9 genotypes. Regression model including age, sex, EDSS, disease duration, previous DMTs, ALC before starting Siponimod, BMI, smoking, alcohol intake did not show any predictor of ALC reduction.
Discussion: In a real-world cohort, we observed a higher ALC reduction (42.8%) and a higher percentage of grade 3-4 lymphopenia (64.5 and 9.6%, respectively) compared with those observed in the EXPAND study (30% reduction of ALC and 1% grade 4 lymphopenia, respectively). We did not identify any predicting risk factor for lymphopenia, but this was probably due to our small sample.

Conclusions: Siponimod-induced lymphopenia in clinical practice is more relevant than that reported in the EXPAND study. No risk factors for lymphopenia have been identified.
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## AGE AT ONSET EFFECT ON COGNITIVE PHENOTYPES AND PROGRESSION OF GRAY MATTER DAMAGE


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Background: Compared to typical MS onset in young adulthood (ie, adult-onset – AOMS), the minority of pediatric- (POMS – ie, before age 18 years) and elderly-onset (EOMS – ie, after age 50 years) MS patients might experience faster cognitive decline. We aimed to describe cognitive phenotype (Ph) distribution and related MRI substrates in POMS and EOMS vs AOMS patients, over time.

Methods: We enrolled 1262 MS patients and 238 healthy controls (HC). All subjects underwent cognitive evaluation with Rao's Brief Repeatable Battery and Stroop Color Word Test, of whom 222 MS patients and 88 HC also underwent 3T MRI with pulse sequences for atrophy and lesion assessment. Probabilistic models were applied to attribute previously described Ph ("preserved-cognition", "mild verbal memory/semantic fluency", "mild-multi-domain", "severe-attention/executive", and "severe-multi-domain") to patients; and to estimate the probability of attribution to each Ph over increasing disease duration (DD), considering the effect of age at onset. Similar models were used to estimate the probability of MRI alterations over increasing DD.

Results: Among POMS and AOMS patients, the probability of "preserved-cognition" or "mild-verbal memory/semantic fluency" Ph decreased with increasing DD; while that of "mild multi-domain", "severe executive/attention" and "severe multi-domain" Ph increased (p from <0.001 to 0.03). Among EOMS, the probability of "cognition preserved" Ph was lowest at disease onset and it hardly changed over DD; the probability of "mild-verbal memory/semantic fluency", "severe executive/attention" and "severe multi-domain" Ph reduced over DD; while that of "mild multi-domain" increased over DD (p from 0.01 to 0.03). Compared to AOMS, POMS patients showed a steeper increase in the probability to experience deep GM and hippocampal atrophy after 20 years DD (p from <0.001 to 0.03), as opposed to similar trajectories over time for cortical GM atrophy and lesion volume. Compared to AOMS, EOMS patients showed higher probability of hippocampal and cortical GM atrophy at disease onset, and a steeper increase in this probability after 5 years DD (p from <0.001 to 0.01); moreover, they showed higher probability of greater lesion volumes and deep GM atrophy at disease onset (p from <0.001 to 0.03), but with less steep increase over DD (p from 0.01 to 0.05).

1Conclusions: Age at MS onset significantly influences Ph distribution among MS patients, as partly explained by underlying trends of regional GM atrophy.

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## CARDIOGENIC SHOCK AFTER OCRELIZUMAB INFUSION: A POSSIBLE CORRELATION?

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Background: Ocrelizumab is an intravenously administered, humanized anti-CD20 monoclonal antibody authorized for the treatment of relapsing forms of multiple sclerosis or primary progressive multiple sclerosis. We report the case of a patient with remitting-relapsing multiple sclerosis (RRMS) who developed a cardiogenic shock after the second 300 mg infusion (first cycle) of Ocrelizumab.

Case report: A 42-year-old man with a history of active RRMS was started on Ocrelizumab after fingolimod discontinuation. Roughly 24-36 hours after the second infusion of Ocrelizumab, the patient started developing worsening dyspnea, associated with cough and throat irritation, without fever. On admission at the emergency department, 12 days from symptom onset, systemic oxygen saturation was low, Chest X-Ray showed pulmonary congestion and echocardiography documented left ventricle with normal volume, mild hypertrophy and severe reduction of systolic function (LVEF 25-30%). A supportive therapy with high-flow oxygen and diuretics was started. The patient was then moved to intensive care for persistent hypotension, requiring mechanical support with intra-aortic balloon pump placement. Angiography didn't reveal critical coronary stenoses and Cardiac MRI documented a non-specific picture characterized by areas of myocardial oedema of the interventricular septum with increased T1 signal, consistent with both a drug-induced cardiotoxicity and a myocarditis. However, microbial serologic tests were negative and histological findings at endomyocardial biopsy were not suggestive of myocarditis. The patient gradually improved with rapid normalization of the left ventricular systolic function.

Discussion and Conclusion: Ocrelizumab is generally well tolerated. The most common side effects reported in trials include infusion-related reactions and infections, which were mainly mild to moderate in severity. Since our patient did not show systemic allergic symptoms during or within 24 hours of infusion and symptoms had gradual progression, a hypersensitivity-associated acute coronary syndrome can be excluded. Nevertheless, the time correlation between drug administration and symptom onset, fortunately followed by complete recovery, and the exclusion of other causes, suggest Ocrelizumab may have played a role in determining the cardiac functional injury. To date, no cardiac adverse events have been reported in association with Ocrelizumab, but a few cases of myocardial infarction, atrial fibrillation, pulmonary oedema and cardiogenic shock have been described following the first infusion of Rituximab, another B cell–depleting antibody. Although the underlying mechanism of cardiac toxicity of anti-CD20 is not known, a dysregulation of the immune system can be hypothesized, as some studies suggest that depletion of B cells may induce up-regulation of proinflammatory cytokines.

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## NK CELL LEVELS PREDICT DISEASE ACTIVITY IN PATIENTS WITH MULTIPLE SCLEROSIS ON OCRELIZUMAB/RITUXIMAB THERAPY

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Objectives: The primary objective was to identify predictors of response to treatment with infusional anti-CD20 drugs in patients with Multiple Sclerosis; the secondary objective was to study the effect of Ocrelizumab/Rituximab on laboratory immune parameters. Materials and Methods: A retrospective single-center study was conducted among patients who received infusion therapy with anti-CD20 drug for the treatment of Multiple Sclerosis.

Results: A total of 64 patients met the inclusion criteria, with 277 total cycles of therapy studied. Disease activity at 6 months after drug infusion occurred in 97 of 277 total evaluations, identifying on multivariate analysis that a reduced percent level of NK cells at 3 months after infusion is a possible predictor of disease activity at 6 months after Ocrelizumab/Rituximab administration (p=0.041). Anti-CD20 infusions result in absolute and percent decreases in B lymphocyte levels and an increase in absolute and percent levels of NK cells at 3 and 5 months after therapy compared with baseline values ($p < 0.001$). EDSS assessed before drug initiation is the only variable that predicts any disease activity at 6 months after the first Ocrelizumab/Rituximab infusion ($p = 0.044$).

Discussion: The pathogenesis of multiple sclerosis (MS) still appears to be unclear [1]. Recent years have focused on the role of B lymphocytes and the possibility of using specific drugs, such as Ocrelizumab and Rituximab, directed toward these cells to reduce inflammation and slow disease progression [2]. The effect of these therapies on NK cell and how these cells may influence disease progression is poorly understood.

Conclusions: Ocrelizumab/Rituximab therapy results in a reduction in B lymphocyte counts and an increase in NK cells. Lower percentage levels of NK cells at 3 months after anti-CD20 infusion predict the presence of disease activity at 6 months after such therapy, confirming a possible role of NK cells in the pathogenesis of Multiple Sclerosis. Repopulation of B lymphocytes at 3 months has not been shown to predict disease activity at 6 months after drug infusion.

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## PSYCHOTIC ONSET OF MULTIPLE SCLEROSIS MISTAKEN FOR SCHIZOFRENIA: A CASE REPORT

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Introduction: Here we describe the case of a 22-year-old male presented with an episode of flue in October 2022. Ten days later, while the patient and his family were on a pilgrimage, he experienced acute onset of a mystical-religious-themed delirium associated with psychomotor agitation, verbal and physical aggression towards his mother. The patient was taken to the emergency room; head CT scan was performed, found to be normal. Due to the persistent state of psychomotor agitation, he was subjected to compulsory medical treatment. An acute onset of schizophrenic disorder was diagnosed, and the patient was treated with daily intramuscular paliperidone, with a good control on delirium; he was discharged after a week with the indication to continue oral antipsychotic therapy. At discharge, however, the patient presented a severe ideomotor slowing, with significant diffuse stiffening of trunk and limbs and a severe iatrogenic extrapyramidal rigid-akinetic syndrome was suspected. On neurological examination the patient presented severe hypomimia, hypophonic and dysarthric speech; dexterity tests revealed severe bradykinesia, plastic hypertonus in limbs and trochlea phenomenon were present. Further diagnostic investigations were performed: EEG showed fronto-temporal sharp waves and spikes focality; brain MRI showed hyperintensities in T2 FLAIR sequences in bilateral temporal periventricular areas, left frontal iuxtacorticale areas, frontal pericallosal periventricular areas, with a radial aspect as perivenular distribution. In the suspicion of CNS demyelinating disease, cervical spine MRI was also performed documenting the presence of two dorsal lesions in T2 FLAIR sequences. Visual evoked potentials were normal. Lumbar puncture revealed the presence of an isolated intrathecal oligoclonal synthesis with (type 3 profile). Anti-aquaporin antibodies on CSF were negative. Multiple Sclerosis was diagnosed, antipsychotic therapy was gradually discontinued, with total resolution of parkinsonism. The patient was referred for clinical and therapeutic follow-up at the Multiple Sclerosis Centre of this hospital.

Discussion and Conclusion: Several CNS demyelinating diseases can present with clinical manifestations of psychosis. Production of psychotic symptoms may result from functional asynchrony of interdependent regions, due to alterations in critical circuits as result of pathology. The nature, location and timing of white matter pathology seem to be crucial in the development of psychosis, especially during the critical adolescent period of association area myelination. This case report points to the pivotal role of clinical ability to differential diagnosis, considering schizophrenia-like psychosis as a possible manifestation of organic disease. White matter results fundamental in maintaining CNS connectivity and its pathology may contribute to the neurobiology of psychosis.

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## PAEDIATRIC-ONSET MULTIPLE SCLEROSIS TREATMENT: AN ONGOING OBSERVATIONAL STUDY OF NATALIZUMAB AND COMPARISON WITH FINGOLIMOD

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Objective: Natalizumab is currently prescribed off-label for Paediatric-Onset Multiple Sclerosis (POMS), despite its well-known efficacy in

real life experiences. Conversely, Fingolimod is the only second-line treatment already approved in POMS. The aim of this study is to compare the efficacy of Natalizumab versus Fingolimod in POMS.

Materials/Methods: This is an observational longitudinal multicentric study: we included natalizumab-treated POMS (N-POMS) (retrospectively and prospectively) and fingolimod-treated POMS (F-POMS). We collected Annual Relapse Rate (ARR), Expanded Disability Status Scale (EDSS), Symbol digit Modality Test (SDMT) and MRI activity at baseline (T0), at 12-18 months (T1), and at last observation (T2).

Results: We enrolled 55 N-POMS and 28 F-POMS from 6 Italian MS centres. The two groups were well-balanced for age, gender, disease duration, number of previous disease-modifying treatments (DMT) and MRI lesion load. Compared to F-POMS, N-POMS showed higher EDSS (2.2±1.4 vs 1.4±1.1, p=0.008), higher ARR (1.01 [0-5.2] vs 1.00[0.1-4.4], p=0.045) and a lower SDMT (49.4±7.9 vs 60.2±9.2, p=0.045) at treatment start. N-POMS had a lower rate of at least one relapse between T0 and T1 (8 N-POMS [14.5%] vs 9 F-POMS [36%], p=0.03). EDSS score between T0 and T1 significantly decreased in N-POMS. (2.2± 1.4 vs 1.6± 1.3, p<0.001), but not in F-POMS. Between T1 and T2, 9 N-POMS switched to another DMT after 64±39 months (1 for inefficacy and 8 for safety concerns). Moreover, among 30 N-POMS not undergoing DMT switch, we observed a further EDSS reduction over time (1.52±1.27 vs 1.4±1.3, p=0.03).

Discussion: Notwithstanding the higher activity at baseline in N-POMS, natalizumab outperformed fingolimod in reducing the relapse rate and promoting disability improvement

Conclusions: Although a definite comparison is difficult and is hampered by the need of a larger sample size to perform a proper propensity score matching, our result suggests a better efficacy profile of natalizumab in POMS.

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## SARS-COV-2 VACCINATION AND MULTIPLE SCLEROSIS: A LARGE MULTICENTRIC STUDY ON RELAPSE RISK AFTER THE THIRD BOOSTER DOSE


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Background: COVID-19 vaccines have been recommended to people with multiple sclerosis (pwMS) and, to ensure a long-lasting immunity, a third booster dose has been administered in several countries [1, 2]. Data about potential risks associated with the third booster dose in pwMS, such as vaccine-triggered disease exacerbations [3], are still limited.

Objective: Herein, we investigated whether the administration of a third booster dose of mRNA COVID-19 vaccines was associated with an increased risk of short-term disease reactivation in a large cohort of pwMS.

Methods: Twenty Italian MS tertiary centres participated to this study. We retrospectively selected 1265 consecutive pwMS who received a third booster dose of an mRNA COVID-19 vaccine. Demographic and clinical data were collected, including the presence, number and characteristics of relapses within the 60 days before and after the administration of the third booster dose.

Results: In the selected cohort, the relapse rate in the two months following the third booster dose of mRNA COVID-19 vaccines did not increase when compared to the preceding two months. Indeed, the rate of pwMS experiencing relapses in the 60 days after the administration of the third booster dose was 2.1%, similar to the rate recorded in 60 days prior to vaccination, which was 1.9%. The incidence of relapses in the two-month period before and after vaccination was not statistically different (B= -1.42, 95% CI -2.916 to 0.076, p=0.063). Furthermore, we studied whether demographic and clinical disease characteristics influenced the occurrence of relapses in response to vaccination. We found that pwMS relapsing after the booster dose were younger, presented a higher disease activity in the year before the third dose and were more frequently untreated compared to pwMS that not relapsed after the booster vaccination.

Discussion and Conclusions: The third booster dose of mRNA COVID-19 vaccines proved safe for pwMS. Our findings suggest that the occurrence of relapses after vaccination is influenced by established risk factors for disease activity and emphasize the importance of disease modifying treatments (DMTs) in preventing relapse recurrence.

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## EXTENDED INTERVAL DOSING OF OCRELIZUMAB IN MULTIPLE SCLEROSIS: A SINGLE-CENTER, REAL-WORLD EXPERIENCE

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Aims: Ocrelizumab, an anti-CD20 monoclonal antibody, is approved for treating relapsing remitting (RR) and primary progressive (PP) multiple sclerosis (MS). The standard dosing regimen requires intravenous infusions every six months. Experience of extended dosing due to COVID-19 pandemic-related issues suggests that this strategy may provide comparable efficacy while reducing treatment burden and healthcare costs. This study aimed to evaluate the safety, effectiveness, B and T cell count changes associated with extended interval dosing of ocrelizumab in a real-world setting.

Methods: This retrospective study included patients with RRMS or PPMS who received ocrelizumab at our center. We included patients that had already completed 2 cycles of therapy and with at least 1 year of follow-up. Patients were divided into two groups: standard dosing (SID; every six months) and extended interval dosing (EID; ≥4 weeks delay). Outcome measures were annualized relapse rate (ARR), disability progression, changes in B and T cell counts, immunoglobulin levels, MRI activity, and adverse events. Statistical analyses included t-tests, chi- square tests or Mann-whitney U test as appropriate, correlations, linear and logistic regression models.

Results: We screened 112 patients; 24 were excluded due to insufficient data or short follow-up. Patient were divided into EID (N=35, 45% female, 3% PPMS) and SID (N=53, 54% female, 26% PPMS). Baseline age (median 45 and 43), ARR (0.41 and 0.39) and disease duration (11.8 and 11.4 years) were similar between the SID and EID groups ($p>0.05$) The mean observation time was $25 \pm 11$ months. The EID group had a median dosing interval of 7.8 months (range: 7.2-8.4 months). 9 patients (8 RR, 1 PP) had >2 delayed administrations. Preliminary analyses did not reveal significant differences in ARR, MRI activity nor disability progression between EID and SID. B cell counts were effectively suppressed in both groups ($p=0.43$). Delayed dosing did not affect CD8+ and CD4+ counts nor immunoglobulin levels. Adverse events were infrequent and comparable in both groups.

Conclusion: Extended interval dosing of ocrelizumab beyond the standard six-month regimen appears to be a feasible option in the treatment of RRMS and PPMS, with comparable outcomes to SID.
Discussion: These findings provide insights for a tailored schedule of ocrelizumab in MS. Further studies in larger cohorts are awaited to validate this option.
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## CLADRIBINE AS EXIT STRATEGY FROM NATALIZUMAB: A SINGLE-CENTER RETROSPECTIVE OBSERVATIONAL STUDY

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Objectives: Natalizumab (NTZ) is a highly effective treatment in patients with Relapsing-Remitting Multiple Sclerosis (RRMS) but there is a risk of disease reactivation after its withdrawal due to the rapid decay of α4β1 integrin saturation. Several exit strategies have been proposed to minimize this risk, but limited data are available regarding the efficacy, safety and immunological impact of cladribine tablets (CLAD)after treatment with NTZ, which is the aim of this study.

Methods: A retrospective observational study was conducted in RRMS patients starting CLAD after NTZ discontinuation. The main variables analyzed were: relapse rate, new T2 and Gadolinium enhancing T1 lesions, EDSS, lymphocyte count and adverse events.

Results: 14 RRMS patients (11 female, median age 43 (range 27-59) years old), with a median disease duration of 12 (5-30) years and a median EDSS of 1.25 (1.0-3.0) were enrolled. Annualized relapse rate (ARR) in the year before NTZ was 1.0 and no relapse was documented under NTZ treatment. The median number of NTZ infusions was 52 (23-138), 13/14 patients received NTZ according to an extended dose schedule. NTZ discontinuation was due to the risk of developing progressive multifocal leukoencephalopathy (PML) in all the cases. The mean wash out interval between NTZ and CLAD was $33,8 \pm 16,7$ days and the median follow up after switching to CLAD was 24 months (12-48). New MRI T2 lesions were detected in 2 asymptomatic patients within 6 months after switch while one patient had a relapse without EDSS progression four months after the second cycle of CLAD. At present, median EDSS is unchanged in the whole group (1.5, range 1.0-3). Transient grade 3 lymphocytopenia was detected in 1 patient during the first year and in 3 patients during the second year after switch. No patients experienced grade 4 lymphocytopenia. The most frequent side effects were headache (n=3), hair loss (n=2), mild upper respiratory tract infections (n=5) and candidiasis (n=1). No serious adverse events were recorded.

Conclusions: According to our results, CLAD represents an efficacious and safe exit strategy from NTZ in patients with high risk of PML. However, a larger sample size is needed to confirm these findings and to establish the prognostic factors predicting an optimal treatment response.
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## DEVELOPMENT OF A WEB APP FOR THE ROUTINE CLINICAL MANAGEMENT OF INFUSION THERAPIES FOR MULTIPLE SCLEROSIS PATIENTS

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The routine clinical management of infusion sessions dedicated to infusion therapies for Multiple Sclerosis (MS) is challenging because of the high number of patients being treated, the time/space constraints of the infusion room, the need to share clinical data with the MS team. From this background we aimed to develop a web app to help managing clinical data collected during infusion sessions. In order to implement the web app in the everyday clinical practice, we worked to make it user-friendly and smartphone-compatible, offering quick access to patients profiles and MS-related clinical data. To ensure the privacy and security of patients information, the web app was developed to adhere to the highest standards of data protection and comply with industry regulations, utilizing secure encryption protocols, access controls and authentication mechanisms. At the time of each patient's examination/infusion the web app allows to collect the following data: referring neurologist, date of the examination, name and cycle of the infusion therapy, medical history update, EDSS (supported by an EDSS calculator), T25FW, 9HPT, MRI report, blood chemistry tests (with a prespecified checklist for each infusion therapy), date of the next examination/infusion (calculated automatically, based on standard/personalized schedule), and open fields for further/detailed description of other relevant data (e.g. neurological examination, ongoing MS-related and non-MS-related therapies, prescribed therapies upon discharge, clinical events such as relapses, infections, pregnancies, etc). The web app has already been set for two different infusion therapies, Natalizumab and Ocrelizumab/Rituximab. For Natalizumab-treated patients is possible to enter the following data: infusion frequency (every 4 to 6 weeks, with the possibility to modify/personalize the schedule and calculate the date of the following examination/infusion), JCV index, monitoring blood tests. For Ocrelizumab/Rituximab-treated patients is possible to enter the following data: infusion frequency (every 6 months, with the possibility to modify/personalize the schedule and calculate the date of the following examination/infusion), linfocyte subsets, immunoglobulin (IgG, IgM and IgA) levels and hepatitis B markers status. Finally, the web app can: i) generate a full report of each examination, ii) create a dot graph for each available clinical measure (EDSS, T25FW, 9HPT, etc) in order to better monitor disease evolution, iii) send an email with a summary of the infusion session to the MS-team. The routine clinical management of infusion therapy sessions at the MS centers can be efficiently supported by modern-digital tools such as a web app, which facilitates standardized collection, monitoring and sharing of clinical data.

## GENETIC REGULATION OF INFLAMMATORY CYTOKINES: HOW SINGLE-NUCLEOTIDE POLYMORPHISM VARIANTS PREDICT CENTRAL INFLAMMATION, DISABILITY, AND RADIOLOGICAL MEASUREMENTS IN MULTIPLE SCLEROSIS

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Background: Genetic variability of cytokines expression in multiple sclerosis (MS), a chronic inflammatory disease of central nervous system, is poorly understood. rs2227306 IL-8 polymorphism influences neuroinflammatory diseases course [1], and rs2069812 IL-5 polymorphism is associated with more severe manifestations of Th2-mediated pathologies [2], with contrasting evidence in Th1 diseases [3].

Objectives: To identify whether IL-5 rs2069812 and IL-8 rs2227306 SNPs effectively predict central neuroinflammation at diagnosis and possible clinical and radiological outcome measurements in MS.

Materials and Methods: In 202 European patients diagnosed with relapsing-remitting (RR-MS), primary progressive (PP-MS) and secondary progressive MS (SP-MS), we performed clinical and radiological assessments at diagnosis, exploring the associations between rs2069812 and a large set of inflammatory molecules, and evaluating EDSS at first (176 patients) and second year (162 patients) after diagnosis. In a second group of 141 relapsing-remitting (RR)-MS patients, rs2227306 polymorphism, CSF IL-8 levels, clinical and demographical characteristics were determined, with assessment of structural MRI measures in 50 patients.

Results: We identified in the first group an association between the presence of recessive (T) allele for rs2069812 and CSF levels of IL-2 ($p = 0.017$), IL-6 ($p = 0.015$), IL-17 ($p = 0.013$), GM-CSF ($p < 0.001$), MIP-1b ($p = 0.008$) and IL-15 ($p = 0.011$). In patients carrying the natural (C) allele, we found an association between CSF levels of IL-5 ($p = 0.012$) and IL-1ra ($p = 0.027$), while no differences emerged in clinical and radiological parameters. In C-carriers we found a negative correlation between CSF levels of IL-5 and EDSS at the first year ($r = -0.244$, $p = 0.040$) and EDSS at second year ($r = -0.314$, $p = 0.013$) after diagnosis, while no significant correlations emerged in T-carriers. In the second group, an association between CSF IL-8 and EDSS at diagnosis was found ($r = 0.207$, $p = 0.014$). CSF IL-8 concentrations were significantly higher in patients carrying the T variant of rs2227306 ($p = 0.004$), with a positive correlation between IL-8 and EDSS at diagnosis ($r = 0.273$, $p = 0.019$), and a negative correlation between CSF levels of IL-8 and cortical thickness ($r = -0.498$, $p = 0.005$).

Discussion and Conclusions: We described for the first time a role of IL-5 and IL-8 SNPs in MS central inflammation, identifying a protective function on disease progression for common variant of rs2069812 and a detrimental function for rs2227306 in terms of radiological impairment and disability.

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## CHARACTERIZATION OF T-CELL RESPONSE TO RECOMBINANT VZV VACCINE IN PWMS UNDER DMTS

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Background: People living with MS (pwMS) are at increased risk of Herpes zoster (HZ), mainly due to DMT mechanism of action. Due to several neurological sequelae of VZV, like post herpetic neuralgia, the recombinant VZV gE vaccine has been approved for immunocompromised individuals with a schedule of two-dose administration without interrupting current DMT. However, as observed in response to other vaccines, among DMT-treated pwMS, dissimilar and reduced humoral and cellular responses to vaccination could been observed. The study aimed to characterized cellular immune responses to recombinant VZV vaccine in pwMS under different DMTs.

Materials and Methods: From February 2023, at the Neuroinfectious Unit, during the assessment of infectious risk, recombinant VZV vaccine has been proposed to pwMS. First, pwMS at increased risk of HZ have been considered, according to vaccine guidelines. Before (T0) and after two months (T1) from first dose, pwMS were enrolled. For the two time points IFNg, IL2 and TNFa production by T-cells upon VZV gE peptide library stimulation was performed. "Activated" T-cells were defined as those producing any of IFNg, IL2 and TNFa, while "triple-positive" T-cells as those simultaneously producing all 3 cytokines.

Results: Among the 76 pwMS at increased risk of VZV reactivation, 12 pwMS underwent recombinant VZV vaccine schedule (10 females/2 males, median age [IQR] 50 [40-60] years). Among them, 50% were ocrelizumab-treated, 8% fingolimod, 17% dimethyl fumarate, 8% natalizumab, 8% cladribine and 8% with peginterferon β1a. To date for 3 pwMS an evaluation at T1 has been performed. No differences in the percentages of CD4+ and CD8+ activated T-cells was observed between T0 and T1 (CD4+: 0.0 [0.0-0.0] and 0.18 [0.17-0.18], respectively; CD8+: 0.0 [0.0-0.0] and 0.0 [0.0-0.0], respectively). The same results were observed for percentages of CD4+ and CD8+ triple-positive T-cells between T0 and T1 (CD4+: 0.0 [0.0-0.0] and 0.02 [0.01-0.02], respectively; CD8+: 0.0 [0.0-0.0] and 0.0 [0.0-0.01], respectively).

Conclusion: In line with current literature on other vaccine responses, such as influenza and SARS-CoV-2, our preliminary data showed that T-cell responses to vaccination in pwMS seems to be significantly influenced by DMTs mechanism of action.

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## IMPACT OF SLEEP QUALITY ON NEUROPSYCHOLOGICAL FEATURES IN MULTIPLE SCLEROSIS

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Objective: Multiple sclerosis (MS) is a chronic neurodegenerative condition characterised by a wide range of symptoms. Sleep disturbances affect most MS patients, and could present as sleep-disordered breathing, insomnia, daytime sleepiness, narcolepsy and restless legs syndrome. Sleep disturbances can contribute to pain, depression, anxiety and fatigue, which are commonly observed in patients with MS, with a negative effect on their Quality of Life. However, the impact of sleep quality on neurocognitive functions in this population is still poorly explored. Therefore, the aim of the study is to assess the interplay between sleep quality, cognition, fatigue, anxiety and depression in MS patients.

Material and Methods: Consecutive MS patients underwent clinical (EDSS, age, gender), cognitive (Symbol digit modality test [SDMT], Brief Visuospatial Memory Test [BVMRT], California Verbal Learning Test [CVLT]), and psychosocial (Modified Fatigue Impact Scale [MFIS], Beck Depression Inventory [BDI], Beck Anxiety Inventory [BAI]). Sleep quality was assessed through the Pittsburgh Sleep Quality Index [PSQI] total score. Cognition was calculated as the sum of cognitive tests failed according to Italian normative data (Cerebral Functional System [FS] score). Multiple linear regression models were applied to explore association between PSQI total score (dependent variable) and BDI, BAI, MFIS total scores and subscores and cerebral FS (independent variables) by accounting for age, gender and EDSS (covariates)

Results: We enrolled 522 MS patients (353 female; mean age 42.61 ± 13.02 years; mean EDSS 3.08 ± 1.59; 424 relapsing-remitting and 98 progressive patients). 266 patients (51%) presented with cognitive impairment. Mean physical MFIS was 9.84 ± 11.08; mean cognitive MFIS was 7.99 ± 10.02; mean psychosocial MFIS was 1.69 ± 2.39. Patients presented with a mean BDI 7.26 ± 9.73, mean BAI 4.67 ± 10.86 and mean PSQI of 2.71 ± 3.83. Higher scores at PSQI correlated with MFIS physical fatigue (coeff. 0.76, 95%CI 0.51 – 1.00, p<0.001), MFIS cognitive fatigue (coeff. 0.75, 95%CI 0.52 – 0.98, p<0.001), MFIS psychosocial fatigue (coeff. 0.12, 95%CI 0.07 – 0.18, p<0.001), BDI (coeff. 1.13, 95%CI 0.92 – 1.35, p<0.001), BAI (coeff. 0.93, 95%CI 0.64 – 1.22, p<0.001) but not with cerebral functional system score (p=0.15).

Conclusion: Sleep quality greatly influences neuropsychological features in patients with MS. A worse quality of sleep is related to higher levels of fatigue (psychosocial, physical and cognitive), depression and anxiety. These findings strongly support the need to evaluate sleep disorders in MS in order to improve its quality to reduce long-term consequences. Therefore, enhancing sleep quality could slow down disease progression.

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## EFFICACY AND SAFETY OF TIXAGEVIMAB-CILGAVIMAB (EVUSHELD ®) IN PEOPLE WITH MULTIPLE SCLEROSIS ON OCRELIZUMAB: PRELIMINARY EVIDENCE

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Background and aims: Evusheld (EVS) was authorized by FDA and EMA as pre-exposure prophylaxis (PrEP) in people at high risk of severe Covid-19 outcomes, including people with Multiple Sclerosis (pwMS) on B-cell depleting (BCD) therapies - such as Ocrelizumab (OCR). In this population, no data on possible adverse drug reactions (ADRs) to EVS, B-lymphocytes (CD20+) counts pre- and post-EVS injection, and comparison of percentage increase of IgG antibodies directed against SARS-CoV-2 trimeric spike protein (anti-TSP IgG) post-Evusheld and Covid-19 vaccine was available. The aim of this study was to better characterize the efficacy and safety profile of EVS in pwMS on BCD agents.

Materials and Methods: 17 pwMS on OCR agreed to receive EVS as PrEP for Covid-19. Sera samples were collected before the first dose of Covid-19 vaccine (T0), 4 weeks after the second dose (T1), 4 weeks after third dose (T2), immediately before (T3) and 4 weeks after (T4) EVS.

Results: Covid-19 vaccine ADRs were mild-to-moderate, whereas no ADRs were reported after EVS injection. A significant increase of anti-TSP IgG was found only at T0-T1 ($Z = -3.059$, $p=.002$) and T3-T4 ($Z= -3.621$, $p<.001$) time-points. The median percentage increase between T3-T4 was significantly higher with respect to the T0-T1($Z = -3.296$, $p=.001$) and T1-T2 ($Z = -3.059$, $p=.002$) time-points.

Conclusions: These results further support EVS safety and efficacy in boosting anti-TSP IgG titers in pwMS on OCR, with a statistically greater increase than that observed after completion of a full Covid-19 vaccine cycle, plus a booster dose.

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## HYPOCALORIC DIET IMPROVES FATIGUE AND ANXIETY IN OVERWEIGHT PERSONS WITH MULTIPLE SCLEROSIS

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Objectives: Overweight and other cardiovascular risk factors are known contributors to disability accrual in Multiple Sclerosis (MS) [1,2,3]. We aimed to explore the impact of different dietetic approaches on cardiovascular risk and clinical status in overweight persons with MS (pwMS).

Material and Methods: Overweight pwMS (body mass index-BMI>25 kg/m2) were prospectively enrolled, randomly allocated to three hypocaloric dietetic plans differing in macronutrients composition (carbohydrates/proteins/lipids diet A 65%/15%/20%; diet B 35%/25%/40%; diet C 50%/20%/30%) and followed-up for 1 year (6 months of dietetic intervention and 6 months of observation). The Multiple Sclerosis Performance Test, a self-administered, iPad®-based system for quantifying cognition, upper and lower extremity motor function, and vision was performed at baseline, 6 and 12 months. Questionnaires for the evaluation of sleep quality, fatigue, anxiety, depression, stigma, social participation and satisfaction were administered. Information about cardiovascular risk parameters (BMI, waist circumference-WC, umbilical circumference-UC, hip circumference-HC, blood pressure, total, HDL and LDL cholesterol, triglycerides, glycemia) were collected. Adherence to the diet plan was quantified as days of complete to insufficient adherence across the treatment period. Between-group comparisons were performed with Chi-square and ANOVA; longitudinal analyses with one-way ANOVA for repeated measures and mixed-design ANOVA.

Results: Fifty-three patients were analyzed (diet A n=19, diet B n=18, diet C n=16). The three groups were well matched for sex, age, disease duration and EDSS. Along the 6 months of dietetic intervention, no difference in adherence was detected across the three dietetic plans ($p=0.84$). Overall, patients showed a significant weight reduction over time ($p<0.001$), with a mean weight loss of 4 kg at 6 months, and substantial weight stability from month 6 to 12. No difference in weight loss over time was observed across diets ($p=0.34$). BMI, WC, UC, HC, HDL and LDL cholesterol improved over time (p ranging from 0.03 to 0.001), with no differences across diets (p ranging from 0.16 to 0.55). Among all tested clinical variables, fatigue and anxiety improved significantly at 6 months in comparison with baseline ($p=0.004$, $p=0.013$), with no differences across diets ($p= 0.58$, $p=0.89$).

Discussion: Dietetic interventions in overweight pwMS, irrespective of the specific macronutrients composition, are able to improve their cardiovascular profile. Although no variations in objective disability scores could be detected, during the treatment period anxiety and fatigue were significantly decreased.

Conclusion: Hypocaloric dietetic interventions should be encouraged in all overweight pwMS, to ameliorate their cardiovascular profile and the perception of subjective symptoms such as anxiety and fatigue.

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## RELAPSE RISK FOLLOWING DE-ESCALATION FROM FINGOLIMOD TO DIMETHYLFUMARATE IN MULTIPLE SCLEROSIS PATIENTS

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Objective: Currently, there is no consensus on the sequencing of Multiple Sclerosis (MS) therapies, resulting in variable use of disease-modifying therapies (DMTs) in routine practice. The discontinuation of lymphocyte sequestering agents such as fingolimod (FTY) is known to leave the patient vulnerable to disease reactivation, especially in case of long wash-out periods before the subsequent DMT. Since several real-world studies directly comparing dimethylfumarate (DMF) and FTY largely demonstrated similar effectiveness between these DMTs, we aimed to assess the effectiveness of DMF following FTY discontinuation using data from the Italian MS Registry.

Methods: We included MS patients who discontinued FTY and started DMF or a cell-depleting agent (ocrelizumab, alemtuzumab, cladribine or rituximab) within six months, and assessed differences in the occurrence of relapses between the groups and, among patients on DMF, between those discontinuing FTY due to lack of efficacy versus other reasons.

Results: We included 822 patients; 163 started DMF and 659 started a cell-depleting agent after a median of 10 weeks (IQR: 6-15) from FTY termination. Relapses occurred after a median of 8 months (IQR:2-18) in 61 patients (37%) on DMF compared to 87 (13%) on depleting agents ($p<0.001$). They occurred in a greater proportion of patients discontinuing FTY due to lack of efficacy (24/47-51%) as opposed to other reasons (37/116-32%) ($p=0.022$). In the latter group, a washout period >6 weeks significantly increased the risk of a relapse (OR: 2.47, 95%CI: 1.03-5.92; $p=0.042$). Predictors of relapses in the DMF-treated group at monovariable analyses were: relapses during the washout-period (OR:3.80, 95%CI:1.23-11.73; $p=0.020$), FTY discontinuation due to lack of efficacy (OR: 2.23, 95%CI: 1.11-4.45, $p=0.023$), relapses in the year preceding FTY treatment (OR: 2.25, 95%CI: 1.05-4.84, $p=0.038$) and age (OR: 0.97, 95%CI: 0.93-0.99; $p=0.042$). At multivariable analysis, only relapses during the washout-period were independently associated with relapses during DMF treatment (OR:3.43, 95%CI: 1.07-10.98; $p=0.038$).

Discussion and Conclusion: Patients de-escalating from FTY to DMF for any reason have a significantly greater risk of relapsing compared to patients transitioning from FTY to cell-depleting agents, especially in case of treatment switch to DMF due to lack of efficacy, with over half of these patients relapsing. Relapses during the washout period are independent predictors of a relapse during DMF treatment and should lead to consider the option of a high-efficacy treatment following FTY discontinuation.

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## BASELINE WHOLE BRAIN VOLUME AND DISABILITY PROGRESSION IN OZANIMOD-TREATED PATIENTS WITH RELAPSING MULTIPLE SCLEROSIS

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Objective: In people with multiple sclerosis (MS), brain volume loss correlates with long-term disability progression. This secondary analysis assessed disability progression over 5-7 years of ozanimod treatment stratified by high or low baseline whole brain volume (WBV).

Materials and Methods: In the 24-month phase 3 RADIANCE (NCT02047734) trial, patients with relapsing MS (RMS) were randomly assigned ozanimod 0.46 or 0.92 mg/d or IFN beta-1a 30 μg/wk; completers were eligible to enrol in DAYBREAK (NCT02576717) and receive ozanimod 0.92 mg. Kaplan-Meier analyses of 3-month confirmed disability progression were performed for patients with high versus low RADIANCE baseline WBV.

Results: At the February 2, 2021, data cutoff (5-7 years of ozanimod treatment), high baseline WBV was associated with a lower proportion of patients with and slower rates to disability progression when compared with the low baseline WBV group in those who switched from IFN beta-1a to ozanimod 0.92 mg (high/low hazard ratio (HR) [95% CI]: 0.56 [0.32–0.96], nominal $P=0.0365$). A relatively similar numerical trend was observed for patients who received continuous ozanimod 0.92 mg (high/low HR [95% CI]: 0.85 [0.49–1.47], nominal $P=0.5587$).
Conclusion: In RADIANCE and DAYBREAK, high baseline WBV was associated with numerically less disability progression over 5-7 years of ozanimod treatment compared with low baseline WBV in patients with RMS; however, these subgroup analyses assessed a small sample size and are hypothesis generating rather than declarative.
Funding. This study was supported by Bristol Myers Squibb.

## HOW TO INTEGRATE PROXIMITY CARE IN MULTIPLE SCELROSIS MANAGEMENT: THE STAYHOME PROJECT EXPERIENCE

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Objectives: The objective of the StayHome project is to integrate proximity care into the management of Multiple Sclerosis (MS) patients in Italy, addressing the organizational complexity that patients currently face. The project aims to identify improvement areas for proximity care implementation, define a desired care model, and implement, monitor, and support proximity care in MS Centers by adopting a bottom-up approach involving healthcare professionals and patient associations.

Materials and Method: First, a mixed method survey has been conducted involving 50 Centers to identify the main improvement areas for proximity care implementation and to build a cross-Center analysis framework. 14 Multiple Sclerosis Centers in 9 Regions were then involved on a voluntary basis to map the AS IS and define a TO BE care model, based in each Center on face-to-face interviews, collection of organizational data, on-site assessment, and roundtables. More than 150 healthcare professionals, hospital managers and regional stakeholders have been involved in such activities with a potential impact for about 14,000 patients. A Steering Committee, including KOLs, PAG and Scientific Association representatives, supervised progresses and methodologies adopted in the project, including Key Performance Indicators to monitor the patient pathway and a Maturity Model to assess and support MS Centers in the path towards proximity care.

Discussion: Implementing proximity care in MS management posed challenges due to the complex nature of the disease. It became evident that a uniform approach is suboptimal, given the influence of regional and local specificities. Instead, a bottom-up approach, which involved collaboration with local healthcare professionals and patient associations, emerged as a more effective strategy. The active involvement and support of hospital and regional managers played a crucial role in addressing the unique challenges faced by each MS Center. In addition, different areas of intervention have been identified as a priority, including the formalization of integrated Hospital – Territory pathways, the digitalization of patient pathways and the empowerment of a multidisciplinary approach especially for neurological rehabilitation.

Conclusion: The findings highlighted the limitations of a uniform approach in the implementation of proximity care for MS in Italy and underscored the importance of context-aware strategies. In addition, the findings identify the priority areas to address and provide Key Performance Indicators and Maturity Model as practical tools to assess and support the implementation of proximity care. Finally, the project outcomes provide valuable insights for scaling up proximity care models at the regional and national levels.

## IN VIVO EFFECTS OF THREE DISEASE MODIFYING THERAPIES (DIMETHYL FUMARATE, NATALIZUMAB AND CLADRIBINE) ON IMMUNOLOGICAL SUBSETS IN RELAPSING REMITTING MULTIPLE SCLEROSIS

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Objectives: Using flow cytometry, we aimed to assess immune cell subsets differences in terms of myeloid, T- and B-cell subsets in peripheral blood of relapsing–remitting multiple sclerosis (RR-MS) patients treated with different disease modifying therapies (DMTs).

Materials: This cross-sectional, prospective, observational study was conducted at the MS Center of University of Catania, Italy.

Methods: We included follow-up RR-MS patients treated with DMTs with different mechanisms of action (cladribine [CLD], dimethyl fumarate [DMF] and natalizumab [NTZ]), in the period between July 2022 and September 2022. Each patient underwent a clinical and radiological evaluations and blood sample collection.

Results: Out of 52 RR-MS patients screened, 43 (83.7% women; mean age at diagnosis 34.7±11.1 years; median EDSS 2.0, IQR 1.0–2.8) were finally enrolled. A total of 24 (55.8%) patients were treated with DMF, 10 (23.3%) with NTZ and 9 (20.9%) with CLD. At follow-up (after a mean period of 20 ± 4 months of treatment), patients treated with DMF showed reduced percentage of total CD3+ (74±6.9 vs 64.2±12.1, p =.001), of the CD3+CD8+ (T-cytotoxic) (26.7±7 vs 18.5±6.4, p<.001), and of the CD4+CD25+CD127low/− (T-reg) (8.1±2.5 vs 5.9±3, p =.009). The DMT group also showed a significant increase of the percentage of the CD15+/CD33+/CD14-/HLADR−/low (G-MDSCs) (59.9±9.8 vs 67±7.7, p =.008), of the CD4+/CD8+ ratio (1.9±0.8 vs 2.6±0.9, p=.004), of the CD4+CD45RA+ (T-naïve) (40.3±14.7 vs 51.7±16.8, p=.02) and of the percentage of the B-naïve (56.2±11.8 vs 70.5±10.8, p< .001). In the NTZ group, a decreased percentage of total CD3+ (73.3±7.5 vs 64±7.8, p =.02) was found, while the percentage of the total CD19+ was increased (9.9±3.1 vs 16.1±8.1, p=.04). Finally, a reduction in the percentage of total CD3+ (76.4±6.3 vs 59.3±9.7, p<.001), of the CD3+CD4+ (T-helper) (46.7±8.8 vs. 33.6±6.2, p =.002), and of the CD3+CD8+ (T-cytotoxic) (29.7±8.4 vs 22.1±7.2, p=.05) was found in patients treated with CLD.

Discussion: DMTs induced significant modifications in myeloid, B-, and T-cell immunophenotypes. Conclusions. The characterization of the immunologic changes, occurring during MS and in response to DMTs, might represent a new parameter for the monitoring of disease activity, progression and therapy efficacy.

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## USE OF TERIFLUNOMIDE IN YOUNG WOMEN WITH MULTIPLE SCLEROSIS: A RETROSPECTIVE STUDY ON THE DETERMINANTS OF CHOICE

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Objects: Teriflunomide is a once-daily oral immunomodulatory agent for relapsing–remitting multiple sclerosis (MS). While safety concerns about pregnancy historically drove the propensity to prescribe teriflunomide to men rather than women, over the years, the use of teriflunomide has changed, increasing significantly among women [1,2]. In this context, this study explored determinants of the choice of teriflunomide in MS women of reproductive age.

Materials and Methods: This retrospective study included women between 20 and 40 years of age with MS diagnosed according to

McDonald's criteria and recruited from Multiple Sclerosis Centre of University of Cagliari. Patients were classified as naive and switchers for tolerability or safety. The determinants of the choice of teriflunomide were detected with an ad hoc questionnaire aimed at assessing the presence of conditions complicating the use of other first-line disease modifying treatments (DMTs) (i.e., needle phobia, gastrointestinal problems, allergic diathesis). It was also recorded whether the MS woman already had children.

Results: A sample of 77 MS women between 20 and 40 years of age treated with teriflunomide were included in the analysis. Mean age and disease duration were 38.7 ±8.2 and 8.1±6.3 years, respectively, with mean drug exposure of 19,1±22,7 months. Mean EDSS was 1.3 ± 0.7. Seventeen (22.1%) patients were naïve, and 60(77.9%) were switched from other DMTs, of which 60(77.9%) for tolerability and safety reasons (19 after dimethyl fumarate discontinuation and 41 after injectable DMTs).The presence of needle phobia in 9(11.7%) patients,allergic diathesis in 16 (20.8%), and gastrointestinal problems in 28(36.4%), all conditions interfering with the use of other DMTs,and having already had children in 34(44.2%) patients,were the determinants of teriflunomide choice most frequently reported.

Discussion: Recent real-world experience has shown that the use of teriflunomide is constantly evolving [1,2].The efficacy, safety,and tolerability profile of teriflunomide is well established in real-world experience, and its use is associated with a high level of treatment satisfaction [3]. Based on this evidence, its use has increased in all categories of patients, older and younger ones, including women.

Conclusions: Teriflunomide is a valid therapeutic option due to its tolerability both in naïve women and in switchers. In particular, its use is to be considered for those patients with needle phobia, gastrointestinal problems or allergic diathesis, which would complicate or have complicated the use of other first-line DMTs, and for those women who have already had children or who do not want any in the short term.

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## HOW TO BEHAVE IN A PEDIATRIC PATIENT WITH MYELIN-OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY-ASSOCIATED DISEASE (MOGAD) AND A SUBCLINICAL RELAPSE: TREAT OR NOT? A CASE REPORT

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Background and Aims: Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) is an inflammatory demyelinating disease of the central nervous system (CNS). MOGAD is typically associated with acute disseminated encephalomyelitis, optic neuritis, or transverse myelitis, and is less commonly associated with cerebral cortical encephalitis, brainstem presentations, or cerebellar presentations. MOGAD can present as either a monophasic or relapsing disease course.

Materials: We performed brain and spinal cord MRI, physical examination, laboratory exams and electroencephalography (EEG) with and without sleep deprivation.

Methods: We report the case of a patient with typical features of MOGAD with a subclinical relapse.

Results: In March 2022, a 3-year-old girl presented to hospital with seizures, gait imbalance, ipovisus in right eye and behavioral changes. Brain and spinal cord MRI showed occipital cortical and subcortical T2-FLAIR hyperintensities, as well as inflammatory lesions in basal ganglia, in the right optic nerve and in the spinal cord (C4-C5 and in the conus, D12-L1). Laboratory work-up showed MOG-antibody positivity (qualitative dosage), while other tests, including aquaporin4 antibody were normal. Considering MRI and laboratory findings, we made a diagnosis of MOGAD and the patient started a therapy with high dosage of methylprednisolone followed by oral tapering of prednisone for one month. Later, the patient made clinical, neuroradiological and EEG follow-ups, with and without sleep deprivation. The exams showed an improvement of patient condition. Furthermore, we repeated a quantitative dosage MOG-Ab that showed, initially, an alteration (August 2022, titer of 1:640) and, subsequently, a negativization (November 2022, titer of 1:40). The patient did not show any symptom. However, but in an EEG follow-up, (February 2022) we found a new epileptogenic focus in left occipital lobe and generalized epileptiform abnormalities. So, we made a new dosage of MOG-Ab that showed a positive titer (1:320) and a brain and spinal cord MRI, negative for new lesions.

Discussion: It is difficult, for a clinician, to treat a patient only for abnormality laboratory or electroencephalography findings, without clinical manifestations. On the other hand, we know that MOGAD could be a relapsing disease with a complete or incomplete/partial recovery.

Conclusions: The possibility of starting a treatment and the potential type of treatment were discussed. We decided to wait and evaluate the situation over time. We were also wondering whether to treat with corticosteroids (high dosage followed by tapering) or with immunoglobulin intravenous every 28 days, as seems to be effective in MOGAD with relapses, but could be a complex treatment in such a young patient.

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## NEUROMYELITIS OPTICA SPECTRUM DISORDER WITH POSITIVE ANTI-AQUAPORIN-4 ANTIBODY RELATED TO THE IMMUNE CHECKPOINT INHIBITOR NIVOLUMAB

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Background: Immune checkpoint inhibitors (ICIs) development has greatly improved survival of patients with advanced malignancies. Nevertheless, ICIs can cause immune-related adverse effects (irAEs) involving any organ. Neurological irAEs are infrequent and mostly reported in patients with melanoma.

Case presentation: A 62-year-old man without any previous illnesses was diagnosed with melanoma of the pectoral region. Following resection, adjuvant ICIs with nivolumab (an anti-programmed cell death protein 1 antibody) was recommended. Since a bilateral immune-related pneumonitis was diagnosed, nivolumab was stopped after one year of treatment (10 cycles of therapy). Four months later, the patient developed lower extremity weakness with paresthesia and urinary retention. His neurological examination revealed paraparesis with brisk knee jerks and a sensory level at T7. Magnetic resonance imaging (MRI) of the spinal cord showed centrally located T2-hyperintensity from C2 to C7 level and from D4 to D8 with contrast enhancement and spinal cord edema. Analysis of the cerebrospinal fluid (CSF) showed an increased white cell count of 52 cells/μL (83% neutrophils), protein concentration of 275 mg/dL, normal glucose concentration; oligoclonal bands were not detected. CSF bacterial cultures were negative as well as viral panel and citology. An investigation for markers of autoimmune disorders, anti-neuronal antibodies, and myelin-oligodendrocyte glycoprotein antibodies yielded negative results. In contrast, anti-aquaporin-4 antibody (AQP4-Ab) tested positive (titer 1:10). Brain MRI and ophthalmologic examinations were normal. Neuromyelitis optica spectrum disorder (NMOSD) was diagnosed, and high-dose intravenous methylprednisolone was administered (1 g/daily for 7 days), followed by tapered oral steroids and 5 days of intravenous immunoglobulins therapy. Two weeks later, spinal MRI showed improvement in the cervical region, but remnant dorsal lesions without contrast enhancement. Also CSF improved after treatment (cell count: 5 cells/μL, protein concentration: 78 mg/dL); AQP4-Ab tested negative after one month. Nevertheless, paraparesis and sensory loss improved only minimally; after extensive discussion between oncology and neurology, mutual decision was made to move forward with rituximab.

Discussion: Our patient developed anti-AQP4 antibody-positive NMOSD after four months of nivolumab therapy discontinuation. To the best of our knowledge, this is the fourth known case of nivolumab-induced NMOSD; all described cases showed limited response to glucocorticoids and poor functional outcome.

Conclusions: The mechanism of ICIs causing NMOSD is not completely understood and predicting emergence of NMOSD after nivolumab injection is currently difficult. Therefore, clinicians should be aware of this kind of neurological irAEs and start treatment of these complications as soon as possible.

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## A MULTIDIMENSIONAL SELF-REPORTED EVALUATION OF FRAILTY IN PEOPLE WITH MULTIPLE SCLEROSIS


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Objective: Multiple Sclerosis (MS) is a neurodegenerative disease of the central nervous system. People with MS (pwMS) have a high risk of frailty that could be measured by different tools. We aim to evaluate frailty using the Tilburg frailty indicator (TFI), a multidimensional self-reported questionnaire, and to explore its relationship with autonomy, quality of life (QoL), and disability.

Methods: All the patients with MS enrolled completed TFI (frail with a TFI score $\geq$ 5 points), the Groningen Activities Restriction Scale to evaluate autonomy, and the Multiple Sclerosis Impact Scale-29 to evaluate QoL. We collected the Expanded Disability Status Scale (EDSS) score, age and gender. Data were analysed using descriptive analyses, hierarchical multiple regression, and ANCOVA.

Results: A total of 208 adults with MS (mean age 44 years, SD=11; 75% of women; 89.4% relapsing-remitting) were enrolled. The mean TFI total score was 5.7 points (SD=3.0; range 0-14), with the 62.5% of participants exhibiting frailty. After controlling for age and gender, the EDSS score was revealed to influence the total ($\beta$=0.469; R2=0.255; $p<0.001$) and the physical ($\beta$=0.571; R2=0.349; $p<0.001$) frailty score, with an explained variance of 25.5% and 34.9%, respectively. No effects on psychological and social frailty domains were detected. The proportion of frail patients with EDSS $\geq$ 6.0, EDSS within 3.5-5.5, and EDSS $\leq$ 3.0 was 91.7%, 83.3%, and 66.0%, respectively. Frail patients exhibited higher autonomy impairment (p=0.017) and worse QoL ($p<0.001$).

Discussion: We found a high frequency of frail patients with MS. Frailty is more common in patients with higher disability, but it affects also those with low EDSS.

Conclusion: In people with MS frailty could be influenced by factors other than disability.

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## NATALIZUMAB IN THE SETTING OF PEDIATRIC-ONSET MULTIPLE SCLEROSIS: A REAL-WORLD EXPERIENCE IN COMPARISON WITH A MATCHED ADULT POPULATION


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Introduction: Pediatric-Onset Multiple Sclerosis (POMS) is characterized by a more aggressive disease course and earlier development of physical and cognitive disability compared to Adult-Onset MS (AOMS). Therefore, early introduction of highly effective treatment, such as Natalizumab (NTZ), is mandatory.

Objectives: To evaluate the efficacy of NTZ in POMS on both clinical and radiological outcomes compared to an AOMS matched control group.

Methods: We enrolled 36 POMS in a single-centre retrospective study and compared them with a propensity-matched AOMS control group. Both POMS and AOMS were treatment-naïve and were matched for gender, baseline Expanded Disability Status Scale (EDSS), and disease duration. Both radiological (i.e. no evidence of new/enlarging

white matter lesions or gadolinium-enhancing lesion) and clinical (i.e. no evidence of clinical relapse or EDSS worsening) no evidence of disease activity (rNEDA and cNEDA respectively) were evaluated at 12 and 24 months. Survival analysis was conducted on whole observation period. Disease activations occurring within the first six months of NTZ were not considered.

Results: 36 POMS and 36 AOMS control patients were enrolled in this study. Baseline characteristics were as follows: (i) M/F = 14/22 in both POMS and AOMS; (ii) median EDSS = 1.0 (range 0-2.5) in both groups; (iii) median disease duration = 3 months (IQR 2-5.5) in POMS and 3 months (IQR 2-6.25) in AOMS; (iv) mean age (±SD) = 14.6 (±2.0) in POMS and 30.0 (±6.8) in AOMS; and (v) median follow-up time = 37.5 months (range 6-136) in POMS and 24 months (range 12-105) in AOMS. None of the POMS patients and one AOMS experienced a clinical relapse during the first 2 years of treatment. While at month 12 no difference was observed between AOMS and POMS (p=1.0), at month 24 93.1% (27/29) of POMS and 77.8% (21/27) of AOMS fulfilled the NEDA condition (p=0.137). Survival analysis confirmed this trend (log-rank test p=0.16). Wilcoxon's signed-rank test showed no significant changes in EDSS values among AOMS from baseline to last follow-up (p=0.52 with a median follow-up of 24 months). On the other hand, statistically significant sustained improvement on EDSS score emerged in POMS (p=0.005 with a median follow-up of 37.5 months).

Conclusion: This study provides evidence that NTZ is highly effective in treating POMS. Additionally, NTZ treatment in POMS determined a significant EDSS improvement. Our findings support the use of NTZ as the first treatment option for POMS.

## THE NEUROPSYCHOLOGICAL CORRELATES OF IMPULSIVENESS IN MULTIPLE SCLEROSIS

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Objective: The aim of the present study was to explore the association between impulsiveness and neuropsychological profile in people with Multiple Sclerosis (MS).

Materials: Forty-four people with MS underwent a comprehensive cognitive battery (Rao's Brief Repeatable Battery of Neuropsychological Tests1), and behavioral scales tapping impulsiveness (Barratt Impulsiveness Scale; BIS-11), apathy (Dimensional Apathy Scale; DAS), depression (Beck Depression Inventory-II; BDI-II), and interoceptive sensibility (Self-Awareness Questionnaire; SAQ).

Methods: We performed correlation and regression analyses to investigate the relation between impulsiveness and neuropsychological profile in MS.

Results: Correlational analyses showed that the BIS-11 total and Non-Planning subscale scores had high correlations with the Symbol Digit Modalities Test score (SDMT: $r \geq -0.469$, $p = < 0.001$); and with the DAS total score ($r \geq 0.493$; $p<0.001$). Moreover, the BIS-11 Attentional subscale score showed high correlations with the DAS executive subscale score ($r= 0.505$, $p< 0.001$), the BDI II total score ($r=0.584$; $p<0.001$), and SAQ total score ($r= 0.485$; $p<0.001$). All other correlations did not survive after Bonferroni's correction level of significance (p=0.001). Linear regression analyses showed that the BIS-11 total and Non-Planning subscale scores predicted the SDMT ($\beta \geq -1.272$; $t \geq -3.702$; $p \leq 0.001$) and the DAS score ($\beta \geq 0.435$; $t \geq 4.160$; $p \leq 0.001$); whereas the BIS-11 Attentional subscale score predicted the SAQ ($\beta= 2.197$, $t = 3.593$, p=0.001), the BDI-II ($\beta= 1.129$, $t = 4.664$, $p<0.001$), and the DAS executive subscale score ($\beta= 0.613$, $t = 3.794$, $p<0.001$).

Discussion: Our findings suggest that sub-traits of impulsiveness are differentially related to cognitive and behavioral aspects in MS. In particular, Non-Planning impulsiveness would be mainly related to behavior-based measure of executive functioning [1,2]; whereas Attentional impulsiveness would seem to be a significant contributing factor for behavioral disorders and to reflect an overestimation of bodily sensations [3].

Conclusions: The present study suggests a new approach for investigating the relation between neuropsychological profile in MS and impulsiveness as multi-dimensional construct. Our behavioral results fit neurofunctional evidence suggesting a disfunction of prefrontal regions subserving cognitive and emotional aspects of self-regulation.

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## NON-INFECTIOUS PNEUMONITIS AS A RARE ADVERSE REACTION OF ALEMTUZUMAB TREATMENT: A CASE REPORT AND A BRIEF LITERATURE REVIEW

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Objective: Alemtuzumab is an anti-CD52 monoclonal antibody approved for the treatment of active Relapsing Remitting Multiple Sclerosis (RRMS) by European Medicines Agency (EMA) in 2013. Since then, post-marketing evidence has highlighted some rare but severe Adverse Drug Reactions (ADRs), including respiratory complications.

Materials and Methods: We report the case of a patient in follow up at our Neuroimmunology Centre throughout medical records, radiological imaging, and laboratory results. A literature search about alemtuzumab-induced respiratory reactions was performed.

Results: A 37-year-old male diagnosed with RRMS started alemtuzumab treatment and completed the first cycle without complications in November 2021. Twelve months later he initiated the second treatment cycle. After the second infusion he developed persistent non-productive cough and dyspnea. The treatment was discontinued. Vital signs and physical examination were normal except for diffuse bilateral harsh breath sound and rhonchi on chest auscultation. Lab analysis evidenced a slight increase of c-reactive protein and leukocyte count. A chest x-ray showed a thickening of the interstitial tissue with bilateral consolidations. CT-scan documented multiple bilateral ground-glass and pseudonodular opacities with peribronchovascular distribution. A bronchoalveolar lavage (BAL) was performed and the differential cell count revealed 49% macrophages (without hemosiderin inclusions) and 51% neutrophils. All microbiological tests on BAL and serum resulted negative. The patient was left untreated and spontaneously recovered. One month later a CT-scan showed complete resolution of the pulmonary alterations.

Discussion: All the findings in our case supported the diagnosis of an alemtuzumab-induced pneumonitis. This evidence adds to other reports that have placed greater emphasis on diffuse alveolar

haemorrhage (DAH), recently reported by EMA as a severe risk associated with alemtuzumab. However, any induced lung injury is important considering its correlation with serious complications including respiratory failure. Moreover, our case proves these complications can occur not only during the first treatment cycle as usually found. Several pathogenetic mechanisms have been proposed, among which the most significant seem to be cytokine release syndrome and cytotoxic damage mediate by innate immune system cells. These mechanisms need to be further investigated, considering the different onset-time and severity of lung injury described in the literature.

Conclusion: The identification of risk factors and the characterization of premedication/treatment for ADRs, such as pneumonitis, would improve the safety profile of alemtuzumab. Furthermore, it is crucial to increase clinicians' awareness of the potential complications of alemtuzumab for their timely identification.

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## RADIAL SHOCK WAVE THERAPY FOR SPASTICITY IN MS: A PROSPECTIVE SINGLE ARM TRIAL

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Objectives/Aims: To assess the efficacy of radial shock wave therapy to improve lower limb spasticity and deambulation in MS patients.

Materials: The modified Ashworth scale was used to assess spasticity (both for the quadriceps and the triceps surae). The following test were used to evaluate deambulation: timed 25-foot walk (T25FW) test, timed up and go (TUG) test. Pain was assessed using the spasticity visual analog scale and pain visual analog scale (VAS), depression using the Beck depression inventory and finally cognition using the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS).

Methods: This is an ongoing single-arm prospective trial of radial shock wave therapy for lower limb spasticity in MS patients. Patients are treated with radial shock waves (1.5 bar, 4 Hz, 3000 shots for 15 minutes) once every week for 4 weeks. The endpoint of the study is to assess changes in lower limb spasticity, deambulation, depression and cognition from baseline (T0) to after 4 weeks of radial shock wave therapy (T4), and then every month afterwards (T5, T6, T7) up to 3 months from the last treatment.

Results: Up to March 2023, 30 patients have been recruited in the study (mean age 55.8±10.4 years, median EDSS 6.0, range 3.5-7.5). After 4 cycles of radial shock wave therapy (at T4), a significant improvement was observed for the modified Ashworth scale (both for the quadriceps and the triceps surae), timed 25-foot walk (T25FW) test, timed up and go (TUG) test, spasticity visual analog scale and pain visual analog scale (VAS), depression (Beck depression inventory), which was sustained for the 3 months of observation after the end of treatment (at T5, T6, T7). No treatment-related adverse events were reported.

Discussion: Radial shock wave therapy is used to treat pain and spasticity in patients with cerebral palsy and stroke. Previous studies suggest that it could be useful also for the treatment of spasticity in MS patients; our study confirms this data.

Conclusions: Radial shock wave therapy is effective to reduce spasticity and to improve deambulation in MS patients, with effects sustained over time and without significant adverse effects.

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## MUCOSAL ASSOCIATED INVARIANT T (MAIT) CELLS MEDIATE THE GUT-BRAIN CROSSTALK IN PEOPLE WITH MULTIPLE SCLEROSIS (MS)

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Background: Mucosal associate invariant T (MAIT) cells are unconventional T cells with an innate-like phenotype. They recognize microbial-derived riboflavin derivatives presented by the major histocompatibility class (MHC) I-related protein MR1 and their mature phenotype is deeply influenced by the microbiome composition [1].

Objective: The overall goal of this study was to describe the role of MAIT cells in the pathogenesis of multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE).

Methods: MAIT cell activation and effect during Experimental Autoimmune Encephalomyelitis (EAE) was studied in MR1-/- mice [2], lacking completely MAIT cells, and MR1 sufficient (MR1+/+ and MR1+/-) controls by flow cytometry. The effect of the gut microbiome composition on MAIT cells phenotype was inquired in a separate set of experiments changing housing conditions. Peripheral blood (PB) and cerebrospinal fluid (CSF) samples were obtained from newly diagnosed, untreated people with MS (pwMS) and age-matched healthy controls (HCs). MAIT cell number, phenotype and cytokine production were characterized by flow-cytometry. The effect of MAIT cell activation on conventional T cell proliferation was determined by CFSE assay. Gut microbiome composition was determined by 16S, mWGS and ITS sequencing.

Results: MAIT cells are activated during EAE, they acquire a MAIT1 phenotype and have an immunomodulatory role, influenced by the gut microbiome composition. PwMS have lower numbers and defective activation of MAIT cells in both PB and CSF. Activated MAIT cells obtained from pwMS are less effective at suppressing in vitro conventional T cells proliferation compared to MAIT cells obtained from HCs. We linked MAIT cell phenotype to an altered gut bacterial and fungal microbiome composition consisting of low fungal richness, high abundance of Saccharomyces and low abundance of Prevotella.

Conclusions: Our study described a modulatory effect of MAIT cells on both innate and adaptive immunity. In pwMS we demonstrated a decrease and a dysregulation of MAIT cell number and function, possibly linked to an altered gut microbiome composition.

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## EARLY USE OF ORAL CONTRACEPTIVE, MENOPAUSE AND PREGNANCY ARE ASSOCIATED WITH LESS SEVERE DISEASE COURSE IN WOMEN WITH MULTIPLE SCLEROSIS

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Objectives: Multiple Sclerosis (MS) is more common in women than men but, after the onset, women have a more favorable disease course. Evidence shows that changes in sex hormones occurring early affect the risk of MS, but their impact on future disease severity is less explored and poorly understood.

Aim: To investigate how the exposure to environmental factors (EF) provoking changes in sex hormones affects future disease severity in women with MS.

Materials and Methods: An extensive environmental questionnaire was available for 1,117 women with MS (age => 18 years; follow-up from onset =>2 years). From this, we extracted questions regarding the exposure to EF provoking changes in sex hormones: 1) use of oral contraceptive before/at the time of diagnosis; 2) pregnancy before the diagnosis; 3) menopause occurred before the diagnosis; 4) age at menarche. The latest available Expanded Disability Status Scale (EDSS) score and the age at the time of EDSS evaluation were used to calculate the Age-Related Multiple Sclerosis Severity (ARMSS) score. Mean disease duration at the time of ARMSS score was 15 years. Normalized ARMSS score was used as outcome in linear regression models.

Results: Patients who reported use of oral contraceptives prior to the diagnosis had a better outcome in terms of future MS severity (p=0.0048). Conversely, the use of oral contraceptive at time of diagnosis was not associated with disease severity (p=0.182), further suggesting the importance of an earlier exposure. Patients who reported a pregnancy before the diagnosis had lower ARMSS score (p=0.0015), as well as patients in whom menopause occurred before the diagnosis (p<0.001). When studying women reporting an age at menarche => 14 years, we found a trend for association with lower ARMSS score which was not statistically significant (p=0.076).

Conclusions: Our findings replicate previous reports from smaller studies, suggesting an influence of early changes in sex hormones and future disease severity; these results prompt prospective investigations.

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## HIGHER VITAMIN D LEVELS ARE CAUSALLY ASSOCIATED WITH THE NO EVIDENCE OF DISEASE ACTIVITY-3 STATUS IN MULTIPLE SCLEROSIS

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Objectives: Vitamin D (VitD) levels affect the risk of developing multiple sclerosis (MS), but studies on its effect on composite outcomes of disease activity are few and a validation of its causal role is lacking. We evaluated whether serum VitD levels at baseline have a causal role in driving disease activity measured by the No Evidence of Disease Activity-3 (NEDA-3) status at 2-years follow-up.

Materials: We included 230 patients with relapsing-remitting MS from San Raffaele Hospital in Milan (OSR) and Centre Hospitalier Universitaire de Toulouse (CHUT). At the time of sampling, patients were not on Disease-Modifying Treatment (DMT) and wash-out from previous steroid or DMT was considered.

Methods: Serum 25-OH-vitamin-D was measured through an electro-chemiluminescence competitive binding assay. Adjustment for VitD seasonal variation was applied, modelling a sinusoidal function and linear logistic regression was used to assess the association between VitD levels and the NEDA-3 status. To assess whether the association between VitD levels and disease activity is causal, we carried out an inverse-variance weighted Mendelian Randomization (MR) analysis using the TwoSampleMR tool.

Results: Higher baseline VitD serum concentration was associated with higher probability of fulfilling the NEDA-3 criteria at 2-years (p=0.019). In addition, patients having at least 2 relapses during the follow-up had significantly lower VitD levels at baseline, if compared with patients having no relapses (p<0.001) or one relapse (p=0.037). Taking advantage of a published Genome-Wide Association Study (GWAS) on genetic variation in VitD on 417,580 controls [1], we selected 15 genetic instrumental variables and explored the causal role of VitD on NEDA-3 status in an internal cohort of 1,408 MS patients. The results strongly suggested a causal effect of VitD on disease activity (inverse-variance weighted MR p-value<0.001).

Conclusions: VitD levels are associated with a causal relationship to disease activity in MS.

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## CO-OCCURRENCE OF MULTIPLE SCLEROSIS AND AMYOTROPHIC LATERAL SCLEROSIS: A RARE CASE REPORT IN A LARGE NEUROLOGICAL CENTRE IN CENTRAL ITALY

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Introductions: In Multiple Sclerosis (MS), dissemination of demyelinating lesions in the central nervous system (CNS) is the sign of an autoimmune etiopathology. Amyotrophic Lateral Sclerosis (ALS) is instead a neurodegenerative disease characterized by a progressive loss of motoneurons in brain and in spinal cord. Two seemingly different diseases, but with something in common, since recent evidence showed connection between immunity dysregulation and ALS, as far as a higher incidence of autoimmune diseases in ALS patients. Our case report regards a patient affected by MS and ALS, seen at our Multiple Sclerosis centre.

Case report: A 73-years-old man, in 2017, suddenly developed paraesthesia in the left inferior limbs associated to a progressive gait impairment. During a day hospital at our clinic, he underwent: Brain, Cervical and thoracic MRI showing multiple demyelinating lesions; Lumbar puncture resulting in 2 oligoclonal bands; Infective, rheumatological and anti-aquaporin-4 antibody screening on serum which were unremarkable; Lower limbs electromyography which showed chronic neural injury without evidence of ongoing denervation. He was then diagnosed with MS; his EDSS score was 4,0 and he began a follow up in our centre. Annual 1,5-tesla brain and medulla MRIs were stable, while neurological examination got worse reaching an EDSS score of 7,0, in 2021. At the end of 2022, a 3-tesla brain MRI showed a bilateral thinning and hypo intensity in primary motor cortex, without any new demyelinating lesions. In the meaning time neurological conditions dramatically worsened since the patient developed a dropped head with hypophonic voice and dysphagia. At neurological examination his upper limbs strength was furtherly reduced, with spontaneous fasciculations at the four limbs and a significant muscle atrophy. An electromyography showed acute denervation, while a further cervical MRI did not show spinal stenosis. Total body CT was performed to exclude a paraneoplastic syndrome, which was unremarkable. Criteria for ALS were then met, and he started therapy with Riluzole.

Conclusions: Association of MS and ALS is reported in literature as an unusual event. Even if MS patients can show important lower motor dysfunctions, in our case the presence of a rapid progression of the motor signs or a sudden change in the previous disease course, should rise the question of the co-occurrence of another disease possibly pathologically related.

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## FINGOLIMOD-ASSOCIATED PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML): CASE REPORT AND REVIEW OF LITERATURE

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Objectives: To describe a patient with relapsing-remitting multiple sclerosis (RRMS) who developed a monolocalized progressive multifocal leukoencephalopathy (PML) while being treated with Fingolimod, a sphingosine-1-phosphate receptor (S1PR) modulator.

Results: This case report describes a 65-year-old female RRMS patient, previously treated with immunosuppressive therapy, that subsequently was started on Fingolimod treatment and resulted in clinical and radiological stability for four years. However, the patient presented with a solitary, paucisymptomatic, cerebellar lesion, initially mistaken for a new MS lesion, but later identified as progressive multifocal leukoencephalopathy (PML) after JC virus DNA was detected in her cerebrospinal fluid. The patient discontinued Fingolimod and showed clinical and radiological improvement, with a stability of disease without requiring any further disease-modifying therapy (DMT).

Discussion: This case describes an atypical presentation of PML, as it occurred during Fingolimod treatment, as a single, paucisymptomatic, cerebellar localization, with a favorable clinical and radiological course. Although the incidence of monolocalized PML and the differences in PML presentation during Natalizumab and Fingolimod treatment are not yet fully understood, our case seems to confirm the more favorable course of focal PML compared to the classic multifocal pattern, and the more favorable disease course in patients treated with Fingolimod compared to Natalizumab. An higher risk of Fingolimod-associated PML seems to be related to previous immunosuppressive therapies. Furthermore, some factors could predict a good PML prognosis, such as immunosenescence, a less active phase of MS, the location and extent of the PML lesion and the different mechanism of action of the ongoing DMT.

Conclusions: This case highlights the association between PML and Fingolimod in MS, and the importance of careful monitoring and risk management when using S1PR modulators, especially in patients with a history of prior use of immunosuppressive therapies. Our case confirms the possibility of a favorable outcome with monofocal, Fingolimod-associated PML and identifies some potential positive predictive factors. However, further research is needed to elucidate the mechanisms underlying PML in diverse patient populations receiving different pharmacological treatments. The different mechanisms of action of DMT may in fact play a role in the more or less favorable course of PML.

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## EVALUATION OF LONG-TERM EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PRIMARY PROGRESSIVE AND RELAPSING MULTIPLE SCLEROSIS: A SINGLE CENTER EXPERIENCE

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Objectives: To evaluate long term effectiveness and safety of ocrelizumab for primary progressive (PP), relapsing remitting (RR) and active secondary progressive (SP) multiple sclerosis (MS) patients in a clinical setting.

Material: Patients with ≥ 2 years of treatment with ocrelizumab were retrospectively recruited at the Multiple Sclerosis Center of Bari.

Methods: EDSS changes over time were evaluated using Wilcoxon paired test. 12-month confirmed disability worsening (CDW) and improvement (CDI) were calculated, annualized relapse rate (ARR) before and after ocrelizumab start was estimated and follow up magnetic resonance imaging (MRI) scans were collected. A multivariable logistic regression model was used to evaluate the association of clinical and radiological baseline factors with the risk of CDW. Adverse events were collected.

Results: The final cohort retrieved 140 patients (80 RR, 37 PP, 23 SP), with a mean (SD) follow-up after treatment start of 3.83 (0.06) years. The EDSS score after OCZ start significantly increased compared to the baseline values only in the PPMS group ($p<0.01$), but it remained stable in SP and RR groups ($p>0.05$). The mean ARR decreased from 0.61 (95% CI 0.47–0.74) in the year prior to ocrelizumab start to 0.04 (95% CI 0.01–0.09) in the first year, thereafter all patients remained free of relapses and MRI activity up to six years of follow up. The overall percentage of stable patients increased from the second to the fourth year (64.3% vs 86.4%), in parallel with a reduction in patients with CDW (26.4% vs 7.9%) and CDI (9.3% vs 5.7%). The multivariable logistic regression models revealed that a multifocal onset (OR, 95% CI: 2.96, 1.10–7.94) and the presence of >2 relapses before ocrelizumab start (3.82, 1.46–9.96) were significant ($p<0.05$) risk factors of CDW. Side effects mostly consisted of infusion-related reactions; we also reported 2 neoplasms, 1 organizing pneumonia and 4 localized zoster infections.

Discussion: The increasing amount of data available on the effectiveness and safety of B-cell-depleting therapies in MS led to a growing consideration of these treatments as a viable strategic option. [1] Strong real-word evidence, also based on disease registries [2], demonstrates that ocrelizumab reduces clinical and radiological activity over time, with a favorable safety profile and clinical benefits maintained over years of treatment. Ocrelizumab is also effective in delaying clinical progression [3].

Conclusions: In our cohort, ocrelizumab proved to stabilize disability progression and prevent disease activity over the long term. The safety profile was quite favorable.

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## EVALUATION OF CLINICAL AND RADIOLOGICAL PREDICTORS OF NEDA-3 STATUS ACHIEVEMENT OVER THE LONG TERM IN RELAPSING REMITTING MULTIPLE SCLEROSIS: A SINGLE CENTER EXPERIENCE

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Objectives: To analyze, in a cohort of relapsing remitting multiple sclerosis (RRMS) patients, the prevalence of no evidence of disease activity-3 (NEDA-3) status achievement and to evaluate clinical, radiological, and therapeutic factors associated with its failure.

Material: We included RRMS patients, followed from 2010 at the MS center of University Hospital Policlinic of Bari, with a first visit within one year from disease onset and with ≥1 visit per year.

Methods: DMTs exposure was classified based on the efficacy of the first prescribed DMT in moderate efficacy (ME) and high efficacy (HE) DMTs. Percentages of patients exposed to ME and HE DMTs reaching NEDA-3 status at 2 and at 5 years of follow-up were compared using the chi-square test. A multivariable logistic regression model was used to estimate the association of demographic, clinical and radiological baseline factors with the risk of not achieving NEDA-3 status.

Results: A cohort of 452 patients (female patients n=295, 65%) with a mean (SD) follow-up of 6.37(0.17) years was analyzed. Patients who started their treatment history with HE DMTs (n=119, 26.3%) reached a NEDA-3 status at 2 and 5 years more frequently than those who received ME DMTs (47% vs 28%, p=0.001; 45% vs 24%, p=0.001, respectively). The multivariable logistic regression models revealed that a multifocal onset (OR, 95% CI: 1.47, 1.27–1.68; 1.53, 1.27–1.79), ≥2 relapses before DMT initiation (1.35, 1.14-1.57; 1.07, 1.04-1.10), a longer time to first DMT start (1.26, 1.12–1.40; 1.34, 1.18–1.51), treatment initiation with ME DMT (1.28, 1.14–1.42; 1.38, 1.18–1.59) and the presence of spinal cord lesions at baseline magnetic resonance imaging (1.25, 1.11–1.39; 1.22, 1.09-1.36) were significant ($p<0.05$) risk factors of not achievement of NEDA-3 status at 2 year and 5 years of follow up.

Discussion: NEDA-3 is a composite outcome defined by the absence of relapse, disability worsening and radiological activity. Also given the increasing evidence about disease progression processes independent of inflammation, the study of prognostic factors of non-activity of disease remains fundamental in orienting the choices of the neurologist. [1] HE-DMTs, especially used in an early phase of disease, revealed to play a fundamental role in delaying irreversible central nervous system damage and MS-related disability progression and accrual. [2,3]

Conclusions: Clinical and radiological baseline characteristics play a major role in predicting the NEDA-3 status over the long term. HE DMTs demonstrate superiority in preventing longer-term disability disease activity.

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## COVID-19 INCIDENCE, SEVERITY, AND PROPENSITY TO VACCINATION AMONG PEOPLE WITH MULTIPLE SCLEROSIS: A POPULATION-BASED COHORT STUDY IN WESTERN SICILY

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Objective: Several studies investigated Covid-19 risk and severity in people with multiple sclerosis (pwMS) by means of registry-based analyses [1-2]. On the other hand, some authors explored the relationship between disease modifying drugs and COVID-19 severity in pwMS [3]. However, population-based studies exploring the incidence of COVID-19 in pwMS are still lacking. We planned a study in western Sicily to ascertain the incidence and severity of Covid-19 among a cohort of people affected by MS derived from a population-based study. Secondary objectives were to calculate predictors of willingness to vaccination, and re-infection rates.

Materials and Methods: People diagnosed as affected by MS (pwMS) according to current diagnostic criteria were recruited by means of a previous population-based study in western Sicily. Covid-19 incidence was ascertained by direct contact of each person enrolled in the study and information about swab positivity and vaccination were abstracted by reviewing all the official charts and certification. We calculated cumulative rates of Covid-19 incidence until June 2022. Probability of severe infection, hospitalization or death were also calculated together with 95% CI and two-sided p-values.

Results: Among a cohort of 2751 (prevalent cases of pwMS enrolled in the study) 734 tested positive for SARS-COV-2 during the follow-up period with a cumulative incidence rate of 13.3/% person years. Five people deceased due to Covid-19 (0.68%), while 90.33% had an asymptomatic disease course, and 10 (1.36%) had a severe infection leading to hospitalization or ICU admission. The overall rate of re-infection was 3.41% (25/734). Sex, marital status, education nor employment status were predictors associated to higher propensity to be vaccinated.

Discussion and Conclusion: Results from this study large population-based cohort study investigating Covid-19 incidence and severity in southern Italy showed an overall incidence rate lower than previously reported in the general population in Italy and slightly lower compared to the Sicilian population. Mortality rate appeared to be lower than expected. Rates observed in present the study are probably related to the specific characteristics of the investigated population.

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## INCIDENCE AND CORRELATES OF CARDIOVASCULAR COMORBIDITIES IN MULTIPLE SCLEROSIS: A PROSPECTIVE REGISTRY-BASED STUDY

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Objective: Multiple Sclerosis (MS) is an autoimmune disease affecting the central nervous system [1]. Cardiovascular comorbidities are common in general population although its impact in pwMS is almost conflicting. Some authors found a genetic evidence for the causal associations of MS while others showed that cardiovascular comorbidities may affect the risk of MS progression [2-3]. The aims of this study are to evaluate the frequency of cardiovascular comorbidities in pwMS, the difference between primary progressive MS patients (PPMS) and those with relapsing remitting course (RRMS) and the impact of these comorbidities among disease progression.

Materials and Methods: We collected the presence and development of cardiovascular comorbidities in our MS patients in the outpatients setting. We calculated the cumulative incidence of such comorbidities as well as the hazard ratios (HR) for secondary progression by using Cox regression models.

Results: From a total of 576 pwMS (73% female; 87.2% RRMS; age: 51 +- 9 years; follow up: 14.8 +- 10.2 years), hypertension reached a cumulative incidence of 17.2/100 person/year followed by cardiopathies (10.8/100 person/year), hypercholesterolemia (7.4/100 person/year), type 2 diabetes mellitus (5.2 /100 person7year) and stroke or TIA (0.9/100 person/year). Among cardiopathies, arrhythmias were the more common developed by pwMS (4.7/100 person/year) followed by ischemic acute cardiopathy (2.4/100 person/year). Hypertension and cardiopathies showed higher prevalence in primary progressive pwMS compared to RR MS patients (all $p < 0.05$). The presence of hypertension (HR=0.83 [95% CI: 0.6-1.2]; p=0.23), hypercholesterolemia (HR=0.83 [95% CI: 0.5-1.3]; p=0.42) and cardiopathies (HR=1 [95% CI: 0.7-1.5]; p=0.97) did not affect the risk of progression among RR pwMS whereas diabetes mellitus (HR=1.7 [95% CI: 1-2.7]; p=0.04) was found to be a risk factor for progression.

Discussion and Conclusion: Our study shows a higher prevalence of cardiovascular comorbidities among patients with PPMS compared to those with RRMS as well as the impact of type 2 diabetes mellitus in MS progression suggesting that the accurate evaluation of these comorbidities should be systematically embedded among the routinary management of pwMS, especially in those with PPMS.

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## EARLY INTENSIVE VS ESCALATION APPROACH EFFECT ON DISABILITY TRAJECTORIES: A TEN-YEAR STUDY FROM THE ITALIAN MS REGISTER

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Objectives: To compare the long-term effect of an early intensive treatment (EIT) versus a delayed start, after an escalation approach (ESC), of high-efficacy disease-modifying therapies (HE-DMTs) on disability trajectories and on the risk of progression independent of relapse activity (PIRA) and relapse-associated worsening (RAW).

Material: Patients with relapsing onset MS (RMS), ≥5 years of follow-up, a first DMT prescription within 3 years from disease onset and ≥3 Expanded Disability Status Scale (EDSS) score evaluations were retrieved from the Italian Multiple Sclerosis Register.

Methods: Patients were classified into EIT or ESC group according to the first prescribed DMT and propensity score (PS)-matched. On the matched cohorts, disability trajectories over a ten-year period and the risk of reaching a first PIRA and RAW were compared between the ESC and EIT groups using a linear mixed model for repeated measures (LMMRM) and multivariable Cox regression models, respectively. The recursive partitioning and amalgamation (RECPAM) algorithm was applied to the unmatched cohort to identify subgroups of patients with different risk of reaching irreversible EDSS 6.0, then LMMRM was used to evaluate differences in disability trajectories among them.

Results: The study cohort included 4878 RMS subjects, 914 exposed to a EIT approach and 3964 to an ESC strategy. The PS-matching procedure retrieved 907 pairs. Estimated annual delta-EDSS values were all significantly ($p<0.01$) higher in the ESC group compared with the EIT group. The estimated delta-EDSS (95%CI) differences increases over time, going from -0.16 (-0.25– -0.07, $p=0.0005$) at 1 year to -0.44 (-0.57– -0.31, $p<0.0001$) at 5 years and to -0.68 (-0.89– -0.47, $p<0.0001$) at 10 years. ESC strategy was associated to a significant higher risk of reaching a first PIRA and RAW event in comparison to the EIT strategy (HR, 95%CI: 1.17, 1.02-1.35, $p=0.03$; 1.73, 1.31-2.28, $p=0.0001$; respectively). RECPAM analysis identified four groups of patients with a significant different risk of reaching EDSS 6.0 based on EDSS and age at DMT start time. The ESC strategy resulted in a significant higher slope of the disability trajectories compared to the EIT approach in all subgroups.

Discussion: A recent expert opinion [1] presented the EIT as the best strategy to ensure a long-term impact on inflammatory activity and reducing the risk of progression, but until now there has been a slow adoption of this strategy [2].

Conclusions: Our results further confirmed that an early HE-DMTs start may minimize clinical disability accumulation and reduce the risk of reaching a first PIRA event.

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## THE COMPARATIVE EFFECTIVENESS OF NATALIZUMAB AND OCRELIZUMAB ON RELAPSE DEPENDENT AND RELAPSE INDEPENDENT DISABILITY PROGRESSION IN NAÏVE RELAPSING REMITTING MULTIPLE SCLEROSIS: A STUDY OF THE ITALIAN MS REGISTER

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Objectives: To compare the risk of achieving the first 6-months confirmed progression independent of relapse activity (PIRA) and relapse associated worsening (RAW) events in a real life-cohort of naïve relapsing-remitting multiple sclerosis (RRMS) patients treated with natalizumab (NTZ) or ocrelizumab (OCR).

Materials: RRMS patients with a first visit within one year from disease onset, a first DMT prescription with NTZ or OCR and ≥ 3 Expanded Disability Status Scale (EDSS) score evaluations were extracted from the Italian Multiple Sclerosis Register.

Methods: A pairwise propensity score (PS)-matched analysis was performed to mitigate the impact of potential biases. Risk of reaching the first PIRA and RAW events were estimated using multivariable Cox proportional hazards models. The recursive partitioning and amalgamation (RECPAM) algorithm was used to evaluate subgroups of patients who can benefit most from exposure to either of the two HE-DMTs.

Results: A total of 661 subjects were included (NTZ=477; OCR=184). The median (IQR) follow-up after treatment start was 1.44 (0.73-2.49) and 1.43 (0.72-2.36) years, respectively. The PS-matching retrieved 169 pairs. A first PIRA event was reached by 13 (7.7%) NTZ exposed patients and 22 (13.0%) OCR exposed patients. No RAW events were found in the NTZ group and only 1 RAW event was reported in the OCR group. No differences between the two groups (NTZ -treated group as reference) were found in the risk (HR, 95%CI) of reaching a first PIRA (1.75, 0.88-3.48; p=0.11) event. RECPAM analysis identified 4 classes of risk of reaching a first PIRA event. In the subgroup of patients with an age at onset >38 years, a higher number of relapses before DMT start, and a longer time from disease onset to the DMT start, the exposure to OCR was associated to a significant higher risk of reaching a first PIRA event in comparison to NTZ exposure (6.72, 1.23-36.84; p=0.03).

Discussion: NTZ and OCR are commonly used as HE-DMTs for RRMS. Some recent studies have compared the two therapies in terms of effectiveness, impact on relapses and disability accrual. [1-3] No direct comparisons of the effect of these two drugs on PIRA and RAW events are currently available.

Conclusions: Both OCR and NTZ effectively suppress RAW events in RRMS patients. In short-term, the number and the risk of achieving PIRA events were not significantly different between the two groups, but differences in treatment response may exist in specific patient subgroups. A longer follow-up is essential to confirm the effect on disability progression.

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## THE EFFECTS OF CUMULATIVE LIFETIME ESTROGEN EXPOSURE, PREGNANCY AND LACTATION ON MULTIPLE SCLEROSIS-RELATED DISABILITY IN THE PERIMENOPAUSAL PERIOD

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Objectives: Gender differences in multiple sclerosis (MS) pathology emphasize the role of sex hormones. However, the role of low lifetime exposure to female sex hormones as a risk factor for poor prognosis remains uncertain. This study aims to explore the relationship between cumulative lifetime estrogen exposure (CLEE), pregnancy, lactation, and MS-related disability, particularly during the perimenopausal period.

Materials and Methods: This single-center, two-phase observational study enrolled consecutive perimenopausal women with MS. Comprehensive clinical, demographic, and reproductive history data, were collected. Neurological and neuropsychological assessments, 3T MRI, and Optical Coherence Tomography (OCT) were performed. CLEE was calculated by subtracting lactation months (or 1.5 months for pregnancies without lactation) from the reproductive window. Spearman's correlation evaluated relationships, and the sample was divided into two groups (based on the median CLEE) for comparison analysis using multivariate analysis and t-tests.

Results: Our sample consists of 32 women with stable MS (27 RMS, 5 SPMS; mean age 50.5; median EDSS 2.0; median CLEE 461 months). The number of pregnancies correlated with macular retinal nerve fiber layer (RNFL) thickness (coefficient 0.454, p 0.015). Total months of lactation showed correlation with symbol digit modalities test (SDMT) (coefficient 0.632, $p < 0.01$) and with thalamic volume (coefficients 0.618, $p < 0.01$). Age-corrected multivariate analysis showed significant differences between the two CLEE groups in both optic head and macular RNFL thicknesses (-7, -9 μm, respectively; $p < 0.05$). T-test showed significant differences in several neuropsychological tests, including 9-hole peg test (- 4.0 seconds, p 0.018), and multiple sclerosis impact scale-29 (MSIS-29) (-4.2, p 0.002), favouring the higher CLEE group. EDSS was lower in the group with the highest CLEE (- 0.9, p 0.03), while gray matter fraction was higher in the group most exposed to sex hormones (-0.26, p 0.07).

Discussion: Correlations between pregnancies/CLEE and RNFL thickness suggest a protective effect of sex hormones on axonal integrity. Lactation duration associates with improved cognitive performance and increased thalamic volume. Neuropsychological results support a potential beneficial impact of estrogens on motor function and quality of life. The group with higher CLEE exhibited less disability and a trend towards higher gray matter fraction.

Conclusions: Cumulative lifetime estrogen exposure, pregnancy, lactation, and potentially hormonal replacement therapy, may influence disease severity and disability progression in women with MS. Our findings highlight the importance of considering sex hormone influence on MS outcomes and suggest potential avenues for improving disease course in women with MS.

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## THE OCRELIZUMAB AND NATALIZUMAB WEARING-OFF EFFECT IN PATIENTS WITH MULTIPLE SCLEROSIS

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Objective: The objective of this study was to assess the prevalence and predicting factors of the wearing-off effect (WOE) in patients with Multiple Sclerosis (MS) treated with monoclonal antibodies, specifically Natalizumab (NTZ) and Ocrelizumab (OCR).

Materials and Methods: A total of 239 MS patients were included, female-to-male ratio was 3:1. The mean age was 38.6 ± 9.2 years, and the mean EDSS was 2.4 ± 1.7. The patients had received a minimum of 8 NTZ infusions or three cycles of OCR. The Multiple Sclerosis Impact Scale (MSIS-29), Short Form-12 Health Survey (SF-12), Fatigue Severity Scale (FSS), Beck Depression Inventory-II (BDI-II) and a questionnaire specifically addressing the WOE, were completed. The patients were divided into two groups based on the presence or absence of self-reported WOE. The differences between the two groups were evaluated using a two-way ANOVA. Logistic regression analysis was conducted to identify predicting factors of WOE.

Results: Out of the 239 patients, 126 (52.5%) reported WOE (53.3% in the NTZ group and 51.7% in the OCR group). The two-way ANOVA revealed statistically significant higher scores on SF-12, MSIS-29, BDI-II, FSS, EDSS, and BMI in individuals who reported WOE. Logistic regression analysis was performed separately for each treatment group. For the NTZ group, only the FSS was included in the final model: each 1-point increase on the FSS scale was associated with a 2.21 (CI95%: 1.47-3.33) times higher likelihood of experiencing WOE. The logistic regression model was statistically significant ($\chi 2(4) = 21.055$, $p < 0.001$). For the OCR group, only SF-12 was included in the final model, showing that each point increase on the SF-12 scale decreased the likelihood of WOE by 0.90 (CI95%: 0.085-0.96) times. The logistic regression model for the OCR group was statistically significant ($\chi 2(4) = 11.4$, $p = 0.001$).

Discussion and Conclusions: The study findings demonstrate that approximately half of the MS patients treated with NTZ or OCR experience the WOE. Patients who reported WOE exhibited differences in fatigue, quality of life, and disability. In the NTZ group, fatigue emerged as a significant determinant of WOE, while a poor impact of health-related quality of life seemed to influence the WOE effect in the OCR group. Based on these results, careful evaluation of the extended-dose protocol is necessary when patients report significant fatigue.

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## BEING HIGHLY SENSITIVE PERSON NEGATIVELY IMPACTS ON COGNITIVE AND PSYCHOSOCIAL FATIGUE IN MULTIPLE SCLEROSIS PATIENTS


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Objective: Fatigue is one of the most common symptoms in multiple sclerosis (MS), that may affect the cognitive functions. Sensory processing sensitivity (SPS) can be defined as a personality trait that includes the individual characteristics of sensitivity towards endogenous and exogenous stimuli. It is colloquially called High Sensitivity, or Highly Sensitive Person (HSP), a person with a high emotional and empathetic reactivity, and a greater depth in the processing of information. This personality trait renders the individual more vulnerable to external influences and more affected by their environments as they perceive more stimuli than they could process. The trait ultimately results in overarousal, cognitive depletion, and fatigue. Therefore, the aim of the study is to evaluate whether the HSP affects fatigue in MS patients, taking into account the ability to process stimuli, namely the cognitive status.

Material and Methods: Consecutive MS patients underwent clinical (EDSS, age, gender), cognitive (Symbol Digit Modality Test [SDMT] and Trial Making Test [TMT]), and psychosocial (Modified Fatigue Impact Scale [MFIS]) evaluation. Patients were also assessed through the Highly Sensitive Person scale (HPS scale). Linear regression were applied to explore association between HPS total score (dependent variable) and MFIS total scores and sub-scores, by accounting for age, gender, EDSS, TMT, SDMT (covariate).

Results: We enrolled 132 MS patients (84 female; mean age 44.04 ± 12.43 years; mean EDSS 2.86 ± 1.39; 112 relapsing-remitting and 20 progressive patients). 42 patients (32%) presented with a cognitive impairment and a mean TMT score of 46.45 ± 35.27. Mean total MFIS was 23.30 ± 19.6, mean physical MFIS was 11.70 ± 10.09; mean cognitive MFIS was 9.48 ± 8.82; mean psychosocial MFIS was 2.11 ± 2.37. Mean score at HPS was 101.70 ± 33.76. Higher scores at HPS correlated with MFIS total fatigue (coeff. 0.17, 95%CI 0.05 - 029, p=0.005), MFIS cognitive fatigue (coeff. 0.09, 95%CI 0.04 – 0.14, p<0.001), MFIS psychosocial fatigue (coeff. 0.02, 95%CI 0.00 – 0.03, p=0.03) but not with MFIS physical fatigue (coeff. 0.05, 95%CI -0.01 – 0.12, p=0.08).

Conclusions: HPS individuals process sensory information in a deep and complex way, which makes them easily overstimulated for demanding cognitive tasks in ecological contests. This may affect the fatigue perceived by MS patients; in fact, higher level of HPS is related with greater cognitive and psychosocial fatigue.

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## PHENOTYPIC CHARACTERIZATION OF THE PLACENTA FROM WOMEN WITH MULTIPLE SCLEROSIS EXPOSED TO NATALIZUMAB DURING PREGNANCY


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Aims: Recent evidence has consistently demonstrated that continuing natalizumab (NTZ) during pregnancy protects mothers with Multiple Sclerosis (MS) from relapses due to treatment suspension, without causing major fetal hematological or congenital abnormalities. Nevertheless, there is no data about the impact of Natalizumab exposure on placental pathology. The aim of this study was to describe the placental phenotype of mothers with MS exposed to NTZ throughout pregnancy compared to mothers unexposed to treatments.

Materials and Methods: Clinical data and placental pathological specimens from women with MS and growth parameters from their newborns were collected and analyzed. Macroscopic and microscopic analysis on placental specimens fixed in formalin was performed. Placental lesions were classified according to the Amsterdam Placental Workshop Group Consensus Statement.

Results: Seven women exposed to NTZ (mean age at conception 32,4+/-3, median NTZ infusion during pregnancy=4(3-4)) and 7 unexposed (mean age at conception 32,14+/-6) and their newborns were enrolled. No difference was found regarding infant gestational age (39,5±0,7 mg vs. 39,5+/-0,7 weeks, p=0.4) birthweight (3142±431,5 mg vs 3180±336; p=0.8) or placental weight (501,5±147,6 vs 431± 75 mg, p=0.3) comparing women exposed to NTZ and controls. The incidence of microscopic alterations, falling within the spectrum of maternal vascular malformation and fetal vascular malformation, was slightly higher in exposed compared to unexposed women, while inflammatory findings, like villitis or deciduitis, were less frequent.

Discussion: Our results suggest that treatment with NTZ during pregnancy is not associated with major macroscopic placental anomalies, conversely it seems to alter the microscopic placental vascularization pattern. However, these findings do not impact on pregnancy outcomes, fetal gestational age or birth weight. Our data also suggest a potentially positive role of NTZ in the creation of a less inflamed placental microenvironment. We can speculate that NTZ might be able to inhibit the migration of lymphocytes also into the placenta, similarly to the known effect at blood-brain barrier.

Conclusions: Although these results should be confirmed on larger samples to draw definitive conclusions, our preliminary data corroborate the evidence in support of the low risk of NTZ continuation during gestation.

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## A REAL-LIFE, MULTICENTER, OBSERVATIONAL STUDY TO EVALUATE SAFETY AND EFFICACY OF THE SWITCH FROM ALEMTUZUMAB TO OCRELIZUMAB IN MS PATIENTS WITH EVIDENCE OF DISEASE ACTIVITY/PROGRESSION AFTER TWO ALEMTUZUMAB COURSES: THE ITALIAN EXPERIENCE


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Objectives: Therapeutic sequencing after high-efficacy induction treatments is a matter of debate in MS. No safety and efficacy data about the switch to ocrelizumab (OCR) in patients (pts) with evidence of disease activity/progression after two alemtuzumab (ALM) courses have been reported yet. The aims of our study are to evaluate safety and efficacy of the switch from ALM to OCR in an Italian, multicentric cohort of MS patients with evidence of disease activity and/or progression after two ALM courses.

Materials and Methods: Prospective data collection from different Italian MS Centers.

Results: 73 MS patients were enrolled from May 2019 to…[at OCR start: mean age 39.2 (SD9.2) years; female, 63%; Relapsing Remitting, (RR): 78.1%, Relapsing Progressive, (RP): 13.7%; 67 (91.7%) started OCR for relapses/MRI activity, 6 (8.3%) for disability progression; cumulative number of relapses:69; mean number of new T2 and Gd+ lesions:3 (3.2) and 1 (2); median EDSS:3.5 (range 0-8)]. The mean follow-up (FU) from OCR start was 2.3±1 years. Safety: (i) Infusion Associated Reactions (IARs) occurrence was lower than in ALM ($p<0.005$); (ii) infections (n=41, 56.2%): upper airways (n=20), urinary (n=18), HSV (n=1), VZV (n=1) reactivations, appendicectomy (n=1). No patients developed severe forms of COVID19 (n=48); (iii) cancer (n=2, 1 colic, 1 cervix). Considering pts with at least 2-years FU (n=55), immunophenotype and IgG levels were available for 20 and 25 pts respectively: no pts showed evidence of T CD4 +cells lymphopenia and for all pts a complete B CD19+ cells depletion (<5/mm3) was obtained. Hypo-IgG was observed in 8 (32%) pts [with respect to 2/32 (6.25%) pts at 1-y FU]; (iv) autoimmunity: n=1 developed thyroiditis 1 month after OCR start while, out of the 15 pts with TSH abnormality at OCR start, 13 pts (86.7%) showed TSH normalization within 1-year. Efficacy: at 2-y FU (n=55), relapse-free survival was 92.7%, MRI-activity-free survival was 89.1%, progression-free survival was 76.4% [47/55 pts (85.5%) considering only pts with RRMS at OCR start.

Discussion and Conclusions: The results of our study show that the switch to OCR after 2 ALM courses is safe and effective, despite the severity of MS characterizing our patients' cohort. Infectious rate was not higher than that reported in clinical trials involving OCR. In addition, the data show a positive effect on the development/ongoing thyroidal autoimmunity.

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## SAFETY OF ANTI-VARICELLA ZOSTER VIRUS VACCINATION IN PATIENTS WITH MULTIPLE SCLEROSIS TREATED WITH NATALIZUMAB: A CASE SERIES

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Objectives: In multiple sclerosis (MS), risk minimisation of several vaccine-preventable infectious diseases represents an essential need. However, some considerations have to be carefully evaluated when vaccinating patients with MS. Specifically, live vaccines are generally contraindicated during DMDs due to the risk of infection caused by the virus present in the vaccine. Among vaccine-preventable diseases, Varicella Zoster Virus (VZV) immunization represents a common issue in clinical practice, as it is strongly recommended before starting several MS specific DMDs. Nevertheless, the vaccination with live attenuated vaccines (LAVs, i.e., VZV) is generally not recommended during immunosuppressive therapies. Natalizumab (NTZ), despite of its mechanism of action, is currently included in this category.

Materials and Methods: After a risk/benefit evaluation, we decided to vaccinate 4 MS patients considering the following discussion points: (i) a long (i.e.- 3 months, as suggested by Spanish consensus) withdrawal of NTZ before administering LAVs is associated with a very high risk of MS rebound. (ii) in case of vaccine-induced VZV disease, a specific antiviral drug for VZV (acyclovir) can be administered (iii) maternal and fetal complications due to VZV infection during pregnancy represent a well-known phenomenon. (iv) when prescribing treatment with fingolimod and ocrelizumab, the two most common exit strategy from NTZ, a previous anti-VZV vaccination is strongly recommended. Therefore, the Disease Management Team reached a consensus on performing VZV vaccination during NTZ treatment in the following cases: A. Female MS patients who plan a pregnancy during NTZ treatment B. MS patients who withdraw NTZ treatment to switch to DMTs for which VZV immunization is strongly recommended. C. MS patients in treatment with NTZ who require anti-VZV post-exposure prophylaxis.

Results: All patients received two doses of anti-VZV vaccine with an interval of at least 1 months between them. None developed reported vaccine-associated adverse reactions of any type. The mean follow-up (FU) from the second dose of anti-VZV vaccination was 75.2±25.6 days. None of patients developed VZV infection; for 2 patients, qualitative VZV Real Time (RT) PCR on blood was performed 10 and 5 (Pt.1) and 5 and 12 (Pt.2) days after the first and second anti-VZV vaccination cycle respectively, with negative result.

Discussion and Conclusions: Our case series represents the first description of the good safety profile of anti-VZV vaccination in MS during NTZ treatment. No vaccine-related adverse events of any type nor VZV infections were observed. Larger patients' cohorts are needed to confirm our preliminary findings.
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## PROTEOMIC ANALYSIS OF WHOLE SALIVA IN MULTIPLE SCLEROSIS: RELATIONSHIPS WITH DISEASE ACTIVITY IN RELAPSING REMITTING FORMS

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Objectives: The challenge for the future in the field of multiple sclerosis (MS) is to improve the prediction of therapeutic responses by identifying biomarkers. Omics sciences represent an innovative approach for exploring the mechanisms underlying MS evolution [1]. The present study aimed to explore the proteomic profile of saliva, a biofluid mirror of several systemic disease processes [2], to identify biomarkers associated with disease activity in subjects with relapsing-remitting (RR) MS.

Materials: The study included RRMS patients without disease modifying therapy (DMT) for at least three months. Patients were classified as RR_active (with presence of clinical relapses in the last trimester and new/enlarged T2 lesions or gadolinium-enhancing T1 lesions) or RR_non active. A group of sex-/age-matched healthy controls (HCs) was also included.

Methods: Whole saliva was collected from participants. Proteomic data were obtained by nano-HPLC-high-resolution-MS/MS analysis bottom-up pipeline; protein identification was performed by Proteome Discoverer software, while multiple Mann—Whitney test and Random Forest (RF) statistical analysis between groups was performed with R software. Mann—Whitney tests provided indications on the panel of differentially expressed salivary proteins and peptides (p-value<0.05 and FDR<5%) among groups.

Results: Sixty RRMS patients (30 RR_active and 30 RR_not-active) and 22 HCs were enrolled. 138 proteins were found with altered levels in RR-MS_active compared to HCs (11 proteins were decreased and 127 increased); 222 proteins differed in RR-MS_not-active compared to HCs (19 proteins were decreased and 203 were increased); 27 proteins differentiated RR-MS_active versus RR-MS_non-active (21 proteins were decreased and 6 increased). Information regarding Reactome (v.3.7) pathways enrichment analysis was retrieved for unique proteins found after comparison of the three groups: saliva from RR-MS_active patients was enriched in terms related to "Formation of the cornified envelope" and "Keratinization"

while saliva from RR-MS_not-active patients was enriched in terms related to "Immune system". RF analysis evidenced a panel of salivary proteins able to classify with 100% accuracy RR-MS patients versus HCs and with an 86.2% accuracy RR-MS_active versus RR-MS_not-active.

Discussion: The bottom-up proteomic pipeline allowed evidencing the quantitative differences of salivary proteome in RR-MS with respect to HCs; RF analysis revealed the feasibility of the salivary proteome to discriminate HCs group with respect to RR-MS patients and RR-MS_active with respect to RR-MS_not-active.

Conclusion: The proteomic approach may prove useful in the stratification of MS subjects. Further studies are needed to identify proteins associated with disease activity, and how these vary during exposure to DMTs.

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## MOTOR FATIGUE AND SENSORIMOTOR NETWORK EFFECTIVE CONNECTIVITY DYSFUNCTION IN MULTIPLE SCLEROSIS: INSIGHTS FROM PATIENTS TREATED WITH NATALIZUMAB

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Background and Objectives: Motor fatigue is a debilitating symptom in people with Relapsing-Remitting Multiple Sclerosis (RRMS). Transcranial magnetic stimulation-electroencephalography (TMS-EEG) evidence suggested that motor fatigue in RRMS is associated with abnormal post-fatigue facilitation of motor cortex (M1) effective connectivity within the sensorimotor network (SMN). This study investigated whether this SMN dysfunction is driven by inflammation-related dysfunction. We assessed changes in M1 output and effective connectivity within the SMN in patients treated with natalizumab, an inflammation-reducing treatment. We further probed correlations with clinical variables, and possible differences between natalizumab extended interval dosing (EID) and standard interval dosing (SID).

Methods: RRMS patients complaining of motor fatigue were assessed before and two weeks after natalizumab infusion. Motor fatigue was assessed through an index finger contraction task. Decrease in M1 output during the task, i.e., supraspinal fatigue, was assessed by the superimposed force evoked by TMS. Pre- and post-task M1 connectivity within the SMN was evaluated via TMS-EEG. Clinical measures included fatigue severity scales, EDSS, 9-hole peg test (NHPT), SDMT, and BDI-II scores.

Results: Forty-two patients completed the study (21 SID; 21 EID). Motor fatigue along with its supraspinal component decreased after natalizumab. Post-task modulation of M1 effective connectivity significantly changed after natalizumab. Fatigue symptoms severity, SDMT, and BDI-II scores improved after natalizumab. Significant correlations were observed between specific clinical and neurophysiological changes. No difference was found between SID and EID groups.

Discussion: Motor fatigue in RRMS is probably associated with inflammation related SMN dysfunction. Natalizumab mitigates fatigue by modulating M1 output and SMN connectivity.

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## IS FATIGUE IN MS THE SAME ONE MANIFESTING AS WEARING-OFF SYMPTOM IN NATALIZUMAB TREATED PATIENTS?

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Objectives: Recent studies have demonstrated the safety of Extended Interval Dosing (EID) up to 6 weeks in patients receiving NTZ [1]. Patients receiving NTZ experience fatigue as the main Wearing-off Symptom (WoS), regardless of the dosing interval [2]. We previously demonstrated that there was no significant increase in WoS in patients with an EID of 5-6 weeks [2]. Since depression is a very frequent symptom in patients and it can often be hidden by fatigue, the primary objective of the study is to better characterize fatigue as a symptom in order to investigate a possible correlation with the symptom depression and with cognition, in patients undergoing therapy with NTZ, regardless of the dosing interval. Secondary objective of the study is the evaluation of the impact that the explored symptoms have on the patients' quality of life.

Methods and Materials: 87 patients have been evaluated. They were asked on the day of infusion to specify whether fatigue is present and if so whether is habitual or occurs only as the next infusion approaches; assessment of fatigue was done with the FSMC scale. Populations is divided in three main categories: chronic fatigue, end of does fatigue, no fatigue. All patients underwent a clinical evaluation, including EDSS, evaluation of depression with BDI-II, quality of life with MSQoL-29 scale. Anxiety was assessed with the STAI-Y scale, cognitive aspects with the Symbol Digit.

Results and Conclusions: 73 (84%) patients complained of fatigue, 14 (16%) did not. Among the 73 patients, 30 (34.5%) complained of end of dose fatigue and 43 (49.4%) of chronic fatigue. FSMC scale is higher in those who suffer chronically of fatigue compared to those who exhibit end of dose fatigue only (74.7 vs 53, $p<0.01$) with a significantly lower quality of life measured by MSQoL-29 in these patients (82.4 vs 78.4, $p<0.05$). Symbol Digit is similar in all three populations. BDI-II was higher in those complaining of chronic fatigue compared to those complaining of end of dose fatigue only (16.6 vs 9.6 $p<0.01$), while we found no difference in BDI-II between the no fatigue and the end of dose fatigue population, with a normal mean value in both populations (7.2 vs 9.6). We obtained similar results for STAI-Y trait (49.5 vs 46.5, $p<0.05$). These results show that fatigue as Wearing-off Symptom is different and probably strictly related to Natalizumab mechanism of action.

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## QUALITY OF LIFE AND UNMET NEEDS IN PEOPLE WITH MULTIPLE SCLEROSIS (PWMS): PRELIMINARY RESULTS OF AN ITALIAN MULTICENTRE STUDY

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Introduction: Multiple Sclerosis (MS) requires interdisciplinary management involving several clinical and administrative figures to guarantee the most appropriate path of care. People with MS (PwMS) are a heterogeneous population with different needs according to symptoms, individual experiences, and disease severity. Whenever these needs are not fulfilled, the patient is left alone to struggle with the difficulties of his/her illness.

Materials: The aim was to identify the unmet needs of a cohort of Italian PwMS and to ascertain whether they might be influenced by demographic variables, disease characteristics or perceived quality of life.
Methods: We elaborated an online anonymous questionnaire exploring socio-demographic status, MS basic information, perceived quality of life and unmet needs. Health-related quality of life (HRQoL) was measured by EQ-5D-5L, which was then converted in a utility index score, and EQ-VAS. Conversely, unmet needs were assessed with 23 questions designed to examine five aspects of perceived comprehensive care: access to information and primary care, socioeconomic aspect, need for assistance, and doctor-patient relationship.

Results: 690 PwMS responded to the survey: mean age was 43.60 years; 70.14 % were female. Overall, 95 % of subject reported at least one need being unmet; 65.79 % and 69.27 % showed one or more unmet need within the domain of the access to information and primary care; 83.04 % reported at least one socioeconomic related unmet need; 54.45 % revealed at least one assistance unmet need; lastly, 37.39 % reported one or more unmet need in doctor-patient relationship. Presence of unmet needs correlated with a lower age (p=0.029), higher PDDS (0.001) and lower utility index score and EQ-VAS (p=0.001). Moreover, results showed that across Italian regions the central ones reported a significantly lower number of total unmet needs than others (northern, southern, islands; respectively p=0.003, p=0.001, p=0.015).

Discussion: Our data show that most PwMS have unmet needs, and that these significantly correlate with reduced quality of life, younger age and greater disability. In particular, EQ-5D-5L utility index revealed to be the strongest predictor of unmet needs, as it negatively correlates with the number of unmet needs in each domain explored (except for the social aspect).

Conclusions: The general dissatisfaction revealed by our study suggests that the perception of pwMS still needs to be addressed. It is essential to act on modifiable factors that may result in reduced quality of life, since the latter is inseparably linked to the resolution of unmet needs.
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## FRAILTY AND URINARY SYMPTOMS IN PEOPLE WITH MULTIPLE SCLEROSIS: WHAT POSSIBLE INTERACTION?

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Objectives: Urinary symptoms represent a major source of disability in multiple sclerosis (MS). When they appear in early stages may be considered as a negative prognostic factor as well as changes in severity of urinary symptoms may predict transition towards the progressive form of MS. Therefore, presence and severity of urinary symptoms may reflect pathophysiological mechanisms responsible for disease progression in MS. Nonetheless, it remains unclear whether individual factors, not directly related to MS, may increase individual susceptibility to presence and worsening of urinary symptoms. Among these factors, frailty, an age-related condition characterized by an increased vulnerability to stressors due to accumulation of different deficits with a loss of adaptation to physiological changes, has recently been proposed as a descriptor of the health status of people with MS (pwMS). Frailty may facilitate the development and worsening of urinary symptoms in pwMS by acting as a moderator of pathophysiological mechanisms involved in disease progression. Therefore, the aim of the present study was to investigate the relationship between urinary disturbances and their perception and frailty levels in MS.

Materials and Methods: 52 pwMS were enrolled. MS severity was assessed by EDSS. All pwMS underwent the 8-item overactive bladder questionnaire (OAB-v8), the International prostate symptom score (IPSS) and the Urinary Incontinence Quality of Life Scale (I-QOL). Uroflowmetry and Ultrasound for Postvoid Residual were also performed. Frailty was assessed by a validated frailty questionnaire, which results in the fragility index (FI) calculated as the sum of the deficits over the number of variables evaluated resulting in a score between 0 and 1.

Results: FI was significantly associate with the presence and with the disability of urinary symptoms. We also found a positive correlation between FI and age, sex, disease duration, type of MS and EDSS. Two multivariable logistic regression model by using as dependent variable of interest IQoL total score and OAB respectively have showed that only FI scores resulted significantly associated with these two variables. No correlations were found between FI and the lesion load on MRI or data from Uroflowmetry and Ultrasound for Postvoid Residual.

Discussion and Conclusion: FI is associated with the presence and with the burden of disability of urinary symptoms in pwMS by suggesting new insights into the role of frailty as a potential moderator in the perception and impact on quality of life of urinary symptoms in pwMS possibly due to common pathophysiological mechanisms.
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## COMPARING THE SHORT-TERM SAFETY PROFILE OF ANTI-CD20 B CELLS DEPLETING DRUGS IN MULTIPLE SCLEROSIS (OFATUMUMAB VS. OCRELIZUMAB): RESULTS OF A PROSPECTIVE STUDY

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Background: Adult patients with relapsing forms of multiple sclerosis (MS) with active disease are candidates for the treatment with ocrelizumab and ofatumumab. These drugs target CD20 in two different epitopes and differ in the method of administration. Indeed, ocrelizumab is administered through an intravenous infusion, preceded by pre-medication with steroids and antihistamines, while ofatumumab is meant to be administered by subcutaneous injection by the patient themselves, without any premedication. In order to describe and compare the short-term safety profile of ocrelizumab vs. ofatumumab, in terms of occurrence of suspected adverse drug reactions (ADRs), we carried out a prospective observational study.

Materials and Methods: This was a prospective observational study, carried out at the MS Centre of the Cardarelli Hospital (Naples, Italy) in collaboration with the Regional Center of Pharmacovigilance and Pharmacoepidemiology of Campania Region. The study enrolled all MS patients who received first dose of ocrelizumab or ofatumumab from February to May 2023. Patients were monitored for the occurrence of any ADR occurring during the first administration of the drug at the MS centre (through their direct observation) and those occurring within 24 hours following the drug administration (information on these ADRs was collected through a telephone contact). For each patient included in the analysis the following variables were collected: age, sex, Expanded Disability Status Scale (EDSS), MS diagnosis according to the 2017 McDonald criteria, type of MS, type of anti-CD20 medication. Any differences were investigated using the Fisher's Exact test.

Results: During the study period, 22 MS patients (59.1% male) were included in the study. Of these patients, 9 received ofatumumab and 13 ocrelizumab. The EDSS ranged from 1 to 7.5. The mean age of patients receiving ofatumumab and ocrelizumab was 47.9 (11.6) and 42.1 (12.1), respectively. Among patients receiving ofatumumab, 8 (88.9%) experienced at least one ADR within 48 hours vs. 5 patients receiving ocrelizumab (38.5%) (p=0.03). The most common ADRs following ofatumumab injection were flu-like symptoms, fever and gastrointestinal symptoms, while the most common ADRs following ocrelizumab injection were allergic reaction, sleepiness and flu-like symptoms.

Conclusion: Our results showed a higher number of short-term ADRs among patients who received ofatumumab compared to patients treated with ocrelizumab. In this context premedication can represent a useful strategy to mitigate the occurrence of ofatumumab-induced ADRs in the 24 hours following its administration. Our results provide additional data that support the need of additional monitoring of these drugs.

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## PREDICTORS OF CLADRIBINE EFFECTIVENESS IN MULTIPLE SCLEROSIS: 2-YEARS DATA FROM A REAL-WORLD, SINGLE CENTRE COHORT

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Objectives: Cladribine tablets (CLAD) for adult patients with highly active relapsing multiple sclerosis (RMS) have been available in Italy since 2018. We aimed to assess predictors of no-evidence-of-disease-activity-3 (NEDA-3) status after 24 months of the last dose of CLAD.

Materials and Methods: This is a single-centre, observational, real-world study on RMS patients treated with CLAD, with at least 24 months of follow-up after the last dose taken. Clinical and magnetic resonance imaging (MRI) activity together with disability worsening were assessed as outcomes. We evaluated the relationship between baseline characteristics and outcomes to identify predictors of response.

Results: We included 88 patients (70.5% female, mean age at CLAD start 35.4±11.4). Baseline EDSS was 2.5 (1.5-7.0), 77.3% showed MRI activity at baseline (47/88 patients presented Contrast enhancing lesions, 49/88 showed New T2 lesions). Eighteen patients were treatment naïve, 48 switched to CLAD from a First line Disease Modifying Drug (DMD), and 22 from Second line DMDs. All patients were observed for a median follow-up time of 2.4 (1-4) years after the last dose of CLAD. Seventeen patients (19.3%) showed clinical (6/17) and/or radiological (15/17) activity after a median time of 1.31aa (0.7-2.73) from the last dose of CLAD. Twenty-six (29.5%) had 6-months confirmed disability progression ≥0.5 EDSS points at the last follow-up. Forty-nine patients (55.7%) showed NEDA at the last available follow-up. Naïve patients (p=0.001), those with a lower number of previous DMDs (p<0.001) and those switching from first line DMDs (p=0.069) were more likely NEDA3 at the last available follow-up. At the multivariate analysis the number of previous therapies was confirmed as the only predictor of NEDA 3 status (P = 0.035). Twenty-one patients (23.9%) switched to other DMDs, after a median time of 1.8 (0.7-2.1) years.

Discussions: Besides long-term data from Randomised Clinical Trials, other clinical experience provided evidence of a higher efficacy of CLAD when used early in the therapeutic algorithm. To our knowledge, previous real-world follow-up, ranged from a mean of 12 to 43 months post CLAD start. Our experience, instead, provides information for the 2-years after the last dose of CLAD. However, our findings, confirmed a higher effectiveness of CLAD when placed early in the treatment algorithm.

Conclusions: In our experience, CLAD effectiveness on the 24 months follow-up from the last dose was higher with its early positioning in the therapeutic scenario.

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## CSF OSTEOPONTIN IS ASSOCIATED WITH CORTICAL DAMAGE ACCUMULATION AND DISEASE ACTIVITY IN EARLY MULTIPLE SCLEROSIS

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Objectives: Accumulating evidence suggested a key role of Osteopontin (OPN,1) and other inflammatory molecules in driving chronic intrathecal inflammatory processes that have been suggested as one major pathological driver of disability accumulation in patients with multiple sclerosis (MS). Herein, we evaluated cerebrospinal fluid (CSF) inflammatory markers of accumulation of cortical damage as well as disease activity in patients with early relapsing remitting MS (RRMS).

Materials and Methods: CSF levels of OPN and other 66 inflammatory markers were assessed using an immune-assay multiplex technique in 107 patients with RRMS (82F/25M, mean age 35.7±11.8 years). All patients underwent regular clinical evaluation, including Expanded Disability Status Scale (EDSS) assessment, and yearly 3T MRI scans for at least 2 years. A subgroup of 39 patients underwent a similar 4-year clinical and radiological follow-up. White matter lesion number (WMLn) and volume (WMLv), cortical lesions number (CLn) and volume (CLv) and global cortical thickness (CTh) were evaluated together with the 'no evidence of disease activity' (NEDA-3) status, defined by no relapses, no disability worsening and no MRI activity, including CLs.

Results: After applying a random forest approach, OPN, CXCL13, TWEAK, TNF, IL19, sCD30, sTNFR1, IL35, IL16, and sCD163 were significantly associated with changes in global CTh, being Osteopontin (OPN) and CXCL13 the best related. Results were confirmed in the cohort of patients with a 4-year follow-up. In a multivariate linear regression model, CXCL13 ($p < 0.001$), OPN ($p = 0.001$) and sTNFR1 ($p = 0.024$) were increased in those patients with accumulating atrophy (adjusted R-squared 0.615). We then added the ten markers to a model that included age, sex, baseline EDSS, WMLn, WMLv, CLn, CLv, number of spinal cord lesions and Gadolinium enhancing lesions (adjusted R-squared 0.19). OPN ($p = 0.002$) and IL19 ($p = 0.022$) levels were confirmed to be significantly increased in patients developing more cortical atrophy over the follow-up and provided additional value to the abovementioned variables (adjusted R-squared 0.619). CXCL13 and OPN revealed also the best association with disease activity after two years.

Discussion: These data confirm and expand our knowledge on the prognostic role of the CSF inflammatory profile in predicting changes in cortical pathology and disease activity in early MS.

Conclusions: OPN, a molecule involved in many intrathecal inflammatory processes, has a potential key role as a marker of disease progression, providing additional value to clinical, demographic and MRI variables commonly adopted in clinical practice.

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## FUNCTIONAL CONNECTIVITY MODIFICATIONS IN MONOAMINERGIC CIRCUITS UNDERPIN FATIGUE DEVELOPMENT IN MS PATIENTS

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Objectives: Aim of this study was to investigate changes over time of resting state (RS) functional connectivity (FC) in monoaminergic networks and concomitant development of fatigue in patients with multiple sclerosis (MS).

Materials and Methods: Eighty-nine right-handed MS patients and 49 matched healthy controls (HC) underwent clinical and 3.0T RS functional MRI assessment at baseline and after 1.26 year median follow-up (interquartile range=1.01-2.01 years). Fatigue was evaluated at baseline and follow-up using the modified fatigue impact scale (MFIS) score. MS patients were considered as fatigued if MFIS was >38. Monoaminergic-related RS FC was estimated using an independent component analysis constrained to PET atlases for dopamine, noradrenaline and serotonin transporters.

Results: At baseline, 24 (27%) MS patients were fatigued (F) and 65 were not fatigued (NF). Of these, 22 (34%) developed fatigue (devF) at follow-up and 43 remained NF. At baseline, MS patients showed abnormalities of RS FC vs HC in all three PET-guided monoaminergic networks. In particular, F MS patients were characterized by increased monoaminergic-related RS FC in hippocampal, postcentral, temporal and occipital cortices, as well as by decreased RS FC in the insular cortex. NF MS patients showed limited dopamine-related RS FC changes over time. Conversely, devF MS patients showed increased dopamine-related RS FC over time in the left hippocampus, significant at time-by-group interaction analysis. In the noradrenaline-related network, NF MS patients showed decreased RS FC over time in the left superior frontal gyrus. Conversely, the same region showed increased RS FC in both devF and F MS patients; this divergent behavior was significant at time-by-group interaction analysis. Finally, devF MS patients presented increased serotonin-related RS FC over time in the angular and middle occipital gyri, while this latter region showed decreased serotonin-related RS FC at follow-up vs baseline in the F MS group.

Discussion: Fatigue affects a large proportion of MS patients independently from disease stage. Our results suggests that dysregulation of monoaminergic networks has a role in fatigue pathogenesis, with a peculiar involvement of hippocampal, superior frontal and middle occipital cortices in patients developing fatigue.

Conclusion: Specific patterns of monoaminergic networks changes over time characterized MS patients according to fatigue status.

## DISTINCT CYTOKINE PROFILE IN INDIVIDUALS PRESENTING WITH MS FOLLOWING THE SARS-COV-2 OUTBREAK

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Background: Although the etiology of Multiple Sclerosis (MS) remains unknown, the hypothesis that viruses could act as potential triggers of the autoimmune process leading to brain inflammation has been repeatedly postulated. The occurrence of the SARS-CoV-2 epidemic provides an opportunity to investigate whether a neurotropic virus can impact the development of autoimmune diseases like MS and shed light on the immunological mechanism(s) underlying the chronic progression of virus-induced brain inflammation.

Aim: The objectives of this study are as follows: 1) to examine the potential association between the risk of MS and exposure to SARS-CoV-2; 2) to investigate the characteristics of the intra-cerebral autoimmune response triggered by SARS-CoV-2. Here, we present the preliminary findings from our study cohort.

Methods: We analyzed serum and cerebrospinal fluid samples from 80 patients. The cohort included 40 MS patients with symptom onset in 2020 (MS2020), 20 patients with other non-inflammatory and inflammatory disorders diagnosed in 2020 (ONIND and OIND), and 20 MS patients with symptom onset prior to 2020 (MSbefore). Initially, each serum sample was tested for the presence of anti-SARS-CoV-2 IgG antibodies using an Anti-SARS-CoV-2 ELISA kit. Subsequently, we screened both the serum and CSF samples for 49 different analytes, including cytokines, chemokines, and growth factors. We utilized a Simple Plex Cartridge Kit for 4 analytes and ProcartaPlex Multiplex Immunoassay for 45 analytes. Statistical analysis involved Kruskal-Wallis test with Dunn correction for multiple comparisons.

Results: We observed some differences in cytokine levels (CSF BAFF, CXCL-13, HGF, SCF; serum PDGF-BB) between the group with other disorders and MS, all with $p<0.05$. However, no significant differences were observed between MS2020 and MSbefore. Conversely, there was a significant difference in serum IL-18 levels among the groups ($p=0.0015$). Specifically, the concentration of IL-18 was $66.9\pm18.8$ pg/mL in ONIND and OIND, $34.4\pm24.4$ pg/mL in MS2020 ($p=0.048$ compared to ONIND and OIND), and $19.72\pm26.0$ pg/mL ($p=0.0014$ compared to ONIND nad OIND and $p=0.036$ compared to MSbefore).

Conclusions: Our preliminary findings indicate that the CSF cytokine profile differs between MS2020 and both the control group and previous MS cases. Further investigations are warranted to determine whether the SARS-CoV-2 pandemic alters the immunological characteristics in MS.

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## SIPONIMOD, EXPERIENCE OF THE MS CENTER OF FROSINONE

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Objective: The objective of this analysis, based on a small sample size, is to gather real-world experience with siponimod and compare it with data from pivotal studies in the treatment of secondary progressive MS (SPMS). The challenges in treating SPMS include the need for early diagnosis and evaluating treatment effectiveness, especially in patients with higher disability levels [1].

Materials: The analysis included 17 SPMS active patients who started siponimod between April 2022 and May 2023.

Methods: Descriptive statistics such as mean, standard deviation, median, minimum, maximum, frequency, and percentages were used to summarize continuous and categorical variables.

Results: The mean age at treatment start was $51 \pm 6.5$ years, with 76.5% of patients being female. The age is similar to that reported in the Expand study [2], while the proportion of female patients is higher. The mean age at MS diagnosis was $35 \pm 9.2$ years. At entry, the EDSS (mean ± SD) was $5.4 \pm 1.4$. The majority of patients (52.9%) had an EDSS score between 6.0 and 6.5, similar to the Expand study. In the year prior to siponimod treatment, 82.4% of patients had experienced one relapse, with a mean number of relapses of $0.82 \pm 0.32$, higher than that observed in the Expand population. The mean number of new/enlarged T2 lesions on the MRI performed in the 2 years before treatment start was $1.52 \pm 2.19$. Most patients had received more than two treatments before starting siponimod (35.5%). The main reasons for switching from first-line treatments were efficacy and disability progression, while safety or tolerability concerns were the primary reasons for switching from second-line treatments. Since May 2023, 12 patients have remained on siponimod treatment for 12 months, while two patients discontinued treatment after three months (11.8%) due to lymphopenia and patient's decision. The mean EDSS remained stable for the majority of patients after 6 months (93.7%) and 12 months (91.7%).

Discussion: Our patient population is similar to that in the pivotal trial Expand in terms of age and EDSS at the start of siponimod treatment. However, our population appears to have a more active disease, likely due to regulatory prescription criteria. Treatment with siponimod is generally well tolerated, with a safety profile consistent with other treatments in the same class.

Conclusions: siponimod showed a safety and tolerability profile consistent with the phase 3 clinical trial data. Larger real-world studies are needed to confirm these results.

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## REAL-TIME CYTOMEGALOVIRUS (CMV) SEROCONVERSION IN A DIMETHYL FUMARATE (DMF) TREATED MULTIPLE SCLEROSIS (MS) PATIENT

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Objective: We describe real-time seroconversion of Cytomegalovirus (CMV) in a multiple sclerosis (MS) patient who was treated with dimethyl fumarate (DMF).

Materials: A 37-year-old male with a history of relapsing-remitting MS, diagnosed a year ago with diplopia. The patient started DMF within the context of a multicenter clinical study that involves subjects undergoing a diet characterized by a mild calorie restriction. At screening, the patient serology for CMV was negative and positive for EBV.

Method: During the study, in addition to clinical evaluations, patients undergo blood sampling with flow cytometry analysis of lymphocytes every six months. Two weeks before the 6-month sampling, the patient reported mild fever and dyspepsia. At 7 months, ad hoc resampling for Intracellular Cytokine Staining (ICS assay) was performed because of an increase in activated T cells. At 11 months, resampling was performed. The patient did not have a relapse of MS or evident clinical worsening during this period. Blood cells count never showed lymphopenia.

Results: At baseline, the patient had a normal CD4/CD8 ratio. At 6 months, the CD4/CD8 ratio was reversed and there was an increase in senescent CD8 (CD28- CD27-) cells. There was also a burst of activated CD4+, CD8+ and γδ T cells. At 7 months, ICS revealed an antigen-specific response to CMV pp65 by senescent-phenotype CD8+ T cells. At 11 months, the CD4/CD8 ratio returned to >1, and the senescent CD8 cells persisted. The patient serology for CMV was became positive.

Discussion: This case shows an in-vivo expansion of activated T cells in response to CVM infection, and the appearance and persistence of senescent-phenotype CD8+ T cells as expected in a physiological adaptive immune response. The observed phenomenon was caused by CMV and this was confirmed by both ICS and seroconversion. These phenomena are known in the literature but their observation in a real-life context is difficult.

Conclusion: In this case neither DMF nor the calorie restriction affected the immune response to CMV infection in a patient with MS. Moreover it helps solidify knowledge in the field of adaptive immune response to CMV infection. It is not clear whether CMV seroconversion affects the course of MS, certainly there is evidence that it is protective against the development of MS.

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## A CASE OF CEREBRAL VENOUS THROMBOSIS IN MOGAD: CAUSAL OR CASUAL ASSOCIATION?

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Objective: Myelin oligo-dendrocyte glycoprotein-associated disease (MOGAD) is a demyelinating disorder, distinct from multiple sclerosis (MS) and aquaporin-4 (AQP4)-seropositive neuromyelitis optica spectrum disorder (NMOSD). The most common clinical manifestations of MOGAD are optic neuritis, transverse myelitis, cerebral cortical encephalitis, seizures and cranial neuropathies [1]. To date, cerebral venous thrombosis (CVT) has been reported seldom in MS and in only two cases of pediatric-onset MOGAD [2-3], but the physiopathology is far to be elucidated. Here we report a case of CVT in an adult affected by MOGAD.

Materials/Methods: A previously healthy non-smoker 37-year-old male presented with a 2-week history of gait impairment, urinary urgency and hypoesthesia from the thoracic region to the inferior limbs. Spine MRI showed a STIR-hyperintense, continuous cord lesion from C2 to D1, and multiple smaller lesions in dorsal spine, with extensive contrast enhancement. A cell-based assay for anti-MOG serology resulted in a high-titer positivity (1/1280); a high-dose intravenous methylprednisolone course was performed, with improvement in ambulation and sensory disturbances. Oligoclonal bands on CSF and anti-AQP4 on serum were absent. After 3 days, he experienced 4 hours of severe headache, followed by an episode characterized by dizziness, behavioral arrest, loss of consciousness, right arm rigidity and tonic-clonic jerks lasting one minute, consistent with a focal to bilateral epileptic seizure. Somnolence and confusion were noted after the seizure. At neurological examination, the patient was drowsy and confused, with mild left hemiparesis.

Results: Infective, autoimmune and thrombophilic blood work-up was unremarkable. An urgent brain CT and MRI scan with contrast showed a right cortical frontoparietal lesion with superficial cortical veins and superior sagittal sinus congestion, associated with local absence of flow. A diagnosis of CVT was made. He started therapy with oral lacosamide and anticoagulation with subcutaneous enoxaparin followed by warfarin.

Discussion/Conclusion: CVT is a multifactorial cerebrovascular event rarely occurring in demyelinating syndromes. To our knowledge, this is the first adult case reporting the association between CVT and anti-MOG antibodies. Risk factors for CVT (lumbar puncture and corticosteroid therapy) were evident in our case. Nevertheless, a cause-effect hypothesis between MOGAD and CVT cannot be excluded. Indeed, in MS as well as in MOGAD, it has been hypothesized that a shared inflammatory-thrombotic mechanism subsists because of the evidence of lymphocytic infiltration around veins and the coexistence of multiple immunological pathways leading to inflammation of the blood vessel wall [3]. However, more documented cases are needed to better determine the link between these two rare conditions.

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## LONG-TERM MISDIAGNOSIS OF PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS: A CHALLENGING CASE REPORT

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Purpose: Primary progressive multiple sclerosis (PPMS) represents only approximately 10 percent of MS cases and is characterized by disease progression from onset, although occasional plateaus, temporary minor improvements, and acute relapses may occur. Here we report the case of a patient with an uncommon presentation of MS, both in terms of age of onset and clinical features.

Materials and Methods: A 77-year-old woman presented to our clinic with a personal history of hypertensive cardiopathy, diabetes, kidney failure, autoimmune thyroiditis, dyslipidemia, osteoporosis, and psoriatic arthritis. Furthermore, in 2019 she had a urinary tract infection that later evolved into sepsis. At this time, she started having trouble walking requiring bilateral support. Then, she developed a progressive and worsening tetraparesis within about 1 year. Electromyography (EMG) showed neurogenic suffering with signs of denervation and reinnervation on all muscles examined. At this point, amyotrophic lateral sclerosis and polyneuropathy were among the differential diagnoses and she came to our attention. At the neurological examination she presented with normal spatial-temporal orientation, hypophonia, dysphagia and hypomobile pendulous veil. She also had a strength deficit of neck flexor and extensor muscles (MRC 3) and tetraparesis. Hoffmann's sign on both sides, bilateral Babinski's sign and Epstein sign were present. Deep tendon reflexes were normal.

Results: In our clinic, we performed brain MRI that showed approximately 10 hyperintense lesional foci in long TR scans, placed at the periventricular white matter, subcortical white matter in bilateral frontal and right temporal region, on the left anterolateral side of the pons, at the cervical cord-bulbus junction and in the D7-D8 tract of the spinal cord, not taking contrast. She also underwent an EMG that showed an axonal polyneuropathy.

Discussion and Conclusions: Although the clinical features were not diriment, radiological evidence and the presence of oligoclonal bands in cerebrospinal fluid supported the diagnosis of PPMS. Primary progressive forms of MS are less common and arise at a later age. Therefore, our clinical case highlights the need to consider MS as a differential diagnosis in elderly patients, despite we faced an unusual presentation of the disease, especially considering the very late onset, its rapidly evolving nature and the difficulty in the diagnostic process because of the comorbidities of our patient that masked MS symptoms for a long time.

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## SPATIAL TRANSCRIPTOMICS ANALYSIS OF TSPO GENE EXPRESSION IN MULTIPLE SCLEROSIS BRAIN

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Background and aims: PET targeting mitochondrial translocator protein (TSPO) is an in vivo candidate biomarker for quantifying glia-related inflammation and phenotyping chronic lesions in multiple sclerosis (MS) (1. PMID 34993478). Recent neuropathological studies (2. PMID 34145928) showed by immunofluorescence analysis that TSPO is not increased in activated microglia in MS brains. This finding complicates interpretation of in vivo TSPO-PET imaging of microglia driven-inflammation in MS. In this study we quantified TSPO gene expression and cellular specificity in MS tissue according to pathological lesion stages by combining spatial transcriptomics and single-nucleus RNAseq (snRNAseq).

Materials and Methods: Spatial transcriptomics (Visium 10x Genomics) was performed on 16 tissue blocks (from 9 progressive MS cases, 7 women, age range 39-67), including active, chronic active, chronic inactive, and remyelinated lesions. On each sample anatomical regions (i.e., cortex vs white matter vs lesion core and edge) were defined by manual segmentation and Seurat unsupervised spatial clustering. For each sample and spatial cluster, TSPO+ spots (defined by non-zero TSPO expression) were quantified. To identify TSPO cellular specificity by spatial cluster, spot cell-type deconvolution was performed using SPOTlight and our published snRNAseq MS dataset (PMID 34497421), and the prevalent cell type was recorded for each TSPO+ spot.

Results: The percentages of TSPO+ spots were significantly different across spatial clusters (ANOVA $p<0.0001$), higher in active lesions (27.1%), followed by cortex (5.2%), lesion core (4.1%), chronic active edge (3.3%), and normal appearing white matter (1.2%). There were no significant TSPO differences in the lesion core of chronic active, inactive, and remyelinated lesions. By both snRNAseq and cell-type spatial deconvolution, TSPO was mainly expressed by endothelia, astrocytes, and immune cells. Within active lesions, most TSPO+ spots were enriched in composition by immune cells (36%) and endothelia (23%), while within the chronic lesion core, by endothelia (37%), astrocytes (30%), and, to a lesser extent, immune cells (6%).

Discussion: TSPO gene expression is not specific to immune cells. Our analysis on a limited spatial transcriptomics dataset demonstrates that TSPO gene expression is higher in active than chronic MS lesions, but its quantification was not significantly different among chronic lesion stages.

Conclusions: Our study supports the use of TSPO-PET as biomarker for acute neuroinflammation, although discrimination among chronic lesion pathological stages by quantification of TSPO+ spots was not achievable, hindering its application for the in vivo classification of chronic lesion types.

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## HOME-BASED, COMPUTER-ASSISTED COGNITIVE REHABILITATION FOR ATTENTION IN PEDIATRIC ONSET MULTIPLE SCLEROSIS: A RANDOMIZED, MULTICENTER PILOT STUDY

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Cognitive impairment affects approximately 30% of pediatric onset Multiple Sclerosis (POMS) with a negative impact on everyday life and school activities1. No specific intervention for neuropsychological dysfunction has been proved to be effective in this age range. The aim of this multicentric randomized, double blind, controlled study, supported by a FISM research grant, is to evaluate the feasibility and effectiveness of a home-based, computer-assisted training of attention in patients with POMS. Inclusion criteria were diagnosis of MS, age 9-18 years, impairment on at least one attention test (visual attention or matrices). Subjects were randomized to specific training (ST) or non-specific training (n-ST), delivered through a customized module based on attention exercises implemented in COGNI-TRAcK2, scheduled in 5 daily sessions per week, for 8 weeks. The main feature of the ST is the implementation of automatic adaptive working load algorithms and procedures for intensiveness regulation. The effectiveness of the ST on attention has been primarily assessed on the Symbol Digit Modalities Test (SDMT)3 using an analysis of variance for repeated measures. Secondary objectives include effectiveness on other cognitive domains and everyday-life activities. The clinical and neuropsychological evaluations were performed at baseline, end of training, 3-month follow-up. 22 relapsing-remitting POMS patients were included (15 female, mean education 10.1 + 2.6 years, mean age 15.3 + 2.2 years, mean age at onset 13.3 + 2.6 years, mean Expanded Disability Status Scale (EDSS) 1.2 + 0.8). So far, data of 8 subjects in n-ST and 4 subjects in ST were available. As for the primary outcome, mean score on the SDMT improved in the ST group (from 29.75 at baseline to 39.75 after 3 months) and remained stable in the n-ST group (from 32.0 at baseline to 35.5 after 3 months). However, the difference did not reach the statistical significance (effect size 0.81). The positive effect of ST was evident in another test of attention, the number of correct answers in the matrix visual search (p=0.042). The analysis of other neuropsychological measures is ongoing. These preliminary findings point to a potential benefit of a home-based, computer-assisted training of attention in patients with POMS. Early effective rehabilitation in POMS can mitigate the negative impact of cognitive impairment in patient's lifestyle and school performance. The analysis of the effect of this training on non-trained cognitive domains and everyday functioning will be presented.

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## AUTISTIC TRAIT IN ADULTHOOD IS A MAJOR DETERMINANT OF HEALTH-RELATED QUALITY OF LIFE IN PEOPLE WITH MULTIPLE SCLEROSIS: A CROSS-SECTIONAL STUDY

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Introduction: Multiple Sclerosis (MS) can significantly impact various aspects of quality of life. Autism Spectrum Disorders (ASD) are neurodevelopmental disorders characterized by impairments in social communication, interaction, and restricted interests. The influence of autistic traits on daily functioning is often underestimated, despite their potential impact. Consequently, there is a lack of studies examining the correlation between the severity of autistic traits and the quality of life in adults with MS.

Patients and Methods: A total of 213 adult MS patients were recruited and evaluated for cognitive deficits and anxiety. Participants completed self-assessments of quality of life using a disease-specific tool (MSQoL-54). The presence and severity of autistic traits were measured using the RAADS-14 questionnaire. Additional data on gender, age, degree of neurological disability, and education level were collected to analyze their potential role as confounders or effect modifiers. Correlations were investigated using univariate analysis of covariance, while adjusting for possible confounding factors.

Results: The analysis included 176 subjects with an average age of 46.4±12.6. The data revealed that MS patients with higher levels of autistic traits had lower health-related quality of life (HRQoL) scores in all subdomains ($p<0.001$).

Conclusions: Our findings suggest that the presence of autistic traits in individuals with MS is associated with a negative impact on their quality of life. Further research is necessary to gain a better understanding of the underlying mechanisms and to explore potential interventions that may improve outcomes for MS patients with autistic traits.

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## ASSOCIATION BETWEEN HYPERREFLECTIVE FOCI COUNT AND YKL-40 CONCENTRATIONS IN CEREBROSPINAL FLUID IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS

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Objectives: To investigate in a pivotal cohort the number of Hyperreflective foci (HRF), considered clusters of activated and proliferating retinal microglia, and other OCT parameters and their association with levels of specific inflammation and neurodegenerative biological markers.

Materials and Methods: Fifty-two patients with relapsing-remitting multiple sclerosis (RRMS) were recruited in this study. These patients underwent Spectrum-domain optical coherence tomography (OCT) and cerebral spinal fluid (CSF) examination at baseline. We analized OCT parameters, including HRF count in inner nuclear layer (INL) and retinal ganglion cell layer–inner plexiform layer (GCIPL), peripapillary retinal nerve fiber layer (RNFL) thickness (circular scan centered on optic nerve head) and macular RNFL and GCIPL thickness and volumes (25 vertical scans, centered on the fovea). NfL and YKL-40 levels in CSF were measured using enzyme-linked immunosorbent assay (ELISA), in line with manufacturer's instructions. Linear Regression Analysis was applied to investigate the OCT parameters linked to both CSF molecules, then confirmed by multiple regression analysis.

Results: HRF count in INL and GCIPL correlated with YKL-40 CSF concentration (p=0.0068 and p=0.0355 respectively). Moreover, YKL-40 associated with mGCL total volume (p=0.0348) and inner ring thickness (p=0.0164), mIPL total volume (p=0.0436) and inner ring thickness (p=0.0176). No association was disclosed for CSF NfL. Multiple linear regression analysis confirmed only the association between CSF YKL-40 and INL HRF (β 3.007, p=0.0068).

Discussion: Multiple Sclerosis (MS) pathophysiology includes both inflammatory and neurodegenerative mechanisms. Microglia are the resident immune cells of the central nervous system and the retina. It is widespread activated in the brain of patients with multiple sclerosis and its activation can result in the synthesis of proinflammatory mediators, which further can stimulate astrocytic expression of chitinase (such as Chitinase-3-like protein 1, YKL-40). Neurofilament light chain (NfL) levels and thickness of inner retinal layers are both emerging biomarkers of neuro-axonal damage.

Conclusions: Our pivotal project demonstrated that YKL-40 is specifically linked to HRF INL count, further stressing the link between astrocyte and microglia activation.

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## SAFETY AND EFFICACY OF OCRELIZUMAB: REAL WORLD EXPERIENCE IN A LARGE SARDINIAN GROUP

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Objectives: Ocrelizumab (OCR) is an anti-CD20 treatment approved for active forms of MS relapsing remitting (RR) and primary progressive (PP) patients. Despite its growing use, data on the real-world experience of OCR use are limited. Aim of this study was to examine the OCR use in PP and RR patients, and among these in naïve and switchers, evaluating the predictors of treatment response. Adverse infusion events (AIEs) were also evaluated.

Materials and Methods: MS patients exposed to OCR between 2016 and 2022 were considered. Demographic and clinical features were analyzed, and the patients were categorized as naive or switchers from I° and II° line disease modifying treatments (DMTs). NEDA-3 status at 24 months was evaluated for RR patients; determinants of NEDA 3 and AIEs were explored by regression analyses.

Results: The sample included 421 patients, of which 33(7.9%) were PP and 388(92.1%) RR. Among these, 67(17.3%) were naïve, while the switchers from I° and II° line DMTs were 199 (51.3%) and 122 (31.4%), respectively. OCR use as exit strategy from Natalizumab has been reported in 25 JCV+ patients. Among these, 5 patients had clinical or neuroradiological reactivation in the first 12 months, despite the short latency to OCR initiation (3.4 ± 2.0 months). NEDA 3 status after 24 months was calculated for 192 RR patients and achieved by 163(84.9%). Lower age (p=0.05) and the ARR in the year prior OCR (p=0.005) emerged as determinants. AIEs occurred in 128 (30.4%) patients; a relationship with previous allergic diathesis (p=0.001), reported for 37 (8.8%) patients, was observed, while the short protocol administration, used for 279 (66.8%) patients, was not related.

Discussion: A good efficacy profile was found, with significant reduction of ARR at 24 months and high percentage of patients achieving NEDA-3 status at 24 months (84.9%). Lower age at OCR start and lower ARR in the year prior emerged as significant predictors. OCR appeared also an effective and safe exit strategy from Natalizumab. As for the safety profile, the rate of AIEs appeared in line with current literature, and as expected, previous allergic diathesis emerged as a significant determinant, while the short infusion protocol appeared unrelated and thus a safe option to choose.

Conclusion: OCR is confirmed as a high efficacy option for naïve and switchers patients. Still, further real-world data are needed to better understand its efficacy and safety in different patients' groups.

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## THE IMPACT OF AUTISTIC TRAITS ON SYMPTOM SEVERITY IN MULTIPLE SCLEROSIS PATIENTS: A CROSS-SECTIONAL STUDY

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Introduction: Neuropsychiatric disorders, such as depression and anxiety, are prevalent among individuals with multiple sclerosis (MS). Autism Spectrum Disorders (ASD) are neurodevelopmental disorders characterized by impairments in social communication, interaction, and restricted interests. Despite their clinical significance, the presence and impact of autistic traits in adults are often overlooked. Consequently, no studies have examined the potential influence of autistic traits on the perception of symptoms in MS.

Patients and Methods: A total of 213 adult MS patients were recruited and screened for cognitive deficits and anxiety. Participants completed standardized questionnaires to self-assess fatigue, anxiety, and depression. The presence and severity of autistic traits were measured using the RAADS-14 questionnaire. Correlations were explored using univariate analysis of covariance, while adjusting for potential confounding factors.

Results: The analysis included 176 subjects. The data revealed that MS patients with autistic traits exhibited significantly higher levels of depression, anxiety, and fatigue ($p<0.001$).

Discussion and Conclusions: Our findings suggest that the presence of autistic traits in individuals with MS is associated with a negative impact on disease-related symptoms. These findings emphasize the importance of early investigation of these aspects during diagnosis.

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## PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY IN A PATIENT WITH MULTIPLE SCLEROSIS AND NEGATIVE SEQUENTIAL STRATIFY TESTS: A CASE REPORT

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Progressive Multifocal Leukoencephalopathy (PML) is a rare opportunistic infection of the Central Nervous System (CNS) and a serious complication of Natalizumab (NAT) treatment, due to the reactivation of human polyomavirus 2 (HPyV-2), also known as John Cunningham Virus (JCV). Infection with JCV usually occurs in early life often as a latent and asymptomatic infection and is estimated to reach 60-80% prevalence in the general population. JCV can reactivate in patients with severe immunosuppression, as occurs in patients treated with immunosuppressive therapies like NAT. Normally, most survivors have a poor functional outcome. The most used test which allows the clinician to stratify the risk of JCV reinfection is the Stratify Test, a two-step enzyme-linked immunosorbent assay (ELISA) that detects JCV antibodies in human serum or plasma. It has been estimated the amount of Stratify test false negatives is 2.5%, although several studies show the amount is higher. Here, we present a case of a 43-year-old young woman with a 25-year history of MS treated with Natalizumab who developed PML and was always tested negative to JCV Stratify test, before and after the development of the disease. The patient arrived to our attention with psychomotor impairment, confusion and anomic aphasia disturbances in January 2022. For this reason, she underwent a brain MRI, which reported the presence of two large bihemispheric cortical lesions "consistent with a progression of Multiple Sclerosis". Thus, she was hospitalized and performed JCV Polymerase Chain Reaction (PCR) in serum and cerebrospinal fluid (CSF), that demonstrated 33600 copies/mL. During the hospitalization, numerous Stratify tests were also performed, always showing negative results. We treated the patient with five sessions of plasmapheresis with the aim of removing NAT from blood and administered mefloquine, mirtazapine, ganciclovir, interleukin-7. After a transient reduction in the copies number of JCV in CSF (15030 copies/mL) concurrently with a stabilization of neurological symptoms, the patient showed an abrupt clinical-radiological progression, until the development of a persistent vegetative state four months after the beginning of the disease. Her blood and immunological tests were always unremarkable. This is a very rare case showing permanent negativity to Stratify test disagreeing with current literature. We hypothesized that the index case did not present any immunological response and, consequently, she did not develop humoral immunity. This is important to the clinician in the way he has to consider immunological response for the development of anti-JCV antibodies.

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## CALORIE RESTRICTION AS A NOVEL THERAPEUTIC TOOL TO ENHANCE EFFICACY OF FIRST LINE DRUG TREATMENTS IN MULTIPLE SCLEROSIS

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Purpose: Several studies have shown that calorie restriction (CR) is able to improve clinical course of experimental autoimmune encephalomyelitis (EAE), the animal model of multiple sclerosis (MS) [1]. The purpose of this study is to evaluate the effect of mild controlled CR on MS progression and activity. More specifically, we aimed at evaluating the impact of CR on dimethyl-fumarate (DMF) treatment in terms of circulating immunephenotype and metabolic asset of different immune cell subsets and their correlation with the clinical status of relapsing-remitting (RR) MS patients.

Materials and Methods: We enrolled 92 naïve-to-treatment RR-MS subjects that, after inclusion in the study, started DMF treatment. After enrollment, subjects were randomized to a personalized diet among three different regimes: free diet (FD), caloric restricted (CR) diet (15% reduction of personalized calorie intake) and caloric restricted diet without milk and gluten (CRWMG), with the same 15% calorie reduction as for the CR group. Blood samples for the cellular, molecular and metabolic assessment of immune cells as well as the flow-cytometric extended analyses were obtained from all patients at baseline (T0), and after 6 (T1), 12 (T2) and 24 (T3) months of treatment.

Results: After an initial screening of the cellular and molecular analyses from the completion of the two-years follow up (n = 29), we observed that CR altered different subsets of circulating T cells and in particular those with a pathogenic pro-inflammatory phenotype. These results also associated with an overall increased in the glycolytic metabolism which associated with a better induction of anti-inflammatory regulatory phenotypes.

Discussion: These data suggest that CR could be considered as effective in decreasing the frequency of pathogenic T helper cells and interfering with intracellular metabolism.

Conclusion: Our results suggest that mild CR might influence the outcome of MS and could be a useful tool for improvement of therapeutic potential of first line drug treatments during RR-MS.

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## FAMILY FUNCTIONING AND MULTIPLE SCLEROSIS: PRELIMINARY DATA OF A MULTICENTRIC ITALIAN PROJECT

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Introduction: Multiple Sclerosis (MS) may influence family functioning, with effects on both marital relationships and parental bonding. Our aim is to evaluate family functioning and related factors in patients with MS and their families.

Methods: A dedicated platform has been used for filling in the questionnaires for MS patients and their families. As controls, we selected families with no subjects referring chronic diseases. Sociodemographic and clinical information was preliminary collected. Administered questionnaires included: (1) the short form of the Family Assessment Measure Third Edition (FAM3); (2) the Hospital Anxiety and Depression Scale (HADS); (3) the Multidimensional Scale of Perceived Social Support (MSPSS); Dyadic Adjustment Scale (DAS) and the Inventory of Parent and Peer Attachment (IPPA).

Results: 129 MS patients, 93 family members (21 aged between 13 and 20 years old), and 210 control subjects (100 aged between 13 and 20 years old) completed the online questionnaires. MS family members are more anxious than control subjects (p= 0.0016) and MS partners have a higher degree of dyadic agreement (on finances, leisure time, home organization) than control subjects (p= 0.0167). Young people with ages between 13 and 20 years old who have at least one member with MS in their family, have higher quality attachments with significant others (both parents and peers), as assessed with the IPPA.

Conclusion: MS may affect the psychological state and family functioning by making MS family members more anxious, but also make more compliant partners and mature adolescents.

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## PARAMAGNETIC RIM AND NON-RIM LESIONS SHOW A SIMILAR PERIVENTRICULAR GRADIENT IN MULTIPLE SCLEROSIS: EXPLORING THE CSF-MEDIATED PATHOLOGY AND ITS 7TESLA MRI AND CLINICAL CORRELATES

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Introduction: In multiple sclerosis, paramagnetic rim lesions (PRL), which are characterized by a paramagnetic rim of iron-laden microglia visible on 7T susceptibility-weighted images, represent an important manifestation of chronic white matter (WM) pathology and indicate compartmentalized inflammation [1]. Chronic intrathecal compartmentalized inflammation has been suggested to be a mediator of a cerebrospinal fluid (CSF)–related tissue damage that can manifest with a 'surface-in' gradient of pathological changes as a function of distance from CSF [2, 3]. Whether PRL spatial development and distribution is influenced by CSF inflammatory factors is unknown.

Objectives: To investigate i) PRL distribution as a function of distance from ventricular CSF, compared to non-rim WM lesions (WML);

ii) and its relationship with clinical and imaging measures including cortical lesions, as CSF-driven inflammation with microglia activation is thought to be involved in the pathogenesis of cortical demyelination in MS.

Methods: Ultra-high resolution brain T2*-weighted gradient-echo sequences, yielding magnitude and phase images, were acquired at 7T from 61 MS patients (46 relapsing-remitting MS, RRMS, 15 progressive MS, PMS) to obtain PRL, non-rim WML, leukocortical, intracortical and total cortical lesion (LCL, ICL, TCL) volumes. The WM was divided into 1-mm-thick concentric bands radiating from the ventricular surface toward the cortex, and either PRL or non-rim WML volume was extracted from each band. Correlations between either PRL or non-rim WML and clinical and structural measures were evaluated using linear mixed-effects models and Spearman correlations.

Results: PRL volume was higher in the periventricular WM and declined with increasing distance from ventricular surface (intercept= 78 mm3, slope = -2.1, P<0.001). Non-rim WML showed a similar distribution (intercept= 235 mm3, slope = -6.5, P<0.001). In PMS, the higher the PRL volume in the bands at the closest proximity to the ventricles, the youngest age at disease onset (ρ= -0.637, P= 0.011). No correlations between PRL and cortical lesions were found. Regardless of phenotype and distance from ventricles, non-rim WML volume was significantly correlated with WM and thalamic volume, cortical thickness, and TCL volume (all p-values<0.009), as well as EDSS, disease duration and age at disease onset (all p-values<0.007).

Conclusions: PRL and non-rim WML showed a similar periventricular gradient of distribution, suggesting that CSF may influence WM MS lesion formation, but not its paramagnetic characteristics. Compared to PRL, non-rim WML volume demonstrated a stronger correlation with measures of neurodegeneration and clinical outcome. The pathogenetic basis of PRL generation necessitates further investigations.

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## TOWARDS A NOVEL CLASSIFICATION OF COGNITIVE PHENOTYPES IN PEDIATRIC MULTIPLE SCLEROSIS

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Objectives: Despite the considerable heterogeneity observed in the neuropsychological manifestations among pediatric multiple sclerosis (pedMS) patients, previous research has typically focused on a dichotomous classification of cognitive impairment. Aim of this study was to identify cognitive phenotypes in pedMS using an unsupervised machine learning approach and to characterize their clinical and MRI features, including structural and functional abnormalities within seven cortical networks based on Yeo's parcellation.

Materials and Methods: Seventy-three pedMS patients and 30 age-, sex- and education-matched healthy controls (HC) underwent 3.0T MRI, neuropsychological and clinical examination including Expanded Disability Status Scale (EDSS) score. A comprehensive neuropsychological battery (Selective Reminding Test, Spatial Recall Test, Trail Making Test, Symbol Digit Modalities Test and Semantic and Phonemic verbal fluency test) was administered to all patients. K-means cluster analysis was used to identify cognitive phenotypes based on neuropsychological test scores. MRI analysis included quantification of brain T2 white matter (WM) lesion volume (LV) and normalized brain volumes assessment, network metrics of lesion-related structural dysconnectivity and resting state (RS) functional connectivity (FC) between cortical regions within the seven networks.

Results: The machine learning approach proposed as optimal result a three-clusters solution including a Preserved cognition cluster (27 patients [37%]), a Mild verbal memory/semantic fluency involvement cluster (28 patients [38%]) and a Multidomain involvement cluster (18 patients [25%]). Across cognitive phenotypes, there were no differences in age, sex, disease duration and brain T2 WM LV. Patients with Multidomain involvement had higher EDSS score when compared with patients with Preserved cognition (p=0.006). Compared with HC, patients with Mild verbal memory/semantic fluency involvement exhibited lower normalized cortical volume (p=0.045), while patients with Multidomain involvement exhibited lower normalized brain, WM, cortical and thalamic volumes (p≤0.045). Higher structural dysconnectivity within multiple networks was found in Multidomain involvement phenotype when compared with Preserved cognition phenotype (p≤0.045). Compared to HC, patients with Mild verbal memory/semantic fluency involvement (p=0.045) and Multidomain involvement (p=0.045) experienced decreased RS FC within the frontoparietal network.

Discussion: By employing an unsupervised machine learning approach, this study identified three distinct cognitive phenotypes in pedMS. MRI analysis revealed a differential pattern of structural and functional MRI abnormalities across cognitive phenotypes. This novel classification provides a more comprehensive understanding of cognitive impairment in pedMS and the neural substrates of pediatric MS-related cognitive changes.

Conclusion: The findings highlight the complexity of cognitive impairment in pedMS and provide evidence for the existence of multiple cognitive phenotypes.

## COMPLETE EPSTEIN-BARR VIRUS SEROPOSITIVITY IN A COHORT OF PEDIATRIC ONSET MULTIPLE SCLEROSIS

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Introduction: Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of multifactorial etiology. A role of Epstein-Barr virus (EBV) is supported by the increased MS risk after infectious mononucleosis. Almost all adult patients with MS have evidence of a prior infection while 12-14% of pediatric onset MS (POMS) have been reported to be EBV-seronegative questioning the role of EBV infection. The aim of this study was to retrospectively evaluate EBV infection in our POMS cohort.

Methods: MS patients with disease onset < 18 years of age seen at Bambino Gesù Children's Hospital were included. Anti-EBV nuclear antigen (EBNA) IgG and anti-viral capsid antigen (VCA) IgG and IgM were measured by automated quantitative chemiluminescence immunoassay (CLIA) and were retrospectively evaluated at disease onset. For comparison, we analyzed the EBV seroprevalence in an age-matched cohort from our hospital. Serum samples positive for EBNA-IgG and/or VCA-IgG were considered EBV seropositive. The Fisher's exact test was used to compare the two groups.

Results: Fifty-seven POMS were included and all had a previous EBV infection. Thirty-seven were female and the median age at disease onset was 14 years (range 5-17). In the comparison group, one-hundred and fifty patients were included with a median age of 13 years (range 6-17) and they had neurological (i.e. headache and epilepsy) or other autoimmune diseases (i.e. inflammatory bowel disease, juvenile idiopathic arthritis). One-hundred and two (68%) patients were EBV seropositive. The two age-matched groups were compared and EBV seropositivity was significantly higher in POMS ($p < 0.00001$).

Conclusion: Consistent evidence support the role of EBV as a strong risk factor for MS. In our POMS cohort, EBV seropositivity was 100% like adult MS – higher than prevalence reported in literature for POMS - supporting the role of infectious mononucleosis in MS pathogenesis. Further studies are needed to clarify the role of EBV infection in POMS onset and disease course.

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## SAFETY OF SARS-COV2 VACCINATION AND COVID-19 SHORT-TERM OUTCOME IN PEDIATRIC ACQUIRED DEMYELINATING DISORDERS OF CENTRAL NERVOUS SYSTEM: A SINGLE CENTER EXPERIENCE


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Introduction: Concern of a correlation between disease relapse in patients with acquired demyelinating disorders of central nervous system (CNS) and SARS-CoV2 vaccines has been raised. In this single center study, we retrospectively evaluated safety of SARS-CoV2 vaccination and COVID-19 short-term outcome in pediatric acquired demyelinating disorders of CNS.

Materials and Methods: Patients with multiple sclerosis (MS), myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) and neuromyelitis optica spectrum disorder (NMOSD) with disease onset before 18 years of age were included. Demographic and clinical data, and information regarding previous SARS-CoV-2 infection and vaccination were collected.

Results: We included nine patients with MOGAD. Six patients received SARS-CoV2 vaccination and complained pain at injection site while only one had fever and fatigue. Median follow-up was 28 weeks (range 20-48). Seven patients had COVID-19 occurring with mild flu-like symptoms and median follow-up was 28 weeks (range 24-34). Nobody had disease relapse. Five patients with NMOSD were included. All patients received SARS-CoV2 vaccination (BNT162b2-Pfizer-BioNTech). The median follow-up was 20 weeks (range 14-24) and only two patients complained pain at injection site, fever and fatigue. Three patients had also COVID-19 with mild flu-like symptoms, despite two of them being under immunosuppressive treatment. Lastly, forty-three patients with MS were included. 35 out of 43 received SARS-CoV2 vaccination with a median follow-up of 24 weeks (range 8-36). Fourteen patients had no side effects, while 21 complained mild side effects (mainly pain at injection site) and one experienced a disease relapse with complete recovery after steroid therapy. At vaccination, all but one were under treatment. Sixteen patients had COVID-19 occurring with mild symptoms.

Discussion: COVID-19 outcome was good although many patients were under immunosuppressive treatment. Vaccine-related side effects were frequent but were mild and self-limited. Only one MS patient had a post-vaccination relapse with complete recovery after steroid therapy. In conclusion, our data support the safety of SARS-CoV-2 vaccines in pediatric MS, MOGAD and NMOSD.

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## FEASIBILITY AND EFFICACY OF AN AT-HOME, TECHNOLOGY-SUPPORTED MINDFULNESS PROGRAM IN PEOPLE WITH MULTIPLE SCLEROSIS: A PROOF-OF-PRINCIPLE STUDY


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Background: Multiple Sclerosis (MS) is a chronic disease with great clinical heterogeneity and is characterized by significant emotional distress about the uncertainties relating to disease progression. Not surprisingly, neuropsychiatric symptoms are common in MS, occurring in almost 60% of patients over the course of the disease. Mindfulness is a practice that encourages individuals to cultivate a present-focused, acceptance-based approach to managing their symptoms and helps to reduce anxiety, depression, and stress. Its positive effect on MS has been demonstrated, but learning such a technique is expensive and time-consuming. In this study, we investigated the feasibility and efficacy of an 8-week, at-home, technology-supported mindfulness program in a cohort of MS patients.

Methods: The study included two visits, one at baseline and another after the mindfulness program. Both visits consisted of a clinical and neuropsychological evaluation, together with the recording of a high-density EEG. We measured adherence to the proposed mindfulness treatment and its effect on different neuropsychological scales and in terms of quantitative EEG parameters. All participants received a smart biofeedback device – i.e., a headband with EEG sensors placed along

the forehead – to be used during the therapeutic program consisting of daily meditative exercises.

Results: Twenty-nine patients were recruited for the present study. Among them, 27 (93%) completed the entire program and 17 (63%) completed more than 80% of the scheduled sessions. We observed a statistically significant reduction of the Ruminative Response Scale score and a significant increase in the Digit Span Backward. Regarding neurophysiological data, we found a significant reduction of the whole-scalp beta and parieto-occipital theta power after the intervention.

Conclusion: Our results show that an at-home, technology-supported mindfulness program is feasible for people with MS. Meditative exercises help patients change their perspective on their condition, improving emotional response regulation. In turn, this might help with other related aspects, such as cognition or everyday self-efficacy. The efficacy in terms of reappraisals of stress, cognitive and emotional coping responses is also supported by our neurophysiological data. The major barrier to the diffusion of such practices is that mindfulness requires long and expensive training with specialised instructors. New technologies might help to improve compliance and the efficacy of mindfulness programs, as shown in the present paper. Further studies are warranted to better explore the role of such approaches in managing the psychological impact of MS diagnosis.

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## TUMEFACTIVE MULTIPLE SCLEROSIS: DIAGNOSTIC CHALLENGES AND TREATMENT CONSIDERATIONS


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Aims: Tumefactive multiple sclerosis (TMS) is an uncommon variant of multiple sclerosis (MS), defined by lesions larger than 2 cm that may be accompanied by surrounding edema, mass effect and ring enhancement [1]. Radiological features may be difficult to distinguish from other tumefactive demyelinating lesions (TDLs) as brain tumors or abscesses and often necessitate a brain biopsy for differential diagnosis [2].

Case: A 45-year-old woman presented right limbs hypoesthesia, completely resolved without therapy about one week later. Neurological examination revealed diplopia onupward gaze and brisk deep-tendon reflexes. Brain and spinal MRI revealed one T2-hyperintense lesion with restriction diffusivity and incomplete ring enhancement in left temporal lobe with a diameter of 22 mm and one T1-hypointense and T2-hyperintense lesion in right paramedian pontine area with a diameter of 21 mm. Additional subcortical and periventricular subcentrimetic areas of T2-hyperintensities were described. Cerebrospinal fluid examination showed elevated IgG index and positive oligoclonal bands. Multimodal evoked potentials study was unremarkable. We performed intravenous methylprednisolone (at the total dosage of 5 g). Brain MRI performed after treatment evidenced reduced diameter of left temporal lobe lesion, without contrast enhancement. According to 2017 McDonalds criteria [3], a diagnosis of multiple sclerosis was made. One month later, the patient started disease-modifying therapy (DMT) with ofatumumab, with clinical-radiological stability after three months.

Discussion: Approximately 70% of individuals who initially present with TDL develop definite multiple sclerosis. Despite the estimated median EDSS score is 3.5 at the time of the first attack, our case showed a mild clinical manifestation with minimal disability. Nevertheless, owing to patient's unfavourable prognostic factors such as age (above 40 years) and severe radiological imaging (subtentorial lesion and black hole), a high-efficacy treatment approach was chosen.

Conclusion: Diagnosis of tumefactive demyelinating lesions can be difficult and not always straightforward. Due to limited studies regarding TMS, the choice of DMT may rely on physicians, personal experience. However, it appears evident that certain drugs like natalizumab, fingolimod or alemtuzumab should be avoided because of their potential negative role in triggering or worsening TDL [2].

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## MANAGEMENT OF SPASTICITY IN MULTIPLE SCLEROSIS PATIENTS WITH BOTULINUM TOXIN: REAL-LIFE EXPERIENCE FROM AN ITALIAN CENTRE


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Objectives: Spasticity is a highly prevalent and disabling symptom in Multiple Sclerosis (MS) patients. Botulinum toxin (BoNTA) is a first-line treatment, however real-world data on BoNTA use in MS patients are scarce [1]. Here we report the experience of BoNTA use in MS patients in our centre.

Materials and Methods: Data from MS patients referred to BoNTA centre at Sant'Andrea Hospital in Rome, from 2010 to 2023, were retrospectively analysed. Information regarding Expanded Disability Status Scale (EDSS), disease duration, age at diagnosis, MS phenotype, BoNTA injection sites (upper/lower limb and proximal/distal), oral spasticity treatments before and after BoNTA were extracted. Patients were grouped according to (i) age at diagnosis into adult-onset MS (AOMS, 20-49 years) and late-onset MS (LOMS, >49 years); (ii) those who continued treatment and those who dropped out; (iii) disease phenotype (relapsing-remitting, RRMS; secondary progressive, SPMS; primary progressive, PPMS).

Results: Data from 84 patients were included (median EDSS 6.5; disease duration 16.1±9.3; females 62%). The number of patients treated with BoNTA increased over time (p=0.007) while EDSS and disease duration did not change. No significant differences in BoNTA injection sites were found across groups, even though LOMS patients were more frequently treated in the proximal upper limb and none of the PPMS patients were treated in the upper limb differently from RRMS and SPMS. PPMS and SPMS had a higher median EDSS (p=0.022) than RRMS. At BoNTA initiation, 46% of patients were in treatment with oral Baclofen but only 36% of patients continued it

(p=0.001). Patients in therapy with Nabiximols at BoNTA initiation were 18% increasing to 27% at follow-up (p=0.009).

Discussion: The increased number of patients treated with BoNTA over time could reflect increased attention among neurologists. The reduced access to physiotherapy in the last year due to COVID-19 pandemics could have also played a role. The potential difference in BoNTA injection sites could reflect an underlying biological variability, disease severity, disability and functional needs across disease phenotypes. Our results suggest that oral Baclofen, opposite to Nabiximols, is frequently prescribed before BoNTA initiation and more frequently discontinued afterwards.

Conclusions: Management of spasticity through BoNTA in MS patients increased over the years. However, an earlier initiation of treatment at a lower EDSS, disease duration and disability level are warranted. Future studies will help elucidating the potential differences in spasticity pattern and therapy response across disease phenotypes and the usefulness of combined treatment with BoNTA and oral drugs.

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## SPASTICITY PLUS SYNDROME MODEL IN MULTIPLE SCLEROSIS: AN OPERATIVE APPROACH IN A REAL LIFE COHORT

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Introduction: Spasticity Plus Syndrome (SPS) has been recently conceptualised to enclose several symptoms that might coexist with spasticity in Multiple Sclerosis (MS). In this study we aimed to test the SPS model through a web-based tool exploring the symptomatic profile of a cohort of patients with MS relying on patients reported outcomes (PROs).

Materials and Methods: A web-based questionnaire was sent to MS patients followed at the MS Center of Tor Vergata University to assess the symptomatic burden of spasticity, spasms, pain, fatigue, sleep disorders, depression, anxiety, bladder and bowel dysfunctions and sexual disturbances. The impact of each symptom on daily life was rated from 0 to 5 and symptoms $\geq 3$ were considered for the second level test and then for the analysis. Patients were also profiled according to clinical outcomes.

Results: Analysing 400 questionnaires we found that frequency of fatigue was 64%, depression 26% anxiety 31%, spasticity 33%, pain 25%, spasms 19%, bladder 37% and bowel 21% dysfunctions, sexual disturbances 27%, sleep disorders 29%. Defining SPS as the association of spasticity or spasms plus at least one symptom among pain, urinary dysfunction and fatigue, SPS was detected in 26% of patients with EDSS $\leq$2.5 and in 24% with EDSS 3-4 and 50% with EDSS

Conclusions: Our PROs-web-based questionnaire confirms the validity of SPS model in a real-life setting and provides an operative frame to assess SPS model. Moreover, our analysis shows that SPS can be found also in patients with low disability. Adoption of this self-reported SPS questionnaire in clinical practice might allow an earlier detection of SPS and prompt an innovative earlier model of care.

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## PARAMAGNETIC RIM LESIONS IN NATALIZUMAB PATIENTS: PREVALENCE, INFLUENCE ON MSFC AND PATIENT REPORTED OUTCOMES

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Background and Aims: Paramagnetic rim lesions (PRLs) have been gathered with severe disability and clinical worsening, as measured by EDSS, but their relation with Multiple Sclerosis Functional Score (MSFC), cognitive scores and patient-reported outcomes (PROs) have been poorly evaluated. Aim of this study is to assess whether presence and number of PRLs influence other clinical measures evaluating cognition and patient-reported clinical status in patients treated with Natalizumab.

Materials and Methods: This project plans to compare 50 MS patients treated with Natalizumab and 50 control patients treated with first line/oral Disease Modifying Therapies (DMTs). The study protocol consists of a multimodal 3T MRI scan including susceptibility weighted images (SWI) for the detection of PRLs. Clinical evaluation includes: EDSS, MSFC, Brief international Cognitive Assessment for MS (BICAMS), MS Impact Scale-29 (MSIS-29), EuroQol five-dimensional questionnaire (EQ-5D-3L), Fatigue Symptoms and Impacts Questionnaire-Relapsing MS (FSIQ-RMS), We here report the analysis of the first 42 patients studied (24 Natalizumab and 18 Controls).

Results and Discussion: No difference between Natalizumab and control groups was found in demographic and clinical characteristics. In the Natalizumab group PRL prevalence was 50% (12/24), while in controls was 67% (12/18), with an average PRL number of 1,1 (0-4) vs 2,1 (0-9). In the Natalizumab group, age, disease duration and EDSS, did not correlate with the number of PRLs, while patients with at least one PRL performed significantly worse at the 9-hole-peg-test with the dominant hand than those without PRL. Moreover, a bivariate analysis showed an association between PRLs' number and memory deficits detected by California Verbal Learning Test (CVT-z score).

Conclusions: In this preliminary analysis, Natalizumab seems to be associated with a less prevalence of PRLs compared to first line/oral DMTs. CVLT and 9-hole-peg-test are influenced by PRLs more than EDSS and PROs.

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## (S)MIMIC STROKE: A CASE REPORT

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Objectives: Multiple sclerosis (MS) is a disease usually characterized by an abrupt and recurrent onset of neurological symptoms, opening the scenario to differential diagnoses that can delay the start of disease modifying treatment (relapsing course). Although rarely, MS can also present as progressive disability accrual since inset, characterizing the so-called progressive phenotype. We present the case of a progressive MS patients presenting with an acute onset of neurological symptoms misdiagnosed for stroke.

Materials and Methods: P.G. 52-year-old man, MS diagnosis at age 22, on Siponimod therapy since 2020 affected by hypertension and diabetes under pharmacological treatment. The patient was a former smoker. EDSS 4 in March 2022. Previously the patient was treated with fingolimod, teriflunomide and interferon. Patient presented with a acute onset on December 2022 of dizziness that prevented the patient from standing after waking up, followed the next day by paresthesias and hyposthenia in the left hemilateral. The patient went to the emergency room, where he had a CT Scan. showing a hypodense area at the right brainstem level. Following the hypothesis that the patient may have experienced an ischemic stroke, treatment with Cardioaspirin 300 mg was set, continuing with a dosage of 100 mg in the following days. The patient then decided to request a second opinion at our MS clinical center. Brain MRI with contrast injection was performed. Two hyperintense lesions were found T2 sequences with contrast enhancement in T1: a right bulbar lesion with cercinate appearance and a punctiform lesion at the left superior frontal gyrus.

Results: Therefore, we withdraw the ischemic hypothesis, and we diagnosed MS relapse. Patient was discontinued from the antiplatelet therapy and then methylprednisone 1 gr therapy for 5 days has been administrated, followed by therapeutic switch from Siponimod to Natalizumab.

Discussion: Timely neurological differential diagnosis is essential as to not delay the appropriate therapeutic approach. Patients with MS have an increased cardiovascular risk, demonstrated in various studies in the literature. This is due to lower physical activity, to disability, and to the systemic inflammation status that characterizes autoimmune diseases.

Conclusions: Hence, given the possibility for MS patient to experience stroke, which shows in turn similar clinical manifestations there is a need for proper diagnostic algorithm and exams.

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## LONG TERM EFFECTIVENESS AND SAFETY OF ALEMTUZUMAB IN A REAL LIFE COHORT OF PATIENTS WITH MULTIPLE SCLEROSIS

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Objectives: Alemtuzumab (ATZ) is an anti-CD52 humanized monoclonal antibody approved for highly active Relapsing Remitting Multiple Sclerosis (RR-MS). Long term data from real world clinical setting are still missing. We aimed to assess the effectiveness and safety of ATZ in a single-centre cohort from Italy after 5 years of treatment.

Materials: In this retrospective, single-centre, real-world study we collected data of RRMS patients who received ATZ (n = 23).

Methods: Expanded disability status scale (EDSS), relapses, magnetic resonance imaging (MRI) parameters before and after ATZ were compared; serious adverse events (SAEs) were evaluated. All statistical analysis were adjusted for age, sex, MS history and previous treatment.

Results: Data of twenty-three RR-MS were collected [F=17 (73.9%); mean age 35.38±9.7years; median EDSS score 3.0 (1.5-7.0)]. All patients were followed up for a median time of 4.98 (3.5-5.9) years. Most of them (91.3%) had at least one clinical relapse in the year before ATZ, all of them showed new T2 hyperintense lesions at the baseline MRI scans, while sixteen (69.9%) showed contrast-enhancing-lesions. None of our patients was treatment naïve; most of them (91.3%) switched to ATZ after failure of more than two disease modifying Therapies (DMTs). Two patients were treated with an additional third course of ATZ, both after 18 months, for MRI activity. At the last available follow-up, nine patients (39.1%) achieved sustained No Evidence of Disease Activity-3 (NEDA-3); they didn't receive any other DMTs. Six patients (26.1%) showed improved EDSS at last follow-up. Among baseline characteristics, no predictive factors were identified for reaching NEDA3 status. The median time to first relapse was 2.1(0.17-3.1) years, the median time to another DMT initiation was 1.99 (0.25-3.2) years. Over 5 years, three SAEs were recorded: a case (4.3%) of breast cancer three years after the second course of ATZ, a case of Basedow disease and a case of HPV-related cervical cancer, both after one year from the second ATZ course.

Discussion: ATZ randomized clinical trials (RCTs), recruited treatment-naïve patients (CAMMS223 and CARE-MS I), or mostly patients at the first treatment failure (CARE-MS II). In real world, instead, as in our clinical experience, ATZ has often been proposed after failure of multiple DMTs. Nevertheless, the drug effectiveness was similar to long term data from RCTs.

Conclusion: In this real-world setting, more than one third of pwMS treated with ATZ showed sustained NEDA-3 status five years after treatment. Moreover, SAEs were comparable to RCTs experience.

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## UP-REGULATION OF SERUM MIR-128-3P IS ASSOCIATED WITH LOW GREY MATTER VOLUME IN PATIENTS WITH RECENT DIAGNOSIS OF MULTIPLE SCLEROSIS

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Background: MicroRNAs (miRs) are small non-coding RNAs that regulate gene expression at a post-transcriptional level. Different circulating miRs have recently emerged as candidate biomarkers in Multiple Sclerosis (MS); miR-128-3p has been associated with a progressive disease course in previous studies.

Objectives: To assess the association between miR-128-3p expression in serum samples of patients with MS and disease course, T2-lesion load and brain volumes in two independent groups of MS patients followed at Verona University Hospital.

Methods: We conducted a preliminary retrospective observational study on 74 MS patients (51 relapsing-remitting MS (RRMS), 10 clinically isolated syndrome, 9 primary progressive MS (PPMS), 4 Secondary Progressive MS) with an available brain MRI scan performed within 2 years from diagnosis. Subsequently, we conducted a cross-sectional study on 51 consecutively enrolled patients (33 females) aged 18-40 years recently (≤2 years) diagnosed with MS (45 RRMS, 6 PPMS). A brain MRI scan performed between 6 months before and 1 month after inclusion was mandatory. In both studies, clinical and demographic variables were collected, and T2-lesion, global brain, white matter and gray matter volumes, and presence of gadolinium-enhancing (Gd+) lesions were assessed. Levels of miR-128-3p on serum samples collected at diagnosis were detected by Real-Time PCR and expressed as ratio to miR-425-5p concentration as normalizer.

Results: In the preliminary study, serum miR-128-3p levels were higher in PPMS than in RRMS (median ratio 2.86 vs 0.73, p=0.036) and PPMS patients had an inverse correlation between gray matter volume and miR-128-3p levels (r=–0.807, p=0.009). In the cross-sectional study, serum miR-128-3p inversely correlated with global brain volume (r=–0.31, p=0.034) and gray matter volume (r=–0.31, p=0.035) in the whole cohort.

Discussion and Conclusions: Our data suggest a possible relationship between the expression of serum miR-128-3p and the extent of gray matter atrophy in MS patients, with a putative association with disease progression over time. To confirm these speculative inferences, longitudinal studies are mandatory to assess the possible role of miR-128-3p as a candidate biomarker for prediction of disease progression in MS patients.

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## LONGITUDINALLY EXTENSIVE TRANSVERSE MYELITIS IN MS: A SINGLE CENTRE EXPERIENCE

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Objective: The reported frequency of longitudinally extensive myelitis lesions - LEMs (i.e., spanning >3 contiguous vertebral body segments on spinal cord MRI) in multiple sclerosis (MS) varies, ranging from 0% to 32% [1]. Most prior studies, however, predate the discovery of aquaporin-4-IgG (AQP4-IgG) and myelin oligodendrocyte glycoprotein-IgG (MOG-IgG), potentially resulting in overestimation of LEMs [2]. We sought to determine the frequency of LEMs at first myelitis attack in a single-centre cohort of patients with central nervous system (CNS) demyelinating disorders.

Methods: We retrospectively identified adult (age ≥18 years) patients with CNS demyelinating disorders seen at the University-Hospital of Sassari from January 1, 2017 to December 31, 2022. Among these patients, we included those meeting the following inclusion criteria: 1) First myelitis attack; and 2) available spinal cord MRI during the myelitis attack. The frequency of LEMs was determined and classified according to the diagnosis at last follow-up.

Results: Among 336 patients with CNS demyelinating disorders consecutively seen over 6 years, 158 were included in the study: MS, 138 (88%); AQP4-IgG+NMOSD, 6 (4%); isolated myelitis, 5 (3%); MOG-IgG-associated disease, 3 (2%); and other demyelinating diseases of the CNS, 6 (4%). In total, eleven (7%) cases of LEMs were identified, in the context of AQP4-IgG+NMOSD (n=6), MOG-IgG-associated disorder (n=2), seronegative NMOSD (n=1), isolated myelitis (n=1), and relapsing-remitting MS (n=1). Thus, the overall frequency of LEMs in MS was 0,7% (1/138). The only MS patient with LEMs was a 55-year-old man who developed subacute weakness of right limbs, accompanied by numbness and gait instability. Spinal cord MRI showed a longitudinally extensive T2-hyperintense enhancing lesion extending from C2-D11. Brain MRI showed typical MS lesions. CSF analysis revealed moderate pleocytosis (29 white blood cells) and absence of oligoclonal bands; AQP4-IgG and MOG-IgG were absent in both serum and CSF by live cell-based assay. He was treated with intravenous methylprednisolone (1 g/d x 5 days) and plasma exchange with improvement. Natalizumab was started but after 12 weeks he had a new myelitis relapse and was switched to ocrelizumab with stabilization.

Discussion and Conclusions: LEMs is extremely rare among adult MS patients at first myelitis attack. Although our MS patient with LEMs met the 2017 diagnostic criteria for MS, he showed several atypical features that raise the possibility of an alternative aetiology of the myelitis.

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## BIOMARKERS OF INTRATHECAL SYNTHESIS IN LATE ONSET MULTIPLE SCLEROSIS: KAPPA AND LINK INDEXES PERFORMED BETTER THAN OLIGOCLONAL BANDS

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Objectives: Late-Onset Multiple Sclerosis (LOMS) includes those cases with onset above 50. Although clinical and radiological features have been increasingly described [1], insufficient data focused on pathogenetic mechanisms and fluid biomarkers. We aimed to compare biomarkers of intrathecal IgG synthesis in a cohort of relapsing-remitting (RR) patients with LOMS and adult-onset (AO) MS.

Materials: This retrospective three-center study included 70 patients (35 LOMS and 35 AOMS) who underwent lumbar puncture in their diagnostic work-up for biochemical cerebrospinal fluid (CSF) analysis and to detect CSF oligoclonal bands (OB) of immunoglobulin (Ig). Mean age at onset was 31 years old for AOMS (77% female) and 56 for LOMS (65% female).

Methods: CSF kappa-free light chains (KFLC) and CSF Ig were measured by nephelometry and used to calculate IgG and KFLC indexes. The OB detection was achieved by isoelectric focusing and immunofixation on an agarose electrophoresis system. The one-way ANOVA was used for quantitative data and the $\chi 2$ test for categorical variable.

Results: Despite the 88,6% of patients had OB+ in both groups, LOMS patients showed lower values of KFLC and IgG indexes. In fact, mean values (±standard deviation) were: for k-FLC index 53,76 (± 53,48) in AOMS versus 31,88 (±35,61) in LOMS (p=0.03); 0,75 (±0,3) for IgG index in AOMS versus 0,56 (±0,15) in LOMS (p=0.02). No differences were found in CSF KFLC and IgG values between the two groups.

Discussions: These data might suggest the presence of slight immunopathogenic phenotype difference among the two groups, specifically characterized by a lower inflammatory component in LOMS patients compared to AOMS ones. In addition, previous investigations had already revealed a faster evolution to the progressive phase of the disease and a lower Magnetic Resonance (MR) activity[2], in terms of new or enlarging T1 and T2 lesions at MR Imaging or new Gadolinium+ lesions, in LOMS patients.

Conclusions: Taken as a whole, these results emphasise the possibility of a predominance of neurodegenerative mechanisms to inflammatory ones in LOMS patients. A larger population is needed to confirm these data and draw up a complete profile of this particular subset of patients by integrating the clinical and radiological data with biological ones.

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## TUMEFACTIVE DEMYELINATING LESIONS IN MULTIPLE SCLEROSIS AFTER SARS-COV-2 INFECTION: A DIFFERENTIAL DIAGNOSIS DILEMMA


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Objectives: Herein we aim to describe an atypical case of multiple sclerosis (MS) manifested by the finding of tumefactive demyelinating lesions (TDL) resembling a primary central nervous system lymphoma (PCNSL).

Materials: A 39-year-old woman presented to the emergency department of our hospital reporting a one-week history of confusion, dysarthria and right-sided hemiparesis. She got infected by SARS-CoV-2 a few weeks before the onset of symptoms. The neurological examination also revealed brisk deep tendon reflexes, Hoffman's sign bilaterally and right Babinski's sign.

Method: Blood tests showed positive antinuclear antibodies, positive Viral Capsid Antigen and Epstein Barr Nuclear Antigen IgG. Cerebrospinal fluid (CSF) analysis showed 20 cells, mainly lymphocytes, with increased protein levels. CSF flow cytometry was not decisive. Brain magnetic resonance imaging (MRI) revealed tumefactive T2 hyperintense lesions with incomplete ring enhancement in the corpus callosum, the left caudate nucleus and internal capsule, and the right temporal pole near the ventricular horn and extending to the cortex. The spinal cord MRI was normal, while magnetic resonance spectroscopy was inconclusive. Since the radiological findings were ambiguous and cast doubt on the diagnosis of demyelinating disease over a possible diagnosis of PCNSL, a brain biopsy was performed. No tumour cells were found. After some time, the immunofixation showed the presence of oligoclonal bands (OCBs) with pattern III.

Results: After high-dose corticosteroid therapy, the patient clinically improved. Other brain MRI scans performed over six months showed stability of the findings with a reduction of contrast-enhancing lesions. A diagnosis of MS was done.

Discussion: TDL represent a rare form of demyelination defined as tumour-like lesions of the central nervous system (CNS). TDL can be associated with MS or other demyelinating diseases, although they can also manifest as an isolated disease. Distinguishing TDL from CNS neoplasms may be challenging. In our patient, the main reasons that led to a misdiagnosis were pleocytosis and the location and radiological appearance of the lesions.

Conclusions: A high index of suspicion is necessary to avoid unnecessary procedures as brain biopsy. Information pertaining to clinical history such as age, the presence of other autoimmune diseases and time of symptoms onset, as well as laboratory findings, such as the presence of OCBs, should be carefully evaluated in patients with tumefactive lesions of unknown aetiology. Besides, a recent history of viral infection - as COVID-19 in our case - should be considered as a potential precipitating factor of CNS demyelination in susceptible individuals.

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## DRUG EXPENDITURE EVOLUTION IN THE MULTIPLE SCLEROSIS MARKET IN ITALY: A PROJECTION TO 2027


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Objectives: The objective of this study was to estimate drugs expenditure evolution in the Italian Multiple Sclerosis (MS) market from 2022 to 2027, by the National Healthcare System perspective, to evaluate the system sustainability in sight of new launches (e.g., BTK inhibitors).

Materials: Model inputs integrated quantitative data sources, which included 3 different IQVIA proprietary databases (i.e., patient treated, net prices, negotiation dynamics), and qualitative sources, represented by interviews to Italian experts, both clinicians (4) and payers (2).

Methods: A predictive model with a 5-year time horizon (2022-2027) was built, combining clinical data on patients treated and economic data on net cost of each drug. Model baseline was based on the number of patients treated with each drug in 2020-2022 and current net costs of therapies. Evolution of patients treated was established applying compound annual growth rate, combined with manual adjustments derived from clinician insights. Future expenditure evolution was developed including new launches, losses of exclusivity and renegotiation of already marketed drugs. For each event, assumptions and inputs were based on analogue analyses, market insights and 2 rounds of interviews with expert. Results were validated through a final roundtable involving all stakeholders. Sensitivity analyses determined robustness of the model, varying more uncertain assumptions in an exploratory scenario.

Results: Despite treated patients' increase, Italian MS expenditure decreases from 659 M€ in 2022 to 590 M€ in 2027, with generic and biosimilar market entries having the highest impact on the reduction, followed by renegotiations of already marketed drugs. By 2027, 1L treatments (i.e., interferons, fumarates and teriflunomide) are expected to reduce their market shares from 54% to 33%, while BTK inhibitors are expected to reach 14% of the total patient shares in less than 2 years since launch. Sensitivity analyses showed good model robustness, with a difference in 2027 total expenditure of less than 10% considering assumptions in the exploratory scenario.

Discussion: Reduction of 1L treatment is in line with the clinical trend of anticipating the use of 2L treatments. Expectation of clinicians on BTK inhibitors are high: they will represent the main innovation in the MS treatment, thanks to their new mechanism of action and allowing to treat a population who currently have no treatment options (i.e., progressive patients).

Conclusions: Despite the increase in treated population and new launches, expenditure is estimated to decline over time, especially thanks to savings due to generic and biosimilar market entrance.

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## ASSESSING SPATIO-TEMPORAL PATTERN OF THALAMIC DAMAGE IN MULTIPLE SCLEROSIS PATIENTS

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Background: Thalamic atrophy is one of the earliest changes occurring during multiple sclerosis (MS) disease course. Thalamic structure is extremely complex being composed of gray matter nuclei and white matter bundles. Several pathogenetic mechanisms underlying thalamic damage have been hypothesized including Wallerian degeneration from white matter lesions and CSF-immunocytotoxic factors mediated damage.

Objectives: To identify long-term trajectories of thalamic nuclei damage and the contribution of its progression in determining clinical disability and cognitive impairment.

Methods: Using a 3T scanner, 3DT1- and T2- weighted images were obtained from 55 MS patients at disease onset and yearly for a maximum of 5 years, together with clinical and cognitive evaluation. Thalamic nuclei were segmented by using Freesurfer version 7.2.0. Algorithms of growth models by alternating conditional expectation were used to assess long term trajectories of thalamic nuclei volume changes, and linear regression models were used to assess the relationship of a progression index of thalamic damage with clinical disability and cognitive decline.

Results: Bilateral thalamic nuclei nearest to the CSF (reuniens, parafascicular, laterodorsal and pulvinar) showed a bimodal progression of volume loss, while the remaining ones showed progressive volume loss. By using growth models by alternating conditional expectation, we were able to identify an index of relative progression $\gamma$, considering the shared variance among thalamic nuclei volumes. Significant associations were observed between $\gamma$ and: clinical disability ($\beta$=0.16, p=0.03), information processing speed, verbal memory, visuo-spatial memory, and executive functions ($\beta$ from -3.38 to -0.87, p<0.001).

Conclusions: The different pattern of progression of volume loss between nuclei nearest to CSF and nuclei nearest to white matter confirm the hypothesis of heterogenous pathogenetic mechanisms underlying thalamic damage. The index identified has proven to represent a powerful tool to explain the contribution of thalamic damage to cognitive impairment and clinical disability, thus representing a potential biomarker for disease monitoring.

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## IMPACT OF CYTOMEGALOVIRUS ON IMMUNOPHENOTYPE OF NATURAL KILLER CELLS AND CD8+ T LYMPHOCYTES IN MULTIPLE SCLEROSIS

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Aims: Cytomegalovirus (CMV) causes a persistent infection which may have a multifaceted impact in multiple sclerosis (MS) [1]. Many studies reported the close association between CMV and expansion of Natural Killer (NK) expressing the activating receptor NKG2C, as well as the expansion with senescent CD8+ T cells [2]. In this study we aimed to characterize the phenotype of NK cells and CD8+ T cells to evaluate the impact of CMV infection on MS progression.

Materials: At the Neuroinfectious Unit of Policlinico Umberto I Hospital, untreated MS patients and healthy donors (HDs) were enrolled and the following parameters were evaluated: sex, age, disease duration and EDSS (Expanded Disability Status Scale).

Methods: Serological diagnostic analysis were performed to evaluate CMV serostatus. For a patients subgroup, isolated peripheral blood mononuclear cells (PBMC) were examined by flow cytometry to characterize NK and CD8+ T cells phenotype. By median fluorescence intensity (MFI), NKG2C expression levels on CD56dimCD57+ NK cells were evaluated. Correlations between immunophenotype and clinical parameters were investigated.

Results: Overall, 74 MS patients (39 M/35 F) with median age [IQR] 51 [43-58], median disease duration 11 [6-19] and median EDSS score 5.0 [3.5-6.0] were enrolled. Results showed that 69% (51/74) of MS patients were CMV-seropositive. A significantly higher expression levels of NKG2C (409[274-1304], 318[195.5-424] respectively, p=0.041) and a lower T cells percentage in MS compared to HD (68.9[62.3-71.3], 75.3[70.4-78.9] respectively, p=0.001) were observed. According to CMV serostatus, CMV seropositive MS patients showed a significantly higher expression levels of NKG2C (600.5[375.5-1597], 197[0-399] respectively, p=0.008) and higher CD56dimCD57+ NK cells percentage (36.5[26.2-43.1], 20.0[10.3-30.1] respectively, p=0.021) compared to CMV seronegative MS patients. NKG2C expression levels were significantly higher in CMV seropositive MS patients compared to CMV seropositive HD subjects (600.5 [375.5-1597], 320 [210-750] respectively, p=0.022). Moreover, NKG2C levels were positively correlated with EDSS (p=0.022) and disease duration (p=0.028).

Discussion: Overall, we observed that CMV infection leads to marked changes in the immune system, mainly characterized by the expansion of adaptive NK cells expressing high levels of NKG2C activating receptor and the differentiation of specific subsets of T cells. The NKG2C expression levels significantly higher in MS patients appear to be related to EDSS worsening, suggesting a CMV detrimental role on MS progression.

Conclusions: CMV display a complex interaction with the immune system which can explain their suggested role as co-factors of immune-mediated diseases as MS. However, the role of CMV in MS immunopathology remains controversial and further studies are warranted to define a role of this virus as either culprit or protector.

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## QUALITY OF LIFE AND PSYCHOLOGICAL DISTRESS IN A GROUP OF PATIENTS WITH MULTIPLE SCLEROSIS: LONG-TERM BENEFITS OF GROUP PSYCHOTHERAPY

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Quality of life and psychological distress in a group of patients with Multiple Sclerosis: long-term benefits of group psychotherapy.

Introduction: Neurological diseases are nowadays the most widespread pathological condition in the Western world, more than cardiovascular diseases and neoplasms. These are chronic, degenerative and constantly diseases but not yet curable pharmacologically. For this reason, appears more necessary than ever to implement psycho-social treatments.

Objective: The present study is aimed at analyzing how the CORE-OM test (Clinical Outcome in Routine Evaluation – Outcome Measures), a self-report questionnaire, consisting of 34 items indicated in the evaluation of the outcome in following a psychological treatment, can re-evaluate psychological distress in a group of patients attending a psychological support group.

Methods: The CORE-OM test was administered, in association with the BDI (Beck Depression Inventory), to 10 women, between 21 and 50 years olg aged, who received a diagnosis of Relapsing-remitting Multiple Sclerosis between 2004 and 2018, in charge of the Multiple Sclerosis Center of U.O. of Neurology at the Vaio Hospital. 7 patients take first-line therapies, while 3 second-line therapies and have an average EDSS (Expanded Disability Status Scale) score of 1.5. Patients have attended a psychological support group therapy, once a month. During the treatment only two patients discontinued the sessions.

Tools: The evaluation included the re-administration of the CORE-OM test (Clinical Outcome in Routine Evaluation - Outcome Measures) and BDI after the third year of treatment.

Results and Discussion: Patients who continued to attend psychotherapy group showed good compliance results with treatment, by asking to be able to continue the group therapy with more deferred sessions in time. The re-administered questionnaires confirmed low levels of psycho-emotional distress and depression.

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## BRAIN RESERVE AND TIMING OF CLINICAL ONSET IN MULTIPLE SCLEROSIS

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Objectives: Larger maximal lifetime brain volume (MLBV) provides a genetically determined brain reserve, being linked to lower risk for disability progression in multiple sclerosis (MS)[1,2]. Here, we explored whether such protective effect could also affect the timing of MS clinical onset.

Material and Methods: Clinical and MRI data of relapsing-remitting MS patients were retrospectively retrieved from the MS Centre databases of S. Andrea and S. Camillo Forlanini Hospitals in Rome. MLBV was computed from available 3D T1-weighted images and expressed as the reciprocal of the SIENAX volume scaling factor (with higher values corresponding to larger intracranial volume-ICV), regression-adjusted for sex. A time-to-event analysis was conducted to ascertain the effect of MLBV on the risk of an earlier disease onset. For this purpose, we carried out a Cox proportional hazards regression model stratified by sex. In this analysis, all patients reached the event (i.e., the disease onset) and there was no censored case; the age (years) at disease onset was set as the main time variable.

Results: 329 patients (229 women, 100 men) with a mean age at onset of 28.4 (SD ± 9.4) years (median 27, range 8 to 61) were included in the study. Larger MLBV exerted a protective effect on the time to disease onset: Hazard Ratio = 0.07, 95% CIs 0.01 to 0.51, p = 0.009; we obtained similar results by using a Spearman Rank correlation analysis (rho=0.15, p=0.01). Consistent findings were identified when repeating the same analysis after removing 10 patients with early-onset MS (<16 years) and 8 patients with late-onset MS (>50 years): Hazard Ratio = 0.11, 95% CIs 0.01 to 0.86, p = 0.036; similar findings were found by using a Spearman Rank correlation analysis (rho=0.11, p=0.056).

Discussion and Conclusion: The timing of MS clinical onset seems to be affected by brain reserve. Such relationship remains significant when excluding patients with age at onset at the extremes of the spectrum.

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## CLADRIBINE USE IN MULTIPLE SCLEROSIS: A MONOCENTRIC REAL-WORLD EXPERIENCE

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Objectives: Clinical trials have shown that cladribine tablets are effective and safe in treating multiple sclerosis (MS) [1,2]. However, MS patients in clinical setting differ from those in clinical trials. Thus real-world, data is needed to understand the effectiveness of cladribine in a broader population. This study aimed to describe the efficacy of cladribine in the clinical setting for MS patients and to examine trends in drug use over five years.

Materials: This independent, retrospective, real-world monocentric study analyzed the cladribine use in 131 MS patients, classified as naïve or switchers, between 2018 and 2022.

Methods: Clinical and MRI data were evaluated, and the NEDA-3 status (no evidence of disease activity in three key areas: relapses, disability progression, and MRI activity) was determined at 12-and 24-months. Descriptive statistics and multivariate regression analysis were performed by using SPSS version 20.0.

Results: The study included 131 MS patients exposed to cladribine [98 women (74.8%)]. Of these, 6.9% were naïve, 85.5% were switchers from first-line disease-modifying therapies (DMTs), and 7.6% were switchers from second-line DMTs. During the study period, the use of cladribine increased, with an increase in naïve patients of approximately 10% in the last year of observation. A reduction in the mean age (37.2±9.1 years) and MS duration (8.8±6.8 years) at cladribine initiation was also observed, with use increasingly represented in younger people and early MS. The comparisons between annualized relapse rate (ARR) 12 months before and after cladribine, analyzed for 72 MS patients (naive and switchers), indicated a significant ARR reduction in the naive group (ARR pre 1.67±0.5 vs. ARR post 0.01±0.01, $p = 0.038$), switchers from first-line (ARR pre 0.9±0.8 vs. ARR post 0.1±0.4, $p = 0.001$) and switchers from second-line (ARR pre 1.0±0.7 vs. ARR post 0.1±0.3, $p = 0.006$). NEDA-3 status was achieved in 52/72 (72.2%) patients at 12 months and 24/33 (71.5%) at 24 months.

Discussion: In our court, cladribine is used more frequently in younger individuals with early-stage MS. When comparing the relapse rates before and after cladribine treatment, significant reductions in annualized relapse rates were observed in both naïve and switchers groups. A considerable proportion of patients achieved NEDA-3 status at both 12 and 24 months.

Conclusions: Cladribine is increasingly used in young people at an early stage of the disease with impressive impact on disease activity in both naïve and switcher patients.

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## LEUKOCYTE TELOMERE LENGTH IN WOMEN WITH MULTIPLE SCLEROSIS: COMPARISON WITH HEALTHY WOMEN DURING PREGNANCY AND PUERPERIUM

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Objectives: Several studies indicated leukocyte telomere length (LTL) as a biomarker of multiple sclerosis (MS) evolution [1]. This study aimed to investigate LTL in women with multiple sclerosis (MS) compared to that in healthy women (HW) across different reproductive phases, and to evaluate its relationship with MS activity.

Materials: Blood samples of women with MS and healthy controls (HC) during fertile life, pregnancy and puerperium were collected. Short term lymphocyte culture for each individual was set up, following a standard protocol.

Methods: LTL on metaphase chromosomes, obtained from T cells in short term cultures, was determined using quantitative fluorescence in situ hybridization (Q-FISH), with Cy3-conjugated telomere PNA probe, according to the manufacturer's instructions. Thus, descriptive statistics and multivariate regression analysis were performed by using SPSS version 20.0.

Results: Blood samples from 68 women with MS (22 during fertile life, 23 during pregnancy, and 23 post-partum) and 52 HC (23 during fertile life, 20 during pregnancy, and 9 post-partum) were analysed. During pregnancy, LTL in MS women and HC was 84.7 ± 10.5kb and 77.6 ± 11.5kb, respectively ($p<0.005$). Regression analysis showed that shorter LTL was associated with pregnancy in HC ($p=0.021$); this relationship was not observed in MS women, for whom shorter LTL was related to a higher EDSS ($p=0.036$). A longitudinal analysis was performed in eight MS women, showing LTL shortening from pregnancy to puerperium ($p=0.003$), which was related to MS reactivation ($p=0.042$).

Discussion: Our analysis shown longer telomeres in MS women during pregnancy than in HC at the same stage and age. This could be partially explained by considering the protective action on MS activity played by immune system changes during pregnancy [2]. An inverse association between pregnancy status and LTL independently of age was found in HC and evidence suggests that pregnancy might be associated with telomeres shortening given an increased turnover-cells status [3]. Additionally, we reported an inverse association between LTL and EDSS score in MS women, independently of disease duration, age and biological stage. A cumulative effect played by the same risk factors on both MS progression and LTL shortening leading to oxidative stress might be considered [1]. Moreover, a longitudinal analysis shown that telomeres of MS women shortened after pregnancy, and this was associated with a return of clinical relapses.

Conclusions: Our results highlight the possible associations between LTL, reproductive biological phases, and MS activity after delivery.
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## PEDIATRIC ONSET MULTIPLE SCLEROSIS IS ASSOCIATED TO FATHER'S SMOKING STATUS AND TO FATHER HAVING SMOKED PRIOR TO PREGNANCY OF STUDY CHILDREN: THE PEDIGREE STUDY

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Objectives: Investigating the role of environmental exposures in determining multiple sclerosis (MS) in adults is hampered by long latency, potential for recall bias especially with regards to perinatal exposures. We aimed to investigate whether one such environmental factor, i.e., exposure to cigarette smoking, is associated to pediatric onset MS (POMS) in an Italian population.

Materials and Methods: The PEDiatric Italian Genetic and enviRonment ExposurE Study (PEDIGREE) aims to investigate the independent and interactive role environmental exposures and genetic asset in predisposing children (<18 years of age) to develop MS. The PEQ-IT questionnaire was used to prospectively collect environmental and perinatal exposures [1].

Results: Preliminary results are presented based on 88 children, 58 with MS and 30 controls, 22(25,0%) males and 66(75,0%) females, with mean (SD) age of 14,7 (2,8) years at study time (no difference by sex nor status) and mean (SD) age at MS clinical onset of 12,1 (3,3) years (no difference by sex). Mean(SD) disease duration between clinical onset and study time was 2,6(2,0) years (no difference by sex). Median EDSS was 1 (range 0,0-4,0) at study time (no difference by sex). More cases (14,3%) than controls (3,6%) were exposed to cigarette smoking at home (p=0,230). No association based on mother's smoking status was observed (p=0,274), nor with mother having smoked during pregnancy of participants (7,5% of cases vs. 3,3% of controls were smokers, p=0,438), or before pregnancy (5,6% of cases vs. 0% of controls were smokers, p=0,549). A significant crude association was observed with father's current smoking status, i.e, 76,5% in cases vs. 41,4% in controls, p=0,002; p-trend=p=0,002; OR=4,60 (95%IC 1,72, 12,30) as well as with father having smoked before pregnancy, i.e., 58,0% in cases vs. 26,7% in controls, p=0,010, p-trend=0,007, OR=3,80 (95%IC1,42, 10,17). These associations remained significant even after adjusting for father's educational level at participants' birth: OR=4,72 (IC95% 1,37, 16,23; p=0,014), and OR=4,27 (95%IC 1,18, 15,44; p=0,027), respectively.

Discussion: Our findings are in line with those from a case-control study conducted on 129 MS cases from the French KIDSEP neuropediatric cohort and 1,038 controls showing a 2-fold increased exposure and dose-response effect in POMS [2]. Second hand smoking was 3.7-fold more common in POMS than in monosymptomatic acquired demyelinating syndrome if associated to HLA-DRB1*15 [3].

Conclusions: POMS was over 4-fold associated to father's active current smoking status and over 3-fold with father having smoked prior to pregnancy. No association was observed with mother's smoking status ever.
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## MENOPAUSAL TRANSITION IN MULTIPLE SCLEROSIS: RELATIONSHIPS WITH DISEASE ACTIVITY AND BRAIN VOLUME MEASUREMENTS

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Background: The role of menopause in influencing multiple sclerosis (MS) trajectories represents a controversial issue. Recent evidence has shown a significant association between menopause and MS progression (Lorefice L, 2023); however, the impact of this hormonal transition on MRI findings is still poorly explored. This study investigates the possible role of menopause in influencing MS from clinical and neuroradiological perspectives. In particular, the possible association between menopause and brain atrophy has been explored.

Materials and Methods: The study included MS women of ages ranged 45-55 years. Demographic and clinical characteristics were collected, and the reproductive phase, defined as fertile, perimenopausal, and postmenopausal (Santoro N., 2005) was defined for each patient. Thus, MS activity over the past year, reported as annualized relapse rate (ARR), and MRI activity (defined as new T2 lesions and/or the presence of gadolinium-enhancing lesions) were compared between women in fertile phase and menopause. Brain volume measurements of the whole brain (WB), white matter (WM), grey matter (GM), and cortical GM were estimated using SIENAX (Smith SM, 2002) and the possible relationship with menopausal status was assessed by regression analysis.

Results: The analysis included 147 MS women. Eighty-four (57.1%) patients were menopausal, with a mean age at menopause onset of 48.5

± 4.3 years, and mean duration of menopause of 4.1 ± 1.1 years. When compared for ARR, menopausal patients reported a lower rate than the non-menopausal group (ARR of 0.29 ± 0.4 versus 0.52 ±0.5, respectively; p<0.01). Lower MRI activity, observed respectively in 13.1% of menopausal and 20.6% of non-menopausal patients was observed (p=0.03). Lower cortical GM volumes (578.1 ± 40.4 ml in menopausal patients versus 596.9 ± 35.8 ml in non-menopausal group; p<0.01), have also been reported. Finally, multivariate analysis showed a significant association between lower ARR (p=0.001) and cortical GM volume (p=0.002) with menopausal status after correction for age and other variables.

Discussion: Menopause may represent an adverse prognostic factor for MS progression. Our preliminary results suggest that menopause could facilitate cortical GM atrophy, probably due to the decline of the neuroprotective effects of estrogens, with subsequent shift into a more progressive phase of the disease.

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## MISMATCH BETWEEN PERCEIVED COGNITIVE IMPAIRMENT AND REAL COGNITIVE PERFORMANCES IN PATIENTS WITH MULTIPLE SCLEROSIS

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Objective: The aim of this study was to investigate the mismatch between perceived cognitive impairment and real cognitive performances in patients with multiple sclerosis (MS).

Materials and Methods: A cohort of patients with MS, referring to the Demyelinating Disease Center of L'Aquila from March 2022 to February 2023 was investigated through the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) and the Perceived Cognitive Deficit (PCD) questionnaire, a 11 item self-reported assessment tool exploring the patient perceived degree of cognitive impairment in 6 major cognitive domains (verbal memory, visuo-spatial memory, learning, sustained attention and concentration, speed of information processing, and verbal fluency). The PCD answers, reported on the 5-degree scale, were further converted into dummy variables (yes/no) according to low (grade 1-3) or high (grade 4-5) self-perception of cognitive impairment. Domain-specific perceived cognitive scores were correlated with BRB-N subtests scores exploring verbal memory, visuo-spatial memory, learning, sustained attention and concentration, speed of information processing and verbal fluency. Data were analyzed through descriptive statistics and using the weighted Cohen's kappa (Kw) coefficient to evaluate the rate of agreement between the variables.

Results: 119 patients were included (86 women and 33 men; mean age±SD, 46.8±12.1, minimum 16 years, maximum 67 years, average years of schooling 14.2 years). The most frequent clinical form was relapsing-remitting (RR) MS (n=93; 78%), followed by secondary-progressive (SP) MS (n=26; 22%). Mean disease duration was 10.9±8.9 years for the whole group, 10.1± 8.3 years for RR-MS patients and 14.5±10.2 for SP-MS patients. One hundred and ten patients were treated with disease modifying drugs (Fingolimod n=27, Natalizumab n=21, Dimetil-fumarato n=17, Teriflunomide n=16, Ocrelizumab n=12, Siponimod n=11, Ofatumumab n=2, Interferone Beta n=2, Alemtuzumab n=1, Cladibrina n=1). The Kw coefficient was low for all the cognitive domains explored [verbal memory: Kw 0.10 (95% CI -0.05-0.31), visuo-spatial learning: Kw 0.18 (95% CI -0.02-0.38), learning deficit: Kw 0.18 (95% CI -0.02-0.38), sustained attention and concentration: Kw -0.008 (95% CI -0.15-0.19), speed of information processing: Kw 0.23 (95% CI 0.09-0.31), verbal fluency: Kw 0.01 (95% CI -0.18-0.23). There was a general trend to underestimate the real cognitive deficit in all domains, except for verbal fluency whose impairment was usually overestimated.

Discussion: For most of the cognitive domains explored, a poor agreement between subjective perceived cognitive impairment and real cognitive skills was recognized.

Conclusions: Discrepancy between perceived cognitive impairment and real cognitive performances should be carefully considered, as potentially interfering with well-being and productivity of patients.

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## INCREASED SERUM MARKERS OF NEURONAL AND GLIAL DAMAGE IN PATIENTS WITH HEREDITARY OPTIC ATROPHIES

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Objectives: Non-syndromic hereditary optic neuropathies are neurodegenerative disorders of the optic nerve, resulting in central vision loss and optic atrophy. The main forms are autosomal dominant optic atrophy (ADOA) caused by OPA1 gene mutations, and Leber hereditary optic neuropathy (LHON) due to pathogenic mtDNA variants inherited maternally. Both conditions typically affect young adults, presenting as bilateral, painless, subacute central vision loss. Neurofilament light chain (NfL) and glial fibrillar acidic protein (GFAP) are well-established biomarkers that indicate neuroaxonal and glial injury, respectively. Growth/differentiation factor-15 (GDF-15), a member of the transforming growth factor β superfamily, represents a valuable biomarker of primary mitochondrial diseases caused by defects in mitochondrial translation machinery and mtDNA maintenance. The aim of this study is to assess whether levels serum NfL (sNfL), sGFAP and sGDF-15 are elevated in a cohort of 12 patients with ADOA and 8 patients with LHON when compared with a cohort of 20 age-, sex- and BMI-matched healthy controls (HCs).

Materials and Methods: Blood samples were collected and serum aliquots were stored at −80°C until assay. SNfL, sGFAP and GDF-15

levels were assessed in each serum sample of patients and controls. We used the commercially available immunoassay kits for GFAP and NfL run on the ultrasensitive SR-X™ Biomarker Detection System (Quanterix) following manufacturer instructions. GDF-15 was assessed using Abcam's GDF-15 Human ELISA kit, according to the manufacturer's instructions.

Results: sNfL levels were higher in both ADOA [median sNfL (pg/ml) 31.87, IQR 10.20-60.70] and LHON patients [median sNfL (pg/ml) 27.32; IQR 11.18-50.43] than HCs [median sNfL(pg/ml) 6.78; IQR 5.34-8.25] ($p<0.001$ for both). sGFAP levels were higher in ADOA patients [median sGFAP(pg/ml) 76.99, IQR 64.80-121.35] compared to HCs [median sGFAP(pg/ml) 47.53 IQR 25.57-72.21, $p=0.010$] and were within the normal ranges in LHON. Finally, GDF-15 levels were higher in LHON patients [median sGDF-15 (pg/ml) 896; IQR 514-1181] compared to HCs [median sGFAP (pg/ml) 454; IQR 278-682, $p = 0.033$]. No difference was found by comparing ADOA patients with the other two groups.

Discussion and Conclusions: The observed elevation of sNfL in both ADOA and LHON patients indicates that neuro-axonal degeneration is a shared characteristic of these diseases. Interestingly, the increased levels of sGFAP suggest a significant activation of astrocytes in ADOA. This finding aligns with previous studies conducted on animal models, where the presence of a mutant Opa1 gene was associated with the loss of retinal ganglion cells, accompanied by activation of astrocytes and microglia.

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## INCIDENT EPILEPSY IN MULTIPLE SCLEROSIS: A META-ANALYSIS OF RANDOMIZED CLINICAL TRIALS


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Objectives: Epilepsy is reported to be more common in patients with multiple sclerosis (pwMS) compared to the general population, especially in those with advanced disability and progressive disease course, albeit with heterogeneous data across studies. Cortical/iuxtacortical lesions and brain atrophy are well-recognized pathological substrates associated with seizures in pwMS. However, available data about epilepsy in MS is mainly derived from observational studies, therefore susceptible to selection bias. The objective of the present study is to verify the hypothesis of an increased incidence of epilepsy in pwMS and find the associated risk factors.

Materials: A total of 62 RCTs, with the pooled cohort consisting of 53,705 patients with an average follow-up of 2 years, yielding 105,818 patient-years were considered for data extraction.

Methods: An extensive literature was performed to extract rates of adverse events (i.e. seizure, epilepsy, or convulsion) from phase 3 randomized clinical trials (RCTs) in pwMS with more than 18 years of age, and a duration equal to or above 48 weeks. A random-effect model was fitted to estimate the pooled incidence rate of seizures (effect size) in all study populations, regardless of arm allocation. Variables (moderators) affecting the pooled effect size were analyzed through meta-regressions. Given the rarity of the events of interest, estimates were inserted in equations as double arcsine transformed incidence rates.

Results: The pooled incidence rate for a new onset seizure was 34 (95% confidence intervals: 23 to 45) per 100,000 patient-years. Reporting of events of interest increased over the years (Beta = 0.06, $p = 0.031$). After correcting for the calendar year, higher incidence rates were observed in studies that enrolled patients with either a secondary progressive course (Beta = 0.043, $p = 0.005$), a greater EDSS (Beta = 0.042, $p = 0.019$), or a lower normalized brain volume (Beta = -0.24, $p = 0.028$). Out of 68 total events, 44 occurred in RCTs on sphingosine-1-phosphate agonists (S1Pa), resulting in an increased risk in treated arms versus placebo or the active comparator (odds ratio = 2.5, $p=0.018$).

Conclusion: Our study confirms a higher incidence of epilepsy in pwMS (34 versus 23-31 patient-years in the general population aged 30-60 years) and shows an association between incident epilepsy and both neurological disability and brain atrophy. Moreover, S1Pa would result in potentially epileptogenic agents, which needs further confirmation.

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## CONVENTIONAL VERSUS ROBOTIC ASSESSMENT OF POSTURAL AND BALANCE DISORDERS IN MILD TO MODERATE DISABILITY MULTIPLE SCLEROSIS PATIENTS


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Objective: To quantitatively assess balance disorders in Persons with Multiple Sclerosis (PwMS).

Material: Seventy adult PwMS and mild (EDSS 0-3.5, group A) to moderate (EDSS 4-6.5, group B) disability were recruited.

Method: Clinical assessment was through the robotic device (Hunova®) and the Berg Balance Scale (BBS), Timed Up and Go (TUG), 10 Meter Walk Test (10MWT), Activity Balance Confidence (ABC), Modified Fatigue Impact Scale (MFIS).

Results: The sample population consisted of 46 females and 24 males, mean age 49.27. 37 patients were included in group A (mean EDSS 2.5, mean age 46.29) and 33 patients in group B (mean EDSS 5.0, mean age 52.6). In the descriptive analysis, the clinical scales and instrumental assessment parameters (Hunova) were compared between the 2 groups; the variables were crossed with each other using the Mann-Whitney test for comparison. The most accurate indicators of a balance disorder are: the amount of trunk movement (P-value = 0.0001), the anteroposterior (P-value = 0.0009) and mediolateral

(P-value = 0.0040) sway range with eyes closed, the sway area with eyes closed and open in static balance; the amount of trunk movement (P-value = 0.0079) and mediolateral eyes open sway movements (P-value = 0.0016) in passive balance; the range of mediolateral trunk sway (P-value = 0.038) and forward stabilization time (P-value = 0.038) in "Reactive Balance"; the duration (P-value = 0.008) and rise and sit times (P-value = 0.0015) of the "Five times Sit to Stand test" (5TST). In most clinical trials, such as in the TUG and the T10MWT, the median value recorded in group A is lower than in group B, because they are mutually concordant scales; BBS performs better in group A (median value 56 out of 56) than in group B (median value 49.5 out of 56) and is discordant with EDSS because it has an inverted scale as ABC.

Discussion: Robotic assessment resulted superior to conventional scales especially in slightly impaired PwMS.

Conclusion: Assessment of stabilometric indicators has proven useful in detecting alterations in postural control as early as in unperturbed standing, even in the absence of neuro-motor and balance dysfunction (top BBS score). The robotic platform, with its greater sensitivity, shows the best performance in assessing postural changes in the early phases of MS and might allow pre-clinical identification and rehabilitation of balance disorders.

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## SEXUAL AND SPHINCTER DYSFUNCTIONS IN PEOPLE WITH MULTIPLE SCLEROSIS: ASSOCIATIONS WITH CLINICAL FEATURES AND IMPACT ON QUALITY OF LIFE

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Background and Purpose: Sexual and sphincter dysfunctions (SSD) in people with multiple sclerosis (pwMS) are common but underestimated despite their relevant impact on quality of life. The objective of the study was to analyse SSD in a group of pwMS and evaluate their association with clinical features.

Materials and Methods: PwMs were enrolled and asked to respond to self-administered questionnaires investigating sphincter functions (Wexner scales, Neurogenic bowel dysfunction score-NBD; Constipation Scoring System-CSS; Actionable Bladder Symptom Score-ABSS), sexual functions (MS Intimacy and Sexuality Questionnaire-MSISQ-15; Female Sexual Function Index-FSFI-and the McCoy Female Sexuality Questionnaire-MFSQ for females International Index of Erectile Function-IIEF-15 for males) and quality of life (MS quality of life 54-MSQOL-54). A logistical regression model was used to identify correlation between EDSS, sex, age and SSD.

Results: 217 pwMS (154 females and 63 males; mean age 45.2-11.3 years) were recruited in the study. The following clinical features were collected: disease duration (12.9-9.2 years), disease phenotype (197 RRMS, 20 PMS), median EDSS (1.5, IQR 1-2.5). EDSS was significantly associated with disease duration (p<.005), MSQoL-54, MSISQ-15, FSFI, all the sphincter-related scales (all p<.001) and MSFQ-sexual (p<.009), whereas there was no statistical association between EDSS and IIEF-15. The correlation was still significant after correcting for age and sex, except for Wexner and FSFI. Disease duration was significantly associated only with ABSS (p=.04), FSFI, MSFQ (all p<.001). After correcting for sex and age, disease duration was significantly associated with MSISQ-15 (p<.05) FSFI (p=.02) and showed a trend towards significance with IEF (p=.06). A significant correlation was observed between the presence of sexual dysfunction (MSISQ-15) and all scales related to sphincter disorders (p< 0.001). A worse quality of life (MSQoL54) was significantly associated with higher degree of both sexual and sphincter dysfunctions (all p<.001). When comparing females to males, the formers reported significantly higher level of sexual (MSISQ-15) and sphincter disorders (Wexner, ABSS, CSS, NBD) and significantly lower quality of life in both physical and mental components of the scale.

Conclusions: Our findings confirm the relevance of both sphincter and sexual disorders in pwMS and their significant impact on quality of life. Sexual and sphincter dysfunctions are strongly associated, leading to hypothesize a common anato-functional origin. A higher disability and female sex are risk factors for developing SSD. This study highlights the importance of investigating sex and sphincter functions with proper scales, considering their clinical and socio-psychological impact in pwMS.

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## VALIDATION OF SMAC (SCLEROSI MULTIPLA AUTOVALUTAZIONE COGNITIVA): NORMATIVE DATA IN THE ITALIAN POPULATION

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Objectives: We have previously reported the results of a pilot study suggesting that SMAC could be a promising patient-reported outcome

to evaluate Multiple Sclerosis patient's perspective on their cognitive status (Riccardi et al., 2022). Aim of this work is to provide normative data for the Italian population of SMAC.

Materials: Participants were asked to fill out an online version of SMAC, a 25-item questionnaire that requires about five minutes to be completed.

Method: A sample of 1445 healthy controls (HC) equally distributed for age (mean age= 44.9± 19.3 years), gender (F/M=1:1) and education (mean =14.7±4.6 years) was enrolled in the study. Psychometric properties were calculated, and the best cut-off point was identified via ROCs, comparing the performance of HC with a sample of 130 matched MS patients (mean age=43.4±11.9; mean education=13.2±3.8; F/M=4:1).

Results: The internal consistency was very high (Cronbach's alpha=0.9). Regression analyses showed gender and education significant in predicting SMAC scores. In particular, higher scores were related to education and female gender. ROCs' analysis identified 35.5 as the best cut-off score in distinguishing patients and healthy controls, with a sensitivity of 66% and a specificity of 77% (Area Under the Curve=0.7). The Item Response Theory showed that all items detect the presence of subjective cognitive complaints (Beta range=0.8-1.7).

Discussion: SMAC showed a high internal consistency proving excellent reliability in the evaluation of the construct. Furthermore, SMAC demonstrated good sensitivity and specificity in detecting individuals with subjective cognitive complaints, highlighting its potential in clinical practice.

Conclusions: We provide SMAC normative data for the Italian population. Integrated with a thorough evaluation of psychological and neuropsychological status, SMAC help clinicians to understand the real impact of cognitive decline in MS patients.

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## EFFECTS OF COGNITIVE REHABILITATION ON BRAIN GREY MATTER VOLUME IN PROGRESSIVE MULTIPLE SCLEROSIS: RESULTS FROM THE COGEX STUDY


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Objectives: CogEx is a multi-site, blinded, randomized, sham-controlled trial, aimed at determining if cognitive rehabilitation (CR) and aerobic exercise (EX) are effective in people with progressive (P) multiple sclerosis (MS), and if combining CR and EX has synergistic effects. Here, we present the results of CogEx trial on MRI measures of lesions and atrophy.

Materials and Methods: Participants were randomized (1:1:1:1) to following arms: "CR plus EX", "CR plus sham EX (EX-S)", "EX plus sham CR (CR-S)", and "CR-S plus EX-S" and attended 12 weeks of intervention. Physical and cognitive (BICAMS battery) assessments were performed at baseline, immediately after intervention (week 12) and 6 months post-intervention. Participants in the MRI sub-study underwent MRI scans at the same time points. T2 lesion volume was quantified and new T2 lesions vs previous scans were counted. Normalized brain (NBV), grey matter (NGMV), cortical grey matter (NcGMV) and white matter (NWMV) volumes (FSL SIENAx), normalized thalamic and hippocampal volumes (FSL FIRST) and percentage brain volume change (FSL SIENA) were obtained. Changes of NGMV, NcGMV, NWMV, thalamus and hippocampus were calculated as percentage differences vs previous scans.

Results: 104 PMS people participated in the CogEx MRI substudy ("CR plus EX": n=25; "CR plus EX-S": n=28; "CR-S plus EX": n=25; "CR-S plus EX-S": n=26). At week 12, the number of correct responses at Symbol digit modalities test (SDMT) (p=0.64) were not significantly different among groups, nor SDMT (p=0.67), California verbal learning test (CVLT) (p=0.19) and Brief visuospatial memory test (p=0.92) Z-scores. While the time-by-group interaction for changes at week 12 vs baseline of NGMV (p=0.10) and NcGMV (p=0.09) were not statistically significant, the interactions for both NGMV (p=0.04) and NcGMV (p=0.02) were significant when considering groups performing CR vs those performing CR-S. In groups performing CR, increased NGMV (r=0.42, p=0.004) and NcGMV (r=0.36, p=0.01) at week 12 vs baseline correlated with increased CVLT. No significant differences were found for the remaining MRI variables.

Discussion: Results of the CogEx study did not show any significant synergistic effect of CR and EX on cognitive performances or structural MRI measures of PMS people. However, there was some evidence of an association between increased cortical volume and improved CVLT scores in the two groups undergoing CR.

Conclusion: CR modulated cortical GM volumes in PMS patients and correlated with concomitant improvements of cognitive performances.

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## LONGITUDINAL CHANGES OF FUNCTIONAL CONNECTIVITY DYNAMISM ARE RELEVANT FOR DISABILITY WORSENING AND COGNITIVE DETERIORATION IN MULTIPLE SCLEROSIS: A 2.5-YEAR STUDY

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Objectives: Aim of this study was to investigate changes over time of time-varying functional connectivity (TVFC) at 2.5-year follow-up in patients with multiple sclerosis (MS), and their association with clinical and cognitive worsening.

Materials and Methods: 3T magnetic resonance imaging (MRI) scans and clinical evaluations were obtained at baseline and at median follow-up of 2.5 years from 28 right-handed healthy controls (HC) and 129 MS patients. Of these, 79 patients also underwent baseline and follow-up neuropsychological assessment. At 2.5-year follow-up, MS patients were classified as clinically and cognitively stable/worsened according to disability and neuropsychological score changes. TVFC maps were produced by assessing the coefficient of variation across sliding-windows of degree centrality.

Results: At follow-up, 25/129 (19.3%) MS patients worsened clinically and 14/79 (17.7%) worsened cognitively. MS patients showed reduced baseline TVFC vs HC in orbitofrontal ($p<0.05$, corrected), cerebellar, precuneal and thalamic regions. At 2.5-year follow-up, a widespread reduction of TVFC over time ($p<0.05$, corrected) was found both in clinically and cognitively stable MS patients, especially in temporal, parietal, occipital and cerebellar lobes. Clinically and cognitively worsened MS presented TVFC reductions in default-mode network regions. Clinically worsened MS also exhibited peculiar TVFC reductions in the basal ganglia. Reduced TVFC over time in the left putamen in clinically worsened vs stable, and reduced TVFC in the right precuneus in cognitively worsened vs stable MS patients were significant at time-by-group interaction analysis.

Discussion: Overall, MS patients were characterized by decreased TVFC over 2.5-year follow-up. However, while stable MS patients presented TVFC reductions predominantly in sensorimotor and associative cortices of temporal, parietal and occipital lobes, clinically and cognitively worsened MS patients exhibited reduced TVFC over time in areas of the default-mode network. In addition, reduced connectivity dynamism in deep grey matter characterized clinically worsened MS, while precuneus involvement characterized cognitively worsened MS patients.

Conclusions: TVFC reductions in deep grey matter and precuneal regions may represent useful biomarkers to predict and monitor cognitive and clinical disability accumulation in MS.

## LONG TERM IMMUNOLOGICAL EFFECTS OF MS DISEASE-MODIFYING TREATMENTS: PATIENTS SWITCHING FROM A S1P MODULATOR TO OCRELIZUMAB OR NATALIZUMAB

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Objectives: To assess any differences in absolute lymphocyte counts and lymphocytes subpopulations in patients switching to ocrelizumab or natalizumab from a S1P modulator (fingolimod), in comparison with patients switching from another DMT and with naive patients, with a follow-up up to 48 months.

Materials: We identified 25 ocrelizumab patients switched from fingolimod vs 159 ocrelizumab patients naive or switched from other DMTs, and 20 natalizumab patients switched from fingolimod vs 132 natalizumab patients naive or switched from other DMTs. Methods: retrospective observational study of patients switching from S1P modulator (fingolimod) to ocrelizumab or natalizumab, in comparison with patients switching from another DMT to ocrelizumab or natalizumab and with naive patients starting ocrelizumab or natalizumab. Absolute lymphocyte counts and lymphocytes subpopulation were analyzed, at baseline (pre switch), and post switch at 12 months, 24 months and 48 months.

Results: Lower absolute lymphocyte counts and lower CD4+ lymphocytes counts were observed, at all time points, in ocrelizumab patients switched from fingolimod vs ocrelizumab patients naive or switched from other DMTs (with the highest difference, at all time points up to 48 months included, with patients switched from natalizumab). Number of CD8+ lymphocytes and NK lymphocytes were instead not significantly different, except at baseline (with a lower baseline number in patients switching from fingolimod). Lower absolute lymphocyte counts were also observed, at all time points, in natalizumab patients switched from fingolimod vs natalizumab patients naive or switched from other DMTs.

Discussion: Scarce data are available on the potential long term effects on the immune system of DMTs used in MS. Switching among DMTs is frequent in MS, for safety or efficacy, and frequently MS patients can be exposed to multiple DMTs in sequence over time. S1P modulators are widely used in MS and the results of our study demonstrate their long term immunological effects in MS patients up to 4 years after therapy switch.

Conclusion: A persistence of immunological effects of S1P modulators exposure, with lower absolute lymphocytes number and lower CD4+ lymphocytes number, is still observed after 4 years from fingolimod discontinuation after switching to ocrelizumab or natalizumab.

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## NURSING APPROACH DURING SHORTER AND CONVENTIONAL INFUSION OF OCRELIZUMAB: A SINGLE CENTRE EXPERIENCE

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Aim: Ocrelizumab is an anti-CD20 antibody approved for Multiple Sclerosis administered intravenously (iv) as two initial 300mg doses and subsequent 600mg doses every 6 months. For the latter, two infusion rate protocols are approved: a conventional infusion (CI, approx 3.5 hours) and a short infusion (SI, approx 2.0 hours). SI was employed to patients who did not experience significant events in previous infusions. Iv administration requires supervision by nurses to monitor infusion related reactions (IRRs). We compared the IRRs rate, type and severity during SI versus CI, to consider changes in the current monitoring protocols.

Material: We enrolled 79 patients who received one ocrelizumab 600mg SI from 2016 to 2022 at Carlo Besta Neurological Institute, as currently recommended.

Methods: We monitored blood pressure, heart rate and temperature every 15 minutes during the first hour and then every 30 minutes till infusion end. IRRs were defined as adverse events related to drug administration occurring during the infusion or up to 24h after. 5 covariates were considered for formal test hypothesis: age at ocrelizumab start, sex, comorbidity, previous MS treatments, IRRs at first cycle (300mg).

Results: 79 patient received 452 infusions (158 300mg, 215 CI, 79 SI). The mean CI duration was 233.02 ± 26.44 minutes; 145.7 ± 27.57 for SI. The overall IRRs rate was 0.23, all were grade 1 ore 2 and resolved without sequalae. IRRs were: throat irritation (60%), skin rash (14%), tachycardia (5,7%), significant blood pressure change (2.8%), fever (1.9%). IRRs rate was higher during the first 300mg administration (0.43) than during the second one (0.11). IRRs rates at CI and SI were similar (0.18; OR 0.91, 95% CI 0.34 - 2.43). Only the occurrence of IRRs at the first cycle was associated with increase IRR risk at SI (OR 11.20 95% CI 2.17 - 57.8) at the multilevel mixed-effect model. Symptomatic treatment (plus modifying infusion speed or alone) was given in 76.4% of IRRs, 23% by iv route. 15% of SI and 6% of CI needed symptomatic treatment.

Discussion: SI did not increase IRRs rate or severity and only 10% involved vital signs. IRRs at SI were more likely in patients who experienced IRR at the first 300mg infusion.

Conclusions: The ocrelizumab SI protocol optimizes MS Center nurse activities, reduces monitoring intensity without negative impact on patient safety.

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## MOG-ANTIBODY ASSOCIATED DISORDER (MOGAD) MIMICKING TYPICAL MRI PATTERN OF WERNICKE ENCEPHALOPATHY: A CASE REPORT


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Objectives: MOG antibody-associated disease (MOGAD) has a wide spectrum of clinical-MRI manifestations. We describe a unique neuroradiological presentation of MOGAD resembling typical MRI pattern of Wernicke's encephalopathy (WE).

Materials and Methods: A 42-years-old woman presented to medical attention with a 5-days history of headache followed by blurry vision. She has been suffered from diarrhea for 6 months and she underwent a cholecystectomy 4 months prior. Neurological examination only documented severe bilateral decreased visual acuity. Brain MRI showed bilateral and symmetrical hyperintense FLAIR/T2 lesions in periaqueductal grey matter, dorsomedial nuclei of thalamus, floor of the IV ventricle and mammillary bodies. WE were suspected and thiamine supplementation was promptly started. In the meantime, gastrointestinal exams led to the diagnosis of Chron's disease as a potential cause of thiamine depletion.

Results: After six days of thiamine administration, she showed no clinical improvement. Lumbar puncture detected 14 leucocytes, mostly monocytes, and no oligoclonal bands. Orbital MRI was performed, showing bilateral longitudinally extensive optic nerve lesions. A 5-day high-dose intravenous corticosteroid therapy and a plasmapheresis cycle led to a complete resolution of visual loss; brain-MRI follow-up documented T2-lesions resolution over time. Finally, serum positivity for MOG-IgG confirmed the diagnosis of MOGAD.

Discussion: In MOGAD, brain MRI can show bilateral, large, fluffy lesions located in white matter, middle cerebellar peduncle, brainstem, cortical and/or deep grey matter as features of ADEM, cerebral cortical encephalitis, brainstem and cerebellar symptoms; clinically silent brain or brainstem lesions can be present in patients with clinical optical neuritis or transverse myelitis. We documented a particularly unusual neuroradiological pattern: bilaterally symmetrical FLAIR/T2 hyperintensity in the paraventricular regions of the thalamus, hypothalamus, periaqueductal region, floor of the fourth ventricle and mammillary bodies. This brain MRI pattern has been reported to have a high specificity (93%) for the diagnosis of WE. Our case highlights the heterogenicity of brain MRI pattern in MOGAD and stressed the importance to search for MOGAD specific features like bilateral longitudinally extensive optic nerve lesions, spinal cord H-sign, T2-lesion resolution over time.

Conclusion: We reported a rare MOGAD brain MRI pattern perfectly overlapping with neuroradiological typical pattern of WE. Our case index helps to elucidate the spectrum of MOGAD MRI characteristics with the aim of assisting clinicians in the diagnosis of this heterogeneous disease.

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## MRI CORRELATES OF MANUAL DEXTERITY ASYMMETRY IN PEOPLE WITH MULTIPLE SCLEROSIS


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Objectives: Motor, sensory and cerebellar symptoms are often lateralized in people with multiple sclerosis (pwMS). Asymmetry in hand dexterity has been reported to increase with disability. Also, uneven distributions of lesion distribution and atrophy progression have been

described. This study aimed to assess whether there is an association between asymmetry in hand dexterity and in MRI measures of structural damage in MS, and if these relationships are influenced by disability.

Materials and Methods: Three hundred thirty-four pwMS and 124 healthy controls (HC), all right-handed, underwent 3T MRI acquisition of 3D-T1-weighted and dual-echo sequences, used to extract left and right normalized brain volumes (cortical and deep gray matter and cerebellum) and lesion loads (cerebral and cerebellar). Hand dexterity was evaluated with the nine-hole peg test (NHPT). Asymmetry indexes (AIs) for volumetric and hand dexterity measures were calculated by subtracting left and right z-transformed values, computed based on the HC group. Nonparametric correlations between NHPT AI and AIs of structural measures were assessed in HC and in pwMS stratified by disability, measured with the Expanded Disability Status Scale (EDSS) (mild=0-3.5; moderate=4.0-5.5; severe=6.0-8.0). Differences in overall asymmetry between groups were compared by converting AIs in absolute values and performing one-way ANOVAs.

Results: PwMS of all disability categories had worse NHPT scores than HC ($p<0.001$). No side-specific lateralization of dexterity impairment or structural damage emerged in the examination of AIs in pwMS. Larger degrees of asymmetry (i.e. more dispersed distributions) were observed in patients with moderate/severe disability, whereas mildly disabled pwMS had values ranging closer to those of HC. No correlations between structural and NHPT AIs were found in HC and mildly disabled pwMS. In moderately disabled pwMS NHPT AI correlated with cortical ($\rho=0.31$, $p=0.02$) and deep gray matter volume ($\rho=0.40$, $p=0.001$) AIs, while in pwMS with severe disability it was associated with cerebellar lesion load AI ($\rho=0.37$, $p=0.003$). Cortical and deep GM volume asymmetries were highest in the moderate disability group, whereas NHPT and cerebellar lesion load asymmetries were highest in severely disabled pwMS.

Discussion: Manual dexterity asymmetry correlates with GM atrophy asymmetry in pwMS with moderate disability and with cerebellar lesion load asymmetry in those with severe disability.
Conclusion: Structural asymmetries are associated to asymmetry in NHPT and both increase with disability in pwMS. Different structural substrates at different levels of disability underlie asymmetry in manual dexterity impairment.

## TCD20+ KINETICS IN PATIENTS SWITCHING TO OCRELIZUMAB THERAPY FROM FINGOLIMOD VERSUS DIMETHYL FUMARATE

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Introduction: CD20+T cells have a peculiar immunophenotype because they express inflammatory cytokines and markers of effector function. Anti-CD20 treatment as ocrelizumab (OCR) exerts their action also through this lymphocytes subset. The switching strategy from sequestering or depleting DMTs to OCR could influence the T-CD20 depletion induced by OCR. Here, we investigated lymphocyte subset kinetics, including TCD20+, in patients switching to OCR from fingolimod (FTY) vs those switching from dimethyl fumarate (DMF) and the possible correlations with disease activity.

Methods: Patients switching from FTY or DMF to OCR performed blood counts and lymphocyte subsets at the time of therapy discontinuation (T0), at the first administration of OCR (T1), one month after infusion (T2) and finally at six months (T3). We collected demographic and clinical data at the baseline (number of relapses and disease activity before starting treatment and EDSS) and during treatment with OCR we collected clinical relapses, new T2 lesions, and new gd+ lesions at MRI at T3.

Results: We included 16 patients, of this 37.5% switched from FTY. Annualized relapse rate before OCR were $0.37 \pm 0.31$, 75% of patients showed disease activity, and mean EDSS at baseline was $4.25 \pm 1.83$. At six months, after the start of OCR treatment, no relapses occurred, mean EDSS was $4.12 \pm 1.64$ and 12.5% of patients show disease reactivation. No statistically significant difference was registered between groups for the trend of CD4, CD8, NK, CD20, and TCD20. At T0 we found mean TCD20+ values of 56.6 cells/uL in patient switching from DMF and 34.2 cells/uL in patients switching from FTY. At T1 in FTY, we registered an increase of the same (mean value 50.6 cells/uL). At T2 and T3 we observed a reduction of TCD20+ in both patients switching from DMF and FTY. In patients with disease reactivation in the first six months of OCR treatment, we registered an increase of TCD20 at T2 (p=0,03) independent of the previous treatment.

Discussion and Conclusions: Previous treatment with FTY or DMF does not seem influence the lymphocytes subset kinetics during OCR. Disease reactivation in the first six months of OCR could be pulled by the increase of TCD20 lymphocyt. However, given the small number of patients it is necessary to expand the sample and conduct further studies to assessing the possible correlation with early disease activity.
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## COGNI-TRAIN: AN INNOVATIVE USER-FRIENDLY APPROACH FOR COGNITIVE REHABILITATION IN MS

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Cognitive impairment is commonly referred and disabling in multiple sclerosis (MS). Although there is now good evidence that cognitive rehabilitation is effective in MS, most healthcare providers are unaware of these treatment options and there are still no universally approved approaches for it.

Objective: To investigate the efficacy of a new cognitive rehabilitation approach in patients affected by MS.

Materials e Methods: 15 patients affected by RR MS with EDSS <4 (9F, 6M; age 34,3±8,5; duration of disease 6,8±4,3), referring subjective cognitive disturbances, underwent a six month cognitive rehabilitation program called COGNI-TRAIN that we have created in our Center. COGNI-TRAIN provides Cognitive Rehabilitation exercises through the periodic sending (once every 10 days) by email of structured Powerpoints containing verbal and non verbal material, including videos, to carry out cognitive strengthening. The exercises can be easily approached autonomously and are divided into specific work areas (memory, executive functions, visuo-spatial skills, language, attention). A professional psychoeducational counseling was also provided by a dedicated professional psychologist. One week before the beginning of the program and one after the end of

it patients were evaluated with an extensive and original cognitive-behavioral neuropsychological tests battery including Mini Mental State Examination, Clock Drawing Test, Picture Interpretation Test, Frontal Assessment Battery, Apathy Evaluation Scale, Visual Analogue Mood Scale - Sadness, Epworth Sleepiness Scale.

Results: All the patients improved their performances in at least two cognitive tests and one behavioral test. The neuropsychological domains mostly involved by the improvement were Executive functions, Attention, Apathy and Sleepiness ($p<0.01$).

Discussion and Conclusion: COGNI-TRAIN demonstrated to have positive effects on cognitive performance of patients affected by RR MS. If further research will confirm these data, COGNI TRAIN could become a precious resource for the management of a disease in which non-pharmacological approaches are often neglected.

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## EFFICACY AND SAFETY PROFILES OF PERCUTANEOUS TIBIAL NERVE STIMULATION WITH THE IMPLANTABLE STIMROUTER™ NEUROMODULATION SYSTEM FOR THE TREATMENT OF REFRACTORY LOWER URINARY TRACT SYMPTOMS IN MULTIPLE SCLEROSIS PATIENTS

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Background and Objective: Lower urinary tract symptoms (LUTS) are common in multiple sclerosis (MS) and significantly affect quality of life. Available pharmacotherapy has often limited efficacy and/or is poorly tolerated in MS patients. Conversely growning data support the neuromodulation in the treatment of LUTSs. To investigate the efficacy and safety of the implantable, MRI compatible StimRouter™ neuromodulation system for the treatment of refractory LUTS in patients with MS.

Material and Methods: This is a prospective, single centre, 6 month-trial conducted at the tertiary MS Center, Ospedale Regionale di Lugano, Switzerland, involving MS patients affected with refractory LUTS. Patients previously responsive to PTNS neuromodulation were included. Subcutaneous electrode was implanted in the right or left lower tibia area. All patients were treated with percutaneous tibial nerve stimulation delivered by the implantable StimRouter™ neuromodulation system. Self-administered stimulation sessions of 60 minutes were performed in 5-7 days/week over 6 months. Patients underwent urodynamic assessment and filled in questionnaires concerning LUTS severity and related quality of life at baseline and 6 months after starting neuromodulation.

Results: 23 MS patients [15 females/8 males, median (IQR) age 48 (42.5-53.5) years] were recruited. Six patients had neurogenic detrusor overactivity (NDO), 5 detrusor sphincter dyssynergia (DSD), 12 had both NDO and DSD. Within patients with NDO, median bladder volume at first uninhibited contraction significantly increased from baseline to week 24 (median=136 ml, [IQR 101-244 ml] vs 343 ml [IQR 237-391 ml]; $\beta=138.2$, $p=0.001$). No significant changes of urodynamic parameters were found in patients with DSD. OAB-q symptoms scores progressively decreased and OAB-q quality of life scores increased ($\beta=-0.50$, $p<0.001$ and $\beta=0.47$, $p<0.001$, respectively), while MSQoL-54 scores did not significantly change ($\beta=0.24$, $p=0.084$) in the overall population. Treatment satisfaction was overall high (median=8, IQR 6-9). No serious adverse events were recorded.

Discussion and Conclusion: Neuromodulation through StimRouter™ led to objective and subjective improvements of OAB symptoms and related quality of life in MS patients with refractory LUTS (especially NDO). StimRouter™ represents a minimally invasive, MRI-compatible, wireless self-administered neuromodulation treatment for MS patients suffering from refractory LUTS.

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## SAFETY AND EFFECTIVENESS OF OCRELIZUMAB TREATMENT IN A COHORT OF PATIENTS TREATED IN A MEDIUM MULTIPLE SCLEROSIS CENTRE OF MILAN

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Objective: Multiple Sclerosis (MS) is an inflammatory/degenerative disease of central nervous system (CNS). MS onset is mainly between 20-45 years of age. Many modifying drug diseases (DMD) are now available. Ocrelizumab is a humanised monoclonal antibody that targets anti-CD20 B lymphocytes, determining B cell depletion. It is approved by EMA and AIFA for Relapsing-Remitting (RR) and Primary Progressive (PP) MS with high disease activity [1-2]. Its efficacy is very high and sustained over time. Safety is currently good. Aim of the study was to evaluate the safety and efficacy in a patient cohort followed in our MS centre.

Materials: 18 MS patients (11 females, 7 males) were consecutively treated with ocrelizumab one infusion every 6 months, as scheduled by EMA and AIFA. 10 patients were RR-MS, 5 PP-MS and 3 SP-MS. Age was 20-63 years (mean 43); disease duration 1-30 years (mean 10.5). 7/18 patients were naïve to any treatment. First patient was enrolled in September 2018, last patient in November 2022. All patients performed clinical evaluation every 6 months and brain MRI every year.

Methods: In this retrospective study we compared clinical and MRI activity pre (1 year before) versus post Ocrelizumab treatment. Clinical measures were cumulative relapse number, patients with confirmed progression and mean EDSS score, MRI measures were cumulative number of new T2 lesions and Gd+ lesions post. We also recorded any AE occurred during Ocrelizumab treatment.

Results: Infusions ranged from 1 to 10 (mean 5.1) Cumulative Relapses pre were 16 (mean 0.9), post 0; mean EDSS score pre 3.3,

post 2.6. Progression was confirmed in 4 versus 14 stable/improved patients. Cumulative MRI T2 Lesions pre- were 39 (mean 3.3), post 0. Cumulative MRI Gd+ lesions were pre- were 23 (mean 1.4), post 0. 3 Adverse Event (AE) occurred: sinusitis, bronchitis covid+ and cystitis, all with good outcome. No AE required Hospitalization. All patients are still on treatment.

Discussion: Almost all patients are responder to Ocrevus therapy regardless MS course, disease duration and previous treatments. None of them had relapses and MRI activity during treatment. Better responders are RRMS patients with previous recent high clinical and MRI activity. Progression occurred mainly in SPMS with longer disease duration. No severe safety issues were observed in our cohort.

Conclusions: With the limits of a retrospective study in a small cohort, we confirm previous observation that ocrelizumab is highly effective and a safe treatment for all active MS patients.

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## BEYOND NEGATIVE ONSET MRI: DIAGNOSTIC AND THERAPEUTIC CHALLENGE OF INFLAMMATORY MYELOPATHY IN A PATIENT WITH CROHN'S DISEASE

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Aims: Spinal cord involvement can sporadically occur with Crohn's disease (CD), due to various mechanisms such as abnormal immunological status and side effects of medications, including biological drugs [1]. Magnetic resonance imaging (MRI) of myelopathy can be negative even months after onset, implying a delayed diagnosis and treatment [2].

Case: A 57-year-old man presented three-weeks before a subacute-onset of abdominal numbness spread to lower limbs and distally to upper limbs, with gait imbalance. He was affected by monoclonal gammopathy of undetermined significance and CD, treated with azathioprine and biological drugs. Brain and spine MRI performed at onset resulted negative. Neurological examination showed ataxic gait, positive Romberg test with lower limbs and distal upper limbs hypoesthesia and lower limbs apallesthesia. Blood test revealed anaemia (10,9g/dl,n.v.:14-18) and lymphopenia (0,35x10^3/uL,n.v.:0,9-5,2). Cerebrospinal fluid examination (CSF) showed blood brain barrier dysfunction, but negative oligoclonal bands. Somatosensory evoked potentials (SEP) in upper and lower limbs revealed bilateral increased latency. Brain and spine MRI were again unremarkable. Electroneurography showed decreased velocity of all sensory nerve and lower limbs motor nerve conduction, with prolonged F-wave latencies; needle-electromyography demonstrated distal muscles abnormal spontaneous activity. In suspicion of sensory-motor demyelinating polyneuropathy autoimmune disease-associated, we attempted therapy with 5-day (0.4gr/kg/day) intravenous immunoglobulin (IVIg), with partial benefit. Three weeks later, he complained lower limb weakness and spasms with worsening of gait, possible only with bilateral support, Lhermitte's sign, a T5-sensory level and bowel incontinence. CSF, electromyography and SEP were superimposable, lower limbs motor evoked potentials were absent bilaterally. Spine MRI revealed multiple cervicodorsal T2-hyperintensities, some with contrast enhancement. Aquaporin-4 and myelin-oligodendrocyte-glycoprotein antibodies on serum and CSF were negative. We performed a therapy with intravenous methylprednisolone (at total dosage of 5g), followed by IVIg, with remarkable improvement of gait and limbs strength. One month later, he had a clinical-radiological relapse, successfully treated with intravenous methylprednisolone. Afterwards, he started rituximab achieving clinical-radiological stability during one-year follow-up.

Discussion: We report an inflammatory myelopathy with initial negative MRI plus peripheral demyelinating polyneuropathy associated to CD and successfully treated with rituximab. Despite concerns about rituximab exacerbating CD, its use was justified due to CD clinical remission and high risk of residual disability associated with relapsing myelitis.

Conclusion: This case highlights the importance of accurate clinical and paraclinical evaluation, as well as repeat spinal cord imaging when there is mismatch between clinical symptoms and initial MRI findings, to ensure early and appropriate treatment, minimizing potential disability.

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## TOCILIZUMAB TREATMENT IN PROGRESSIVE MOGAD MIMICKING LEUKODYSTROPHY: A CASE REPORT AND LITERATURE REVIEW

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Introduction: Myelin oligodendrocyte glycoprotein-immunoglobulin G associated disease (MOGAD) is an autoimmune demyelinating disorder of the central nervous system (CNS) which usually occurs with recurrent optic neuritis, transverse myelitis, acute disseminating encephalomyelitis or brainstem encephalitis. To date, the anti-CD 20 drug Rituximab (RTX) is employed in MOGAD although some authors reported the efficacy of Tocilizumab (TCZ) in refractory patients.

Aim: We present the case of a woman affected by refractory MOGAD who was treated with TCZ after therapy with RTX had failed to prevent relapses. We also conducted a current review literature on TCZ use in MOGAD.

Results: A 57-years-old Caucasian woman affected by MOGAD with severe motor impairment and cognitive dysfunction was treated from 2020 to February 2022 with RTX. However, during the follow-up, she experienced progressive clinical and cognitive worsening associated with white matter lesions mimicking leukodystrophy. In February 2022, the patient started therapy with TCZ administered every four weeks with subsequent improvement of cognitive performance, walking ability and brainstem functions. During TCZ (last follow-up considered was on March 2023) our patient reached the condition of NEDA-3 (no relapse, no increase in disability, no MRI activity on neuroimaging follow-up performed in October 2023). Moreover, during TCZ treatment, the patient experienced pauci-symptomatic SARS-CoV-2 infection that did not modify disease course or TCZ schedule. To date, there are few evidence on the efficacy and safety of TCZ in MOGAD. However, all the reviewed cases showed that TCZ represent an effective therapy in drug resistant MOGAD with subsequent improvement of symptoms and disease course.

Discussion and Conclusions: Our case highlights the efficacy of TCZ in drug resistant MOGAD and strengthens previous reports of TCZ safety and efficacy in MOGAD.

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## PREGNANCY EFFECT ON DISEASE ACTIVITY IN WOMEN TREATED WITH CLADRIBRINE

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Introduction: Cladribrine is an oral pulsed therapy for relapsing multiple sclerosis (RMS). Hormonal and immune changes are responsible for the decline of disease activity in the third trimester of pregnancy and disease reactivation in the early post-partum period. To date there are no available studies on the pregnancy effect on disease activity in women with MS who conceived after cladribrine treatment.

Methods: We recruited women of childbearing age with RMS who became pregnant or not after being treated with cladribrine. For both groups, demographic, clinical and radiological data were collected one year before and after treatment to compare the disease activity.

Results:47 childbearing women mean age 35.05 ys were included. 24 women had a pregnancy after a mean of 1.75 years from the first treatment cycle, 5 pregnancies occurred between the first and second cycle. Women with or without pregnancy did not differ for demographics or disease activity pre cladribrine. No significant differences in disease activity post cladribrine were found between women with or without pregnancy (0.12 vs 0.04 for ARR p=0.36;1.9 vs 1.1 p=0.65 for new T2 lesions and 0.29 vs 0.3 p= 0.60 for new gd+ lesions). No significant differences were found between women with pregnancy occurred between the first and second cycle or after the second cycle.

Discussion and Conclusion: Pregnancy does not appear to influence disease activity in women previously treated with cladribrine; further studies with larger numbers are needed to confirm this finding and to identify the best timeframe to conceive after cladribine treatment that guarantees to be still protected from reactivation in the post-partum period.

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## AUTONOMIC NERVOUS SYSTEM (ANS) INVOLVEMENT: A NEW MARKER OF DISABILITY IN PATIENTS WITH MULTIPLE SCLEROSIS

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Objectives: The aim of the study was to investigate the incidence of autonomic dysfunction in people with MS (pwMS). In addition, we tried to evaluate if Expanded Disability Status Scale (EDSS), disease duration and different subtype of MS correlate with the severity of autonomic dysfunction.

Materials and Methods: 73 out of pwMS underwent to Wexner Scales on bowel function, SNF-SIQ and SCOPA-AUT. Ewing tests, Sympathetic Skin Response SSR and Dynamic Sweat Test DST were performed in 22 pwMS.

Results: It was found an elevated incidence of autonomic disfunction symptoms among patients affected by MS (in our study 90% of the total group had at least one autonomic domain affected). The most common affected domains were the genitourinary, gastrointestinal and thermoregulation ones. Furthermore, it was found that scores obtained from the clinical scales correlated with disability but not with disease duration nor type of MS. On the other hand, it was found that data obtained from the diagnostic procedures didn't correlate with disability nor with disease duration nor with type or MS.

Discussion and Conclusion: it is still not clear the involvement of the Autonomic Nervous System in pwMS. Moreover, there are still no validate procedures to study this impairment. Our study confirms this involvement, but a bigger cohort of patients is needed.

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## THE EARLY EFFECT OF CLADRIBINE VERSUS FINGOLIMOD ON CLINICAL AND MRI MEASURES IN RELAPSING REMITTING MULTIPLE SCLEROSIS

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Background and Aims: A treatment protocol with cladribine tablets (CLAD) requires two courses of treatment in Year 1 and Year 2. Data regarding its efficacy during the first 12-months of treatment in comparison with fingolimod (FINGO) in the real-life setting are still sparse. The aim of this study is to compare the early impact of CLAD (I course) and FINGO in terms of clinical and MRI outcomes in a cohort of relapsing-remitting multiple sclerosis (RRMS) patients (pts).

Materials and Methods: A total of 63 patients were included in the analysis, [32 CLAD and 31 FINGO; females: 65.1%; mean age, disease duration, ARR two previous years: 39.4+14.2, 8.6+9.6 years, 0.47+0.56; median (range) EDSS and number of previous DMTs: 1.5 (0-5.5) and 1 (0-3)]. No differences in terms of age, sex, disease duration, ARR two previous years, number of previous treatments, EDSS, total brain volume and lesion load were found between the two groups at baseline. In this ongoing study, RRMS patients underwent complete clinical evaluation [including assessment of Expanded-Disability-Status-Scale (EDSS), annualized relapse rate (ARR), nine-hole-peg–test (9HPT) and timed-25-foot-walk (T25FW] and 3T-MRI (Siemens MAGNETOM) at baseline and after 12-months follow-up. NIH toolbox standing balance test was used to quantify balance impairment. Changes in percentage-brain-volume-change (PBVC) were measured. The probability of disability-/relapse- /MRI activity-free survival, NEDA-3 and NEDA-4 status (defined as NEDA3 + PBVC<0.4% per year) were calculated with Kaplan-Meier estimator.

Results: At 1-year FU, MRI-inflammatory-activity-free survival was 81.3% and 74.2% (p=0.55) and relapse-free survival was 93.8% and 100% (p=0.16) in CLAD and FINGO treated pts, respectively. Progression-free survival was 100% in both groups. Mean PBVC was -0.6+1.5% (-0.48+1.6% in CLAD vs -0.76+1.4% in FINGO pts; p=0.82). NEDA-3 status was achieved in 81.3% and 74.2% (p=0.57) while NEDA-4 in 35.7% and 27.3% (p=0.53) of pts in CLAD and FINGO groups, respectively. Although not statistically significant, there was a decrease of 0.63+3.0 vs an increase of 0.9+3.8 seconds at 9HPT test (p=0.13), an increase of 0.46+3.2 vs 1.3+3.3 (p=0.51) seconds at T25FW tests and a decrease of 0.19+0.55 vs 0.06+0.74 (p=0.57) of NIH Toolbox Standing Balance theta value in CLAD vs FINGO treated pts, respectively.

Discussion and Conclusions: Although a complete CLAD treatment course requires the 2-dose 2-year protocol, our findings suggest that its efficacy is comparable to FINGO even during the first 12-months, though should be confirmed by larger analysis.

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## HYPOGAMMAGLOBULINEMIA AND SEVERE INFECTIONS IN MULTIPLE SCLEROSIS PATIENTS ON ANTI-CD20 AGENTS: A MULTICENTRE STUDY

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Background: Hypogammaglobulinemia (HG) is a known adverse event of treatment with anti-CD20 monoclonal antibodies (mAbs). Information on the safety profiles of the different anti-CD20 mAbs used in the treatment of Multiple Sclerosis (MS) can be useful for therapeutic decisions and for the implementation of de-risking strategies.

Objectives and Methods: Main aim of this retrospective multicentre study was to assess the frequency of HG in MS and Neuromyelitis Optica Spectrum Disorder (NMOSD) patients treated for at least one year with either ocrelizumab (OCR) or rituximab (RTX) and its association with the occurrence of severe infections (SI). Secondary aims were to identify predictors of HG and SI.

Results: We included 556 patients (533MS, 23NMOSD; 190M, 366F, mean age: 47 years) with a mean follow-up of 29 months (range: 12–90). Compared to OCR-treated patients (nr=399), patients on RTX (nr=157) were older (53 vs 45 years), more frequently progressive (67% vs 36%), had a higher disability (EDSS 5 vs 4) and a longer treatment duration (33 vs 28 months). IgG HG occurred in 21% of patients, while IgM HG occurred in 34%. Both were significantly more frequent in the RTX group (27% vs 18% and 45% vs 29%, respectively), and occurred earlier during RTX treatment, but there was no difference in the incidence rate ratio between the two drugs. The risk of IgG HG was influenced by age≥50 years (OR: 1.64) and by the number of treatment cycles (OR: 1.10). The risk of IgM HG was increased by the RTX therapy (OR: 1.78) and the number of treatment cycles (OR: 1.09). A total of 357 infections were recorded during treatment (rate per 100 person years -100PY: 26.3). Of these, 25 were severe, requiring hospitalization (100PY rate: 1.8). The majority (76%) were Covid-related pneumonias. At multivariable analysis, only athe disease phenotype (OR 1.50, 95%CI:1.02-2.20; p=0.039) and IgG HG (OR 2.51, 95%CI: 1.09-5.80; p=0.031) at any time during treatment increased the risk of a SI. The co-occurence of IgG and IgM HG further increased the odds of a SI (OR 3.17, 95%CI:1.27-7.92; p=0.013).

Conclusion: IgG and IgM HG occurred in a substantial proportion of MS patients treated with ant-CD20 mAbs and increased the risk of a SI, highlighting the importance of monitoring immunoglobulin levels at baseline and throughout treatment. IgG and IgM HG were more frequent in RTX-treated patients compared to those treated with OCR, but baseline characteristics and treatment duration differed between the two populations. Further studies, with longer follow-up periods, are necessary to inform on the safety profiles of the different anti-CD20 mAbs.

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## A COMPREHENSIVE PICTURE OF FUNCTIONAL DISORDERS IN NON-DISABLED PEOPLE WITH MULTIPLE SCLEROSIS: A LONGITUDINAL STUDY

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Objective: Functional disorders appear early in the course of the disease and develop gradually over time impacting on social participation and quality of life. Investigating the progression of disability, walking, fatigue, manual dexterity, and cognition in a cohort of People with Multiple Sclerosis (PwMS) in the early stage of the disease.

Methods: We performed a longitudinal 2-year study to unravel functional disorders of 82 non-disabled PwMS with Expanded Disability Status Scale (EDSS) < 2.5 points, disease duration < 5-year, and aged (Mean±Standard Deviation) 39.5±10.6 years.

Materials: Participants were assessed at baseline and after 2-year with clinical and instrumented evaluations. Data on disability and functional disorders were collected using EDSS, Six-Minute Walk Test (6MWT), Multiple Sclerosis Walking Scale-12 (MSWS-12), Fatigue Severity Scale (FSS), Nine Hole Peg Test (NHPT), Brief International Cognitive Assessment (BICAMS), while instrumented data were extracted from 6MWT using wearable devices.

Results: EDSS changed from 1.5±0.7 points to 1.8±0.9 points with 34% of PwMS showing deterioration beyond the Minimally Important Changes of deterioration (MICdet EDSS = 1-point). Conversely, the 6MWT, FSS, and MSWS-12 did not change (6MWT from 559.35±84.5m to 577±93.5m, FSS from 3.3±1.8 points to 3.1±1.8 points, and MSWS-12 from 31.3±15.3 points to 30.0±14.9 points) with 10% and 11% PwMS showing walking deterioration beyond MICdet (MICdet 6MWT= 55m; MICdet MSWS-12= 6 points). We observed similar results considering instrumented variables: stride regularity (from 0.86±0.07 [au] to 0.88±0.08 [au]), antero-posterior gait symmetry (from 81.88±6.60 [au] to 83.74±6.06 [au]) and gait instability (from 0.69±0.11 [au] to 0.74±1.12 [au]). No relevant changes were observed for 9HPT and BICAMS.

Discussion: Even if EDSS deteriorated over time, fatigue, cognition, and upper/lower limb functions were on average spared 2 years after baseline assessment.

Conclusion: The large between-subject variability suggests the use of artificial intelligent techniques to predict subjects prone to deterioration.

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## DEVELOPMENT OF THE HEAT SENSITIVITY IMPACT QUESTIONNAIRE (HSI-Q): AN ONGOING VALIDATION STUDY

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Objectives: An estimated 60–80% of People with MS (PwMS) have been reported as being sensitive to environmental heat. Clinically, increased body temperature in PwMS can result in experiencing a temporary worsening of clinical signs and neurologic symptoms (Uhthoff's phenomenon). There is a lack of validated tools to assess the patients' perspective on heat sensitivity in this population. Through consensus conference of expert and PwMS and content validity analysis, we developed the Heat Sensitivity Impact Questionnaire (HSI-Q). The aim of the study is to validate and test the psychometric properties of the HSI-Q in a sample of PwMS.

Materials: HSI-Q (38 items) was administered to a preliminary sample of PwMS. Subjects completed HSI-Q, Modified Fatigue Impact Scale (MFIS) and Multiple Sclerosis Walking Scale-12 (MSWS-12); a subgroup also 2 Minute Walk Test (2MWT) and Timed Up and Go (TUG).

Methods: We assessed criterion validity, using a general question ("are you heat-sensitive?"), and construct validity, analysing the correlations (Spearman rank correlation coefficient) between HSI-Q total score and EDSS, MFIS and MSWS-12. We reported the correlations between HIS-Q total score and 2MWT, TUG on a subgroup of PwMS.

Results: 70 PwMS completed the HSI-Q (38F/32M, mean age 51.32(10.62) years, mean disease duration 13.90(9.90) years, mean EDSS 5.68(1.70), 30 RRSM, 23 SPSM, 17 PPSM). Scores obtained: HSI-Q tot 3.99(2.58), general question 5.97(3.02), MFIS 34.09(20.49), MSWS-12 33.94(19.52), 2MWT 83.4(54.85), TUG 22.54(17.11). Total HSI-Q score showed high correlation ($r=0.644$, $p<0.000$) with the general question "are you heat-sensitive?", low correlation with EDSS ($r=0.294$, $p=0.013$), moderate correlations with MFIS ($r=0.497$, $p<0.000$) and MSWS-12 ($r=0.430$, $p<0.000$). Regarding the subgroup of 50 PwMS, no significant correlations were found between HSI-Q total score and 2MWT and TUG.

Discussion: The preliminary assessment of HSI-Q validity showed high criterion validity and moderate construct validity.

Conclusion: This is an ongoing study and the sample of PwMS will be implemented in the upcoming months.

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## DOES THE TARGET NEDA COMPLY WITH FUNCTIONAL MEASURE CHANGES AFTER 2 YEARS IN EARLY PHASE OF MULTIPLE SCLEROSIS?

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Objectives: Few studies investigated the longitudinal changes of functional measures in people with MS (PwMS) with low disability. The aim of the study is to evaluate after two years of follow-up (2FU) the evolution of clinical and functional measures stratified for NEDA (no-evident-disease-activity; evidenced by lack of clinical relapses, of disease progression measured by expanded disability status scale and absence of new disease activity on magnetic resonance imaging (MRI)).

Methods: We assessed PwMS at baseline and after 2FU. We analysed the worsened and increased scores at different evaluations in the two subgroups NEDAgroup and noNEDAgroup.

Materials: Evaluation measures: Six Minute Walking Test (6MWT), Timed up and Go test (TUG), Timed-25 Foot Walking (T-25FW), Fatigue Severity Scale (FSS), Twelve-Multiple Sclerosis Walking Scale (MSWS_12), Fullerton Advanced Balance-short (FAB-s), 9-Hole Peg Test (9-HPT), Manual Ability Mesure-36 (MAM-36), Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS).

Results: 57 PwMS were enrolled [baseline: 35F, mean age 38.97 (SD=10.76) years, mean disease duration 2.14 (SD=1.84) years, mean EDSS 1.41), 57 relapsing-remitting MS course; 2FU: mean EDSS 1.83]. At 2FU, 25 PwMS were in NEDAgroup while 32 in noNEDAgroup. In the NEDAgroup the number of PwMS worsened: 12 at 6MWT, 9 at TUG, 11 at FSS, 12 at T-25FW, 7 at MSWS-12, 9 at FAB, 33 at 9-HPT, 3 at MAM-36, 12 at SDMT, 11 at CVLT-II, 8 at BVMT-R. In the noNEDAgroup the number of improved: 11 at 6MWT, 17 at TUG, 16 at FSS, 14 at T-25FW, 11 at MSWS-12, 13 at FAB, 24 at 9-HPT, 8 at MAM-36, 15 at SDMT, 19 at CVLT-II, 13 at BVMT-R.

Discussions: Several subjects showed a clinical improvement underline the importance of an extensive clinical evaluation beyond the EDSS.

Conclusions: Overall, 24 MS subjects classified as NEDA showed a decrease of function in at least one domain at 2FU.

Reference:

– Giovannoni G, Turner B, Gnanapavan S, Offiah C, Schmierer K, Marta M. Is it time to target no evident disease activity (NEDA) in multiple sclerosis? Mult Scler Relat Disord (2015);4(4):329

## TO EVALUATE THE ACTIVITY AND THE EFFICACY OF TRADITIONAL SWALLOWING THERAPY (TST) PLUS NEUROMUSCULAR ELECTROSTIMULATION (NMES) VS TST PLUS SHAM-NMES IN MS PATIENTS WITH DYSPHAGIA

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Objectives: Dysphagia is a disabling, life-threatening symptom that can cause death in people with Multiple Sclerosis (PwMS) through aspiration pneumonia. To date, no randomized clinical trials have shown that rehabilitative strategies are effective. Only one study applied Neuromuscular electrical stimulation (NMES) to swallowing function on PwMS. The aim of this study is to determine whether NMES added benefit to standard swallowing rehabilitation program in PwMS.

Methods: This is a multicentre double blinded, randomized clinical trial with two arms: standard rehabilitative plus Active NMES vs standard rehabilitative with Sham NMES. Inclusion criteria: MS diagnosis, stable disease activity, ASHA score <6 and DYMUS score >2.

Materials: We performed an ad-interim analysis in order to assess if the two groups (NMES vs. sham NMES) are balanced for age, gender, disease duration (DD), disease course and EDSS, and if it is possible to assess a preliminary effect of the treatment.

Results: A total of 125 PwMS were screened, 80 were included in the study, of which 8 dropped out. Till now, 75 subjects completed the treatment. Thirty-three subjects were allocated to the NMES group and 32 in the sham-NMES group. Demographic and clinical characteristics of the two groups: NMES [age 55.9(11.3), DD 17.7(8.9), 7 RRMS, 7 PPMS, 19 SPMS, EDSS 6.8(1.0)] and Sham-NMES [age 56.0(11.8), DD 18.9(9.0), 6 RRMS, 4 PPMS, 22 SPMS, EDSS 7.0(1.2)]. The two groups do not statistically differ for gender, age, disease duration, disease course and EDSS ($p>0.05$). Pre and post-treatment clinical scores: NMES [pre: ASHA=4.67(0.74), DYMUS=4.15(2.2), DOSS=4.63(0.71); post ASHA=5.30(0.73), DYMUS=2.76(2.5), DOSS=5.41(0.89)] and Sham-NMES [pre: ASHA=4.53(0.87) , DYMUS=4.75(2.1), DOSS=4.76(0.79); post ASHA=4.94(0.91), DYMUS=3.56(2.3), DOSS=5.21(0.90)].

Conclusion and Discussion: The two groups are balanced for disease course, age and EDSS. Ad interim analysis highlighted that the use of the device is well tolerated (5 drop-out are unrelated to the treatment).

Reference:

– Solaro C, Rezzani C, Trabucco E, Amato MP, Zipoli V, et al. Prevalence of patient-reported dysphagia in multiple sclerosis patients: an Italian multicenter study (using the DYMUS questionnaire). J Neurol Sci. (2013);331(1-2):94-7

## THE TOPOCHRONIC MAP OF THE LARGE-SCALE BRAIN DYNAMICS

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Background and Objectives: Large-scale brain activity dynamically evolves over time across multiple time-scales. The structural connectome, which represents the spatial network of brain regions, plays a crucial role in coordinating activity through its influence on signal transmission delays and oscillatory signals [1,2]. In this study, we provided a map of the functional delays characterizing the connections across the human brain [3] using in vivo magneto/electroencephalography and integrated them with the structural connectome derived from magnetic resonance imaging (MRI) in patients affected by multiple sclerosis (MS) and healthy controls.

Materials: 18 MS patients and 20 controls were recruited in the study. We combined source-reconstructed magnetoencephalography (MEG) signals and tractography to non-invasively estimate signal transmission delays across the network of white matter bundles.
Method: Integration of functional delays derived from MEG signals with the structural connectome derived from MRI was evaluated. We also performed a statistical analysis and comparison with random surrogate delays to validate the findings.

Results: We found higher signal transmission delays in MS patients compared to controls. Analyzing these delays, we observed that they correlated with the length of the structural bundles, indicating a relationship between structural organization and timing of interactions in the brain network. Moreover, we found that edges directly affected by demyelinating lesions exhibited significantly slower delays compared to healthy edges. However, the delays were not solely determined by bundle length, as demonstrated by using surrogate data obtained from randomized neuronal avalanches. Comparing these random surrogates to the observed delays, we found that the observed delays were significantly correlated with bundle lengths, unlike the random surrogates.

Discussion: In summary, our study provides a practical non-invasive technique for estimating functional transmission delays at the individual level, demonstrating that delays in the brain network are influenced by factoris beyond distance alone. Furthermore, our approach detects and quantifies the impact of myelin lesions on signal transmission delays in MS.

Conclusions: In conclusion, our findings could offer new possibilities for diagnostic and therapeutic interventions in MS. In fact, by considering subject-specific constraints, our technique contributes to the refinement of brain models. Additionally, our findings shed light on the longer delays induced by myelin lesions in multiple sclerosis, contributing to a better understanding of the disease.
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## PAROXYSMAL DYSARTHRIA: AT ONSET AND AFTER A RELAPSE OF MULTIPLE SCLEROSIS. A CASE SERIES

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Background: Paroxysmal dysarthria (PD) syndrome is an uncommon neurological symptom in multiple sclerosis (MS), characterized by brief, stereotyped episodes of slurred speech. The underlying cause is a localized lesion in the cerebellotalamocortical pathway, particularly in the midbrain, which can have various etiologies (inflammatory, vascular, neoplastic). PD is commonly observed during the course of MS or as an initial symptom. Treatment with Carbamazepine has shown positive results. In our center's experience, we encountered two cases of PD: one in a woman who developed it after 10 years of MS and another in a woman with the initial onset of MS.

Case presentation: Case 1: A 34-year-old woman, an elementary school teacher, has been suffering from relapsing-remitting multiple sclerosis (MS-RR) for 10 years. For approximately a month, she experienced multiple daily episodes characterized by difficulty articulating words and writing, lasting only a few seconds, which significantly affected her work. This symptom appeared to be preceded by a subjective sensation of warmth that gradually ascended from her feet to her head. Case 2: A 30-year-old woman with no comorbidities. Two months ago, she began experiencing bilateral visual blurring and a numb sensation in her tongue and upper right dental arch. This symptomatology spontaneously regressed after a week. However, a few days later, she developed a sensation of heaviness in her left upper and lower limbs, accompanied by multiple daily episodes of difficulty articulating words. These episodes also lasted a few seconds, but the woman did not report any prodromal symptoms. Magnetic resonance imaging (MRI) and lumbar puncture confirmed the diagnosis of multiple sclerosis.

Results: The MRI of both patients, despite differing lesion loads, revealed a common lesion affecting the midbrain region. In case 1, the lesion was located in the right paramedian midbrain region, while in case 2, it was in the left paramedian midbrain region. Treatment with CBZ was initiated. However, in case 1, carbamazepine failed to produce improvement, whereas Lamotrigine demonstrated a significant improvement in paroxysmal dysarthria, resulting in nearly complete suppression of the attacks. Conversely, in case 2, carbamazepine proved effective.

Conclusions: It is crucial to pay close attention to patients presenting with paroxysmal symptoms, as they may signify the onset of a more complex neurological condition. In the case of PD, careful examination of the dentatorubroolivary pathway's location is advisable. Importantly, there is symptomatic treatment available for this paroxysmal disorder, which, in addition to carbamazepine, may include lamotrigine.
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## EFFECT OF SIPONIMOD ON LYMPHOCYTES SUBSETS IN ACTIVE SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS AND CLINICAL IMPLICATIONS

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Background and Objectives: Circulating immune cells play a pathogenic role in multiple sclerosis (MS). However, the role of specific lymphocyte subpopulation is not unveiled yet, especially in progressive stages. We aimed to investigate lymphocyte changes in active secondary progressive MS (aSPMS) and association between specific changes in immune cells and worse clinical outcomes during siponimod treatment.

Methods: This was a mono-centric prospective longitudinal study. We enrolled 46 aSPMS patients with 2-years follow-up after the start of siponimod treatment, along with 14 sex- and age-matched healthy controls (HCs). Clinical and laboratory data were collected at baseline, 3rd, 6th, 12nd, and 24th month for MS patients, and at baseline for HCs.
Results: At baseline compared with HCs, SPMS patients presented with reduced T lymphocyte (p=0.05), reduced memory regulatory lymphocytes (p=0.04), increased naïve regulatory T lymphocytes (p=0.02) and a trend toward an increase in CD3+CD20+ lymphocytes (p=0.07). Over time, SPMS patients treated with siponimod showed T, CD4+, B, and memory regulatory B lymphocytes and CD4/CD8 ratio from month 3 thereafter vs baseline. Patients experiencing disability progression while on siponimod treatment showed no B, memory regulatory and CD3+CD20+ lymphocytes reduction nor CD8+ and and naïve regulatory lymphocytes increase vs patients not experiencing progression.

Discussion: Patients treated with siponimod showed a sustained T lymphocytes reduction, especially CD4+, CD3+CD20+ and naïve regulatory T cells as well as B lymphocytes and memory regulatory B cells reduction. In addition, we reported that disability progression while on siponimod treatment was associated with the lack of drug effect on B and CD3+CD20+ lymphocytes.
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## ANTI-GABAAR ANTIBODY-MEDIATED ENCEPHALITIS AFTER ALEMTUZUMAB TREATMENT


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Objectives: To present a case of anti-GABAAR encephalitis triggered by alemtuzumab (anti-CD52 monoclonal antibody for high active relapsing-remitting multiple sclerosis (MS)) presenting with refractory status epilepticus (SE).

Materials: Immunological studies, brain magnetic resonance imaging (MRI), continuous electroencephalogram (EEG).
Methods: Case report and review of the literature.

Results: A 38-year-old woman with relapsing remitting MS treated with alemtuzumab was admitted complaining sensory disturbances in her left leg; new-onset aphasia was also noticed. Subsequently she manifested a generalized tonic-clonic seizure and a progressive worsening of the neurological state with ensuing encephalopathy. Brain MRI revealed several new T2-weighted and DWI hyperintense lesions, which were not compatible with MS nor with a Progressive Multifocal Leucoencephalopathy. Cerebrospinal fluid (CSF) biochemical, microbiological and autoimmune testing performed at the Udine University Hospital were negative. EEG was consistent with left frontotemporal SE. Despite Intensive Care Unit admission, intravenous antiseizure and anaesthetic drugs administration, there was no effect on SE. In light of the suspected autoimmune pathogenesis, treatment with anti-IL6R tocilizumab was started with SE resolution. Given the strong clinical suspicion for anti-GABAAR encephalitis, CSF/serum samples were sent to IDIBAPS (Barcelona, Spain), which resulted positive. Considering the likely pathogenic antibody, treatment with Rituximab was started. At last follow-up, 3 months after onset, the patient is still severely affected (mRS=5). So far, four cases of autoimmune encephalitis triggered by Alemtuzumab were described [Giarola et al. 2019; Buscarinu et al. 2019; Maniscalco et al. 2020; Ratuszny et al. 2023], two of them anti-GABAAR positive (50%) [1;2], suggesting that alemtuzumab could be a relevant trigger.

Discussion: Anti-GABAAR encephalitis is a very rare neurological condition which often leads to refractory SE. Autoimmune encephalitis is a possible, although rare, consequence of Alemtuzumab treatment.

Conclusion: Our case highlights the importance of anti-GABAAR antibody testing in cases of post-alemtuzumab encephalitis and the high risk of refractory SE in this setting. High index of suspicion is mandatory as anti-GABAAR is not present in commercial kits for autoimmune encephalitis diagnosis.
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## COGNITIVE PERFORMANCE, PSYCHOLOGICAL SYMPTOMS AND FATIGUE IN PEDIATRIC PATIENTS WITH MULTIPLE SCLEROSIS: THE ROLE OF THE TREATMENT


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Objectives: Although Multiple Sclerosis (MS) is a rare condition in pediatric age, an increasing rate of patients are diagnosed under the age of 18. The disabling nature of the disease cannot be reduced only to physical symptoms. Cognitive impairment, fatigue and psychological symptoms are also common features of MS [1]. Studies investigating the impact of pharmacologic interventions on cognitive, psychological and fatigue outcomes, in children and adolescents, with MS are limited. We evaluated: 1) the evolution of cognitive skills, fatigue and psychological symptoms in one year follow up; 2) the role of treatment received on patients' cognitive performance and psychological symptoms; 3) the association between cognitive profile, fatigue, psychological symptoms.

Methods: In this retrospective study, thirty-seven children and adolescents with MS were included (13 boys, 24 girls; mean onset age=14; ± 2.05). The cognitive profile was assessed by Rao's Brief Repeatable Battery (SDMT, CLRT, LTS, SPART, PASAT and LWG subtests). The Patient Health Questionnaire-9 (PHQ-9), General Anxiety Disorder-7 Questionnaire (GAD-7) and the Fatigue Severity Scale (FSS), were used to explore depression, anxiety and fatigue. Seventeen patients received infusion treatment (n= 12 Natalizumab; 4 Ocrelizumab; 1 Rituximab) and 20 received non-infusion treatment (n= 2 Glatiramer Acetate; 6 Interferon beta 1a; 2 Dimethyl Fumarate; 10 Fingolimod). Every patient underwent a baseline evaluation (T1) and second evaluation (T2).

Results: Our data showed a general improvement in several subtests of the Rao battery (p=<0.05). Thirty patients (81%) showed significant higher scores in processing speed (SDMT) in T2 compared with T1 (p=< 0.001). An improvement emerged in both patients receiving infusion treatment (p=0.053) and non-infusion treatment (p=0.006). Moreover, our data showed higher scores in T2 in short-term verbal memory (SRT- LTS, p=0.003), short-term visuo-spatial memory (SRT, p=<0.001) and executive functions (LWG, p=< 0.001). A positive association between fatigue and SDMT in T2 was found (p=0.029). Moreover, our data showed a significant association between depression, visuo-spatial memory (p=0.009) and its delayed recall (p>0.001). Depression and anxiety symptoms were very common (>50%) in T1 and T2. No difference (T1 vs T2) according to the treatment in fatigue and psychological symptoms was found.

Conclusions: Our study evidenced a positive cognitive evolution in patients with pediatric MS. Improvements in cognitive skills emerged in both patients receiving infusion and non-infusion treatment. Given the impact that MS can have on emotional development, a special attention should be paid to young patients' psychological symptoms.

Reference:

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## NMOSD ATYPICAL ONSET WITH TONIC SPASMS AND AREA POSTREMA SYNDROME

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Case Report: A 72-year-old female patient with a history of breast neoplasm and rheumatoid arthritis presented to the hospital with subacute onset of nausea, vomiting, and tonic spasms affecting the left limbs. She had not been taking any medications. In her left upper limb, she experienced tonic spasms characterized by flexion of the wrist and metacarpophalangeal joints, resembling the "hand of the obstetrician." The patient also reported tonic contraction of the calf in her left lower limb. These movements occurred simultaneously in both limbs, lasting approximately 10 seconds and recurring 2-3 times per hour, with increased frequency associated with anxiety and hyperventilation. Neurological examination revealed subtle left hemiparesis, increased left deep tendon reflexes, and a positive left Babinski sign. Complete blood count, liver and kidney function tests, electrolyte levels, ionized blood calcium, arterial pH, and C-reactive protein were all within normal range. Trousseau and Chvostek signs were negative. Brain and cervical spine MRI showed a large hyperintense lesion in T2-weighted sequences and isointensity in T1-weighted sequences, with modest enhancement by gadolinium-based contrast agent in the lower brainstem and upper cervical cord. Thoracic and lumbar spine MRI were unremarkable. Cerebrospinal fluid examination showed a normal total protein concentration, absence of cells, and a few oligoclonal bands with a pattern type 4. Electromyographic study of the tonic spasms revealed simultaneous contraction of agonist and antagonist muscles, with an asymmetric pattern observed in the flexor digitorum profundus and extensor digitorum communis muscles. No abnormal spontaneous electromyographic activity was detected before or after the episode. Additionally, serum antinuclear and anti-SSA antibodies were detected. A high titer of anti-aquaporin-4 immunoglobulin G (anti-AQP-4-IgG) was also identified, leading to the diagnosis of anti-AQP-4-IgG positive neuromyelitis optica spectrum disorder (NMOSD). Nausea completely resolved with symptomatic treatment (levosulpiride 25mg three times a day orally), while the tonic spasms responded well to a low dose of carbamazepine (100mg once a day). To investigate a paraneoplastic cause of NMOSD, total body CT and PET scans were performed, ruling out neoplastic lesions.

Discussion: Our patient exhibited tonic spasms and area postrema syndrome as the primary symptoms at the onset of NMOSD. Spinal movement disorders are recognized in up to 40% of NMOSD patients, with tonic spasms being the most common phenotype. These spasms typically occur during the recovery phase, associated with remyelination processes. The atypical presentation could lead to a delayed diagnosis. Treatment with carbamazepine resulted in excellent and rapid clinical response.

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## A DYNAMIC INTERPRETATION OF KFLC INDEX FOR THE DIAGNOSIS OF MULTIPLE SCLEROSIS: ARE OLIGOCLONAL BANDS STILL REQUIRED?

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Aim: To evaluate the diagnostic accuracy of different cut-off values and ranges of κFLC index in a miscellaneous cohort of neurological patients, finally proposing a diagnostic procedural flowchart for the diagnosis of MS.

Materials and Methods: We consecutively enrolled patients admitted to the Neurology Clinic of the University Hospital "Policlinico G. Rodolico" of Catania, who underwent a diagnostic lumbar puncture in the period between January 2017 - February 2022. We analyzed data from 607 patients diagnosed with MS (179), CIS (116), other inflammatory neurological diseases (94) or non-inflammatory neurological diseases (218). Se, Sp and other measures of diagnostic accuracy were reported for κFLC index, IgG OCB and IgG Index. Potential thresholds and ranges were identified for κFLC index and compared with cut-off values proposed in scientific literature.

Results: The highest diagnostic accuracy in our sample was reported for κFLC index cut-off of 5.0 (Se=85.4%, Sp=90.4%, AUC=0.88, Youden index=0.75). A κFLC index threshold of 11.0 exhibited higher Sp (95.5%, 95% CI 93.1-97.1) than IgG OCB (95.2%; 95% CI 93.1-96.7), allowing to restrict the analysis of IgG OCB to patients with κFLC between 5.0-11.0, halving costs and reducing the time needed for the procedure by ten times. The odds of being diagnosed with MS/CIS was 2.2-fold higher for each increase of 5 units in κFLC index value (OR=1.17; 95% CI 1.12-1.23; p<0.001), independently from values assumed by IgG index and IgG OCB detection.

Discussion: κFLC index is considerably sensitive and specific in supporting the diagnosis of MS/CIS, performing better than IgG OCB

and IgG Index, with the advantage of being a quantitative variable. Among different thresholds, a cut-off value of 5.0 proved to be the most accurate in discriminating between MS/CIS and other neurological diseases. Patients exhibiting κFLC index values higher than 11.0 do not need any further assessment, since κFLC index exhibits a higher specificity than IgG OCB and IgG Index for the diagnosis of MS in this range of values. IgG OCB could be used as a second-line assessment in patients with κFLC index values between 5.0-11.0 in case of diagnostic doubts, in order to further increase specificity, saving time and reducing costs.

Conclusion: We propose to use κFLC index as a preliminary test, considering all subjects with values higher than 5.0 as positive results, and thus possible MS. The analysis of IgG OCB could be restricted only to subjects with borderline values between 5.0-11.0, in order to increase specificity and solve diagnostic doubts about other inflammatory conditions.

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## CEREBROSPINAL FLUID NEUROFILAMENT LIGHT CHAINS: A SHORT-TERM PROGNOSTIC BIOMARKER FOR MULTIPLE SCLEROSIS


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Aim: To explore the predictive role of cerebrospinal fluid neurofilament light chains (cNFL) in patients with a recent diagnosis of Multiple Sclerosis (MS), naïve to any disease-modifying treatment.

Materials and Methods: We retrospectively collected data of patients diagnosed with MS, referred to the Neurology Clinic of the University-Hospital G. Rodolico of Catania between January 2005 and December 2015. All patients underwent cerebrospinal fluid (CSF) collection at the time of MS diagnosis and clinical and radiological follow-up for at least three years afterwards. cNFL levels were measured in CSF samples with Simoa NFLight advantage kit at the CRESM (University Hospital San Luigi Gonzaga, Orbassano, Torino). A neuropsychological evaluation with Symbol Digit Modalities test (SDMT) was performed at baseline, at 1-year and at 3-year follow-up. Multivariate logistic regression analysis was performed to investigate cNFL as a potential risk factor for different clinical outcomes.

Results: 244 MS patients (230 relapsing-remitting, RRMS; 94.3%), with a mean age at diagnosis of 37.0±11.1 years, were recruited. cNFL levels did not correlate neither with the Expanded Disability Status Scale (EDSS) at diagnosis and at subsequent evaluations up to 12 years, nor with SDMT performed at diagnosis, at 1 year and at 3 years. cNFL were an independent factor for the occurrence of at least one relapse during the first two years after MS diagnosis (OR=2.75; 95% CI 1.19-6.31; p=0.02) and for the occurrence of gadolinium-enhanced (Gd+) lesions during the first 2 years from diagnosis at brain and spine magnetic resonance imaging (MRI) scans (OR=3.45, 95% CI 1.81-6.57; p<0.001).

Discussion: According to our results, cNFL levels detected at the time of MS diagnosis seem to be a good predictor of short-term disease activity, being associated with the occurrence of clinical relapses and Gd+ lesions at MRI brain and spine scans within two years from MS diagnosis. Conversely, the level of cNFL was not associated with EDSS score and cognitive performance tested with SDMT neither at the time of diagnosis nor at follow-up.

Conclusion: The detection of cNFL at the time of MS diagnosis can be a useful support to predict the two-year risk of clinical and radiological relapses, thus affecting therapeutic choices in the very early phases of the disease.

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## COGNITIVE IMPAIRMENT AND RETINAL THICKNESS IN NEWLY DIAGNOSED MULTIPLE SCLEROSIS PATIENTS: RESULTS FROM A CROSS-SECTIONAL STUDY


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Aim: To explore the role of retinal nerve fiber layer (RNFL) thickness as a predictor of physical and cognitive disability in patients with Multiple Sclerosis (pwMS).

Materials and Methods: We screened all newly diagnosed pwMS referred to the MS centre of the University Hospital "Policlinico-San Marco" in the period 2015-2019. All patients were evaluated at baseline and after 3 years of follow-up. RNFL and ganglionar cell layer (GCL) thickness for right eyes (r.e.) and left eyes (l.e.) were measured with Optical Coherence Tomography (OCT). Disability level and cognitive profile were assessed, using the Expanded Disability status scale (EDSS) and the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery, respectively.

Results: We consecutively enrolled 487 pwMS, including 68 (14.0%) with primary progressive MS (PPMS). At baseline, both RNFL and GCL were bilaterally thinner in PPMS (r.e. 90.4±12.7; l.e. 90.2±13.5, and r.e. 80.1±11.2; l.e. 80.3±12.6, respectively) compared to relapsing-remitting MS (RRMS) (r.e. 94.6±13.1; l.e. 94.3±14.8, and r.e. 85.1±9.5; l.e. 84.9±9.3, respectively) (p<0.01). PPMS patients recorded lower scores at Symbol Digit Modalities Test (SDMT) (24.9±7.7 vs 36.1±12.2; p<0.01, respectively) and both groups performed worse at 3-years follow-up compared with baseline evaluations. A RNFL thickness ≤88.0 μm was an independent predictor of cognitive

impairment (CoI) (OR=5.32; 95% CI=1.84-9.12; p=0.02) and disability worsening (OR=3.18; 95% CI=1.21-10.33; p=0.05), regardless of previous history of optic neuritis (ON) and use of disease-modifying treatment.

Discussion: All MS patients exhibited a significant reduction in both RNFL and GCL over a 3-year follow-up and those with RNFL thickness lower than 88.0 µm exhibited a 5-fold risk to develop CoI in our population. Compared with RRMS, patients with PPMS exhibited thinner RNFL and GCL bilaterally at baseline and at 3-year follow-up and performed worse in motor assessments and SDMT at all time points. CoI at 3-years was independently predicted by EDSS at diagnosis, disease duration, progressive phenotype, annualized RNFL loss and a RNFL thickness lower than 88 µm.

Conclusion: RNFL thickness, as a biomarker of neurodegeneration, could be considered a predictive biomarker of cognitive degeneration and physical disability in MS.

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## UNRAVELLING THE INTERPLAY BETWEEN GENETIC AND NON-GENETIC RISK FACTORS IN PAEDIATRIC MULTIPLE SCLEROSIS (PEDIGREE STUDY GROUP): FOCUS ON THE ROLE OF GUT MICROBIOTA


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Aims: Multiple Sclerosis (MS) is a chronic inflammatory multifactorial disease that occurs between 20 and 40 years of age. We focused on MS with onset before 18 years (paediatric MS-PedMS), which is a rare and more aggressive form of MS, that offers a unique opportunity to gain clinical and biological data in proximity to the actual disease onset, lifestyle and environmental information. An Italian multicentric study group was realized aiming to enroll paediatric MS patients, matched healthy controls (HC), and MS adults with a disease onset < 18 years in order to analyse genetic, epigenetic, transcriptomic, environmental factors, their interactions, and gut microbial composition.

Methods: In a case-control experiment, we performed 16S sequencing, primary analyses by SmartSeq-MicrobAT software, and more complex and comparative analyses by MicrobiomeAnalyst and Qiime2 pipeline that produced analogous outcomes.

Results: We analysed 87 PedMS and 55 HC. Preliminary results showed a similar composition at phylum level between groups, with Firmicutes (44%) and Baciteroidetes (33%) being the most abundant phyla. The heat tree method revealed a significant different abundance ($p<0.05$) at species level: unclassified_Blautia, unclassified_Lachnospiraceae, Butyrate_producing_bacterium_L2_12 and unclassified_Firmicutes were enriched in PedMS, while Bacteroides sp. Smarlab_3302996, Odoribacter and Unclassified_Rikenellaceae were decreased. Alpha-diversity, measured by Observed index, resulted significant in HC compared to PedMS ($p=0.02$), while beta-diversity showed similarity between the two groups.

Discussion: So, we profiled gut microbial composition of PedMS patients and HC. We found significant abundance differences at species level that were confirmed in paediatric and adult literature: Blautia and Odoribacter were respectively found to be increased and decreased both in our study and in PedMS literature, while Lachnospiraceae were increased in our study but decreased in other paediatric studies.

Conclusion: We plan to add new samples, expanding our cohort, and to perform again the analysis. Moreover, we will perform an integration with host-genetic data (GWAS-SNP) and other host-omics, together with clinical and environmental information to explore gene-environment interaction that could lead to a paediatric disease onset.

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## REDUCTION OF GANGLION CELL-INNER PLEXIFORM LAYER THICKNESS IN MS: COMPARISON BETWEEN LOW-MODERATE EFFICACY AND HIGH EFFICACY DMT


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Introduction: Optical coherence tomography (OCT) is a diagnostic tool useful to investigate neurodegeneration associated with MS progression by measuring retinal layers thickness.

Objectives: To assess the impact of disease-modifying treatments (DMTs) on ganglion cell-inner plexiform layer (GCIPL) thickness, measured by optical coherence tomography (OCT).

Material and Methods: We analyzed 47 MS patients (female to male ratio 3:1, mean age 38.8 ± 8.65 years, median EDSS at baseline 2.0 with range from 0 to 6.5, mean disease duration 9.38 ± 9.04) who underwent longitudinal spectral-domain OCT imaging (Spectralis, Heidelberg Engineering, Germany) at the MS Centre of Cagliari between 2017 and 2021. OCT scans were performed for both eyes at baseline (T0) and at two-year follow-up (T1). The primary outcome parameter was macular ganglion cell–inner plexiform layer (GCIPL) volume. Based on the DMT the patients were divided in low-moderate efficacy group (interferon beta, glatiramer acetate, teriflunomide, and dimethyl-fumarate), or high efficacy group (fingolimod, cladribine, ocrelizumab, natalizumab, alemtuzumab). Differences in GCIPL for macular sectors between T0 and T1 were evaluated with mixed ANOVA, setting the treatment groups as independent variables and correcting for age of onset, EDSS and disease duration.

Results: 93 eye scans were acquired from 47 patients, 22 on low-moderate efficacy and 25 on high efficacy DMT. At baseline, low-moderate efficacy group displayed a mean GCIPL global thickness of 67,7 µm and 69,1 µm in outer temporal sector, while high-efficacy group exhibited thicknesses of 65,5 µm and 64,3 µm, respectively. Mixed ANOVA showed a significant difference in the reduction of GCIPL (T0 vs T1) between low-moderate efficacy and high-efficacy DMTs. The high efficacy group showed less GCIPL atrophy compared with the low-moderate efficacy group in both outer temporal sector (66,8 µm vs 64,9 µm, $p<0.001$) and the global thickness (65,6 µm vs 66 µm, $p<0.001$). After correcting for demographic and clinical variables, differences between T0 vs T1 for the two groups were confirmed ($p<0.002$).

Conclusions: According to our data, high-efficacy DMTs can reduce GCIPL atrophy in a two-year follow-up. Hence we confirmed the ability of high-efficacy treatments to potentially alter the trajectory of neurodegeneration in MS and the usefulness of retinal imaging in monitoring treatment efficacy.

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## KAPPA FREE LIGHT CHAINS AS MARKERS OF MULTIPLE SCLEROSIS DIAGNOSIS: A 10-YEAR MONOCENTRIC STUDY

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Background: Cerebrospinal fluid (CSF) kappa free light chain (KFLC) are becoming a diagnostic biomarker for multiple sclerosis (MS).

Aims: To compare the efficiency of KFLC to oligoclonal bands (OB) in diagnosing MS and radiological and clinical isolated syndromes (RIS-CIS).

Methods: We collected 802 patients (59% females) in 10 years, who underwent CSF analysis for intrathecal synthesis in the diagnostic work-up and were classified according to their diagnosis: 296 MS, 170 with other neurological inflammatory diseases (including 28 RIS-CIS), and 336 non-inflammatory. Lymphoproliferative and infective diseases were excluded. KFLC index cut off was 5.

Results: KFLC index were significantly higher in MS patients compared to those with other neurological diseases (mean ±standard deviation: 68.6±154.1 versus 4.7±12.4; $p<0.001$) with high sensitivity (91% similar to that of OB) and moderate specificity (85% if compared to 90% of OB) in diagnosing MS. A KFLC index above 5 was demonstrated in 6/27 MS cases with no OB, and in 4/28 RIS-CIS cases.

Conclusions: The KFLC index markers confirmed the accuracy in MS diagnosis, also in those patients with no OB and in the RIS-CIS population.

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## AN ATYPICAL CASE OF PROGRESSIVE DISEASE IN MOGAD

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Introduction: The myelin oligodendrocyte glycoprotein antibody (MOG-IgG) is a biomarker found in a subset of patients with central nervous system inflammation. The MOG antibody-associated disease (MOGAD) may be associated with a monophasic or relapsing disease course, but clinical progression independent of relapse activity is rare. Herein we describe a patient with a progressive course, initially misdiagnosed as Multiple sclerosis (MS), in which MOG-IgGs were found to be positive after 5 years of clinical follow-up.

Case Description: A 45-year-old woman diagnosed with MS in 2018 based on progressive gait impairment, MRI evidence of inflammatory lesions in the cerebellar hemispheres, (right middle cerebellar peduncle, pons, thalamocapsular region, periventricular white matter) and in spinal cord (C1-C2, C4-C5 and D8 levels) with the presence of oligoclonal bands in cerebral spinal fluid (CSF). The patient started on Natalizumab, suspended after one year for a progression of disability with assistance required to walk for more than 150m (EDSS 5.5). Given the progressive disease course, Siponimod was started on February 2020 with further disability progression in the absence of relapses or new MRI lesions (EDSS 6.5). It was withdrawn in February 2022 for Sars-CoV-2 infection. Notably the patient experienced transient clinical improvement lasting more than 12 weeks after Siponimod was stopped. The patient was referred to our clinic for a second opinion in September 2022 (EDSS at visit 7.0). Given the unusual disease course with several red flags (including severe itching and bilateral VEP alteration), anti-AQP4 and anti-MOG antibodies were requested on serum, which were negative using fixed commercial assays, but anti-MOG antibodies resulted positive at live cell-based assay at high level (End point titre 1:640), confirming the diagnosis of MOGAD.

Discussion: This case report contributes to expand the clinical spectrum of MOGAD, which should be considered when patients present with unexpected response to disease modifying therapies for MS. In these cases, MOG-IgG should be always tested and live

cell-based assays should be recommended in case of negativity for MOG-IgG by commercial fixed tests. Doing a literature review, we found at least 7 other cases very similar to this one, which confirms that a progressive trend, though rare, should be considered in MOGADs.

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## PRELIMINARY RESULTS OF A REAL LIFE MULTIPLE SCLEROSIS COHORT TREATED WITH OFATUMUMAB

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Objectives: Ofatumumab is a fully human anti-CD20 monoclonal antibody approved for the treatment of highly active Relapsing Remitting Multiple Sclerosis (RR-MS). There is few evidence about its effectiveness in the real life. Therefore, we identified a cohort of ofatumumab treated patients, to evaluate the quickness of its effect in a real life cohort.

Materials: The study population included RRMS patients who received ofatumumab in a Southern Italy MS Center, from July 2022. Methods: Descriptive statistical analysis was performed using Statistical Package for Social Science (SPSS) software. We analyzed the following variables: Expanded Disability Status Scale (EDSS), Gadolinium enhancing (GD+) lesions and T2 new lesions, clinical relapses at baseline and at 6 months of follow-up.

Results: We enrolled 52 RRMS patients (14 Male (26.9%), mean age 30.5±10.9, median time from MS onset 8.0 (1-32) years). Thirty-three of them (63.5%) were treatment-naive; the baseline EDSS was 3.0 (1.0-6.5) and the median number of relapses before ofatumumab beginning was 2 (1-4). Only 2 of 52 patients (1.04%) presented clinical relapses at the subsequent follow-up. Of the 19 patients (63.5 %) who had a MRI control at six months, 5 (9.6%) had persistence of radiological activity with new T2-lesions (2 of these GD+). Instead, 14 patients (26.9 %) obtained 6 months NEDA-3. The median EDSS at the 6 months follow-up was 2.0 (1.0-5.0). We have not identified potential predictive factors for persisting clinical or radiological activity.

Discussion: Ofatumumab demonstrated a reduction of clinical and radiological disease activity, according to the current evidence of randomized clinical trials (ASCLEPIOS I/II and ALITHIOS open-lable extension).

Conclusion: Our data confirmed Ofatunumab efficacy in the short term. In consideration to its recent approval, research is needed to confirm these data on the long term and in a larger populations.

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## GUT, SKIN AND ORAL MICROBIOME IN MULTIPLE SCLEROSIS: A MENDELIAN RANDOMIZATION ANALYSIS

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Objectives: Growing evidence links the microbial communities inhabiting the gut and other body surfaces to pathophysiological processes underlying MS. Here we aimed to assess causality between the gut, skin and oral microbiomes and Multiple Sclerosis (MS), by performing Mendelian Randomization (MR) analyses.

Materials: We extracted genetic instruments from summary statistics from 3 large genome-wide association studies (GWAS) on gut microbiome (18340, 8959 and 7738 subjects), 1 GWAS on skin flora (1656 skin samples), and 1 GWAS on oral microbiome (1915 subjects). Exposure data derived from the latest GWAS on MS susceptibility (47429 patients and 68374 controls).

Methods: MR represents an epidemiological study design that allows to estimate the causal relationship between a risk factor and an outcome of interest using genetic variants as proxies for environmental exposures.

Results: Genetically predicted abundance of Ruminococcus (Odds Ratio, OR=2.89, p=0.001), Bacteroides (OR= 1.16, p=0.02), Actinobacteria (OR 1.48, p=0.02) and Bifidobacteriaceae (OR= 1.46, p=0.01) in the gut, Veillonella species (OR=1.06, p=0.02) in the skin, Lachnospiraceae (OR=1.41, p=0.02) and Saccharimonidales (OR=1.33, p=0.03) in saliva are causally linked with MS. Furthermore, we found that microbial lactose and galactose degradation processes (OR=0.71, p=0.0006) in the gut, and abundance of Flavobacteriales Capnocytophaga (OR=0.60, p=0.0006) in saliva may exert a protective effect towards MS susceptibility.

Discussion: Our results provide compelling evidence that specific microbial taxa in the gut, skin, and saliva may play a causal role in the development of MS. Importantly, beyond confirming the role of gut species previously associated with the disease, we highlight other taxa and body sites deserving further investigation.

Conclusion: This work underscores the relevance of the microbiome-brain axis in MS etiology and opening wider perspectives on host-environmental interactions in MS. Targeted modulation of the gut, skin, and saliva microbiota may hold promise for the development of novel therapeutic strategies aimed at mitigating MS risk and progression.

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## MIRNA 106A-5P IN CEREBROSPINAL FLUID AS SIGNATURE OF EARLY RELAPSING REMITTING MULTIPLE SCLEROSIS: A CROSS SECTIONAL STUDY

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Objectives: Aim of the study was to compare the levels of expression of circulating microRNA (miRNAs) 21-5p, miRNA 106a-5p, miRNA146a-5p, miRNA223-3p in cell-free cerebrospinal fluid (CSF) in Relapsing Remitting Multiple Sclerosis (RRMS) patients and other neurological diseases (OND).

Materials and Methods: A cross sectional study conducted at MS centre of Foggia, Italy. We enrolled patients with (1) age between 18 and 55 years, (2) a definitive diagnosis of RRMS per the revised McDonald criteria, and (4) naïve to any disease modifying therapy or 5) patients with other OND. Investigated MiRNAs were extracted, retro-transcripted and then assessed by real-time polymerase chain reaction assay (q-PCR). A receiver-operator characteristic (ROC) curve was used to test MiRNAs as a biomarker for the diagnosis of MS. A linear regression analysis was done to find any association with disease characteristics at the time of diagnosis.

Results: A total cohort of 70 subjects (70% women) was analyzed. Out of them, 35 had a RRMS diagnosis. MiRNA 106a-5p (7.8±3.8 vs 1.3±0.9, p=0.03) had higher levels in RRMS patients when compared to OND. The ROC curve indicated that MiRNA 106a-5p could be considered as disease biomarkers with an area under the curve of 0.812 (p<.001; 95% CI 0.686-0.937). Linear regression analysis showed an association between the number of oligoclonal bands and MiRNA 106a-5p levels (B coeff 2.6, p<.001; 95% CI 1.3-4.9).

Discussion: In our cross-sectional real-world study, we found that CSF miRNA106a was upregulated in RRMS patients at the time of diagnosis and that it was associated to a higher number of OCBs. The altered miRNAs expression in early MS phases would lead to the modulation of inflammation. The major strength of this study is to suggest CSF MiRNAs as useful disease biomarkers because of their easy extraction and stability.

Conclusions: Further studied are needed to characterize their role in early MS as disease biomarker.

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## PLATELET TO LYMPHOCYTE RATIO AND DISEASE COURSE IN MULTIPLE SCLEROSIS PATIENTS

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Objectives: Aim of the study was to describe if any association between platelet to lymphocyte ration and disease course in a cohort if Multiple Sclerosis patients.

Materials and Methods: A cross sectional study conducted at MS centre of Foggia, Italy. We enrolled patients with (1) age between 18 and 55 years, (2) a definitive diagnosis of RRMS per the revised McDonald criteria, and (4) treated with disease modifying therapy. We have collected platelet lymphocyte ratio (PLR) during routinary clinical practice. It was converted to log10 to normalize values. A linear regression analysis was done to find any association with disease characteristics.

Results: A total cohort of 120 subjects (61.8% women, mean age 43.2±12.2 years) was analysed. Out of them, 71.7% were switchers from other DMTs. The mean value of log10 PLR was 2.2±0.3. A correlation was found between PLR and the level of disability measured with Expdanded Disability Status Scale (B coeff 1.3, p<.001; 95% CI .1.1-1.9)

Discussion: In our real-world study, we found that the PLR could be associated to level of disability in a cohort of MS patients.

Conclusions: Further studied are needed to characterize the role of chronic inflammation measured with peripheral biomarkers and disease course.

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## NEUROCOVID

## CEREBRAL VENOUS SINUS THROMBOSIS IN THE VACCINE-INDUCED IMMUNE THROMBOTIC THROMBOCYTOPENIA (VITT): AN ACUTE COVID-19 VACCINATION SYNDROME (ACVS)

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Background: SARS-CoV-2 can lead to acute disease and post-acute-syndrome (PACS-long COVID). Side effects of COVID-19-vaccines have been increasingly noted and studied. Post-COVID-19-vaccination-syndrome (PCVS) needs to be distinguished between acute-COVID-19-vaccination-syndrome (ACVS) and post-acute-COVID-19-vaccination-syndrome (PACVS). Moreover, there are mixed forms of disease caused by natural SARS-CoV-2-infection and COVID-19-vaccination.

Case report: We describe a case-study of a 61-year-old woman, affected by migraine, paroxysmal-supraventricular-tachycardia. She was previously treated with atenolol. On May 8th2021 she underwent vaccination with adenovirus-vector–based-vaccine (ChAdOx1/nCoV-19). In the following two days, she reported fever. On May 11th, she'd an onset of headache with intensity up to 10NRS, unresponsive to NSAIDs. On May 18th, she was admitted to Emergency-Room. Neurological evaluation was initially normal. After few hours, aphasia, right hemianopsia and mental confusion appeared. Few tests performed were reported below.

Blood-tests: PLT 41,000/mmc, INR 1.41, D-dimer 32.000 ug/l.
Cerebral-CT: Hyperdensity of the sulci in the left temporo-parietal-region and ipsilateral transverse sinus.

Cerebral angio-CT: Transverse and sigmoid sinus thrombosis. She was admitted in Stroke-Unit for cerebral venous sinus thrombosis in thrombocytopenia post-COVID-19-vaccination. After excluding HIT and thrombotic microangiopathy she performed transfusion of 1 bag of PLT, IVIG 1g/kg (which inhibits FcRγIIA-mediated-platelet-activation), dexamethasone 8 mg, fondaparinux 2.5 mg. She was transferred to Intensive-Cure-Unit of Neurosurgery in order to evacuate the hematoma. Dexamethasone 8 mg was administered 4 times a day, mannitol and another transfusion of PLT (platelet level rising to 110,000 /mmc). Levetiracetam was started after the onset of seizures. On May28th, the angio-CT showed a greater patency of the sigmoid-transverse sinus. On June4th, the T-P-O hematoma was almost completely reabsorbed at the cerebral CT. Ab anti-complex-heparin-PF4 were positive. The suspicion of brain sinus thrombosis associated with the adenovirus-vector–based-vaccine was finally confirmed (five diagnostic-criteria-of-the-UK-Haematology-Expert-Group-developed-consensus for VITT). On June15th, she came back to our ward. She was alert, collaborating, understands simple delivery, spoke poorly, fairly fluent and communicative, notes of ideo-motor-apraxia, right mild hemianopsia.

Conclusion: We describe an acute vaccine-induced-immune-thrombotic-thrombocytopenia (VITT) with cerebral-venous-sinus-thrombosis. It's a rare but severe immunological reaction particularly associated to the adenovirus-vector-based-COVID-19-vaccines that can afford in low-middle-income countries. A possible mechanism for side effects could be that the vaccine triggers the formation of anti-platelet factor-4-antibodies, which cross-react with membrane-bound or soluble proteins involved in thrombus formation. Extreme activation of platelets and the coagulation system leads to a high risk of death from venous or arterial thrombosis or secondary hemorrhage. Rapid recognition and treatment of VITT could reduce the brain damage.

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## HYPOSMIA AFTER SARS-COV2 INFECTION: WHEN THE SIMPLEST ANSWER IS NOT THE RIGHT ONE


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Background: Hyposmia is a non-specific symptom associated with both local conditions and neurodegenerative diseases, including Lewy body disease (LBD) [1]. During the COVID-19 pandemic, hyposmia gained significant attention as a possible consequence of Sars-CoV-2 infection [2]. It is crucial to recognize and evaluate hyposmia within a comprehensive clinical framework to prevent overlooking other potential etiologies.

Case Report: In 2020, a 77-year-old woman developed ageusia and anosmia during Sars-CoV-2 infection. Despite recovery from the infection, she continued to experience hyposmia along with concentration and memory difficulties, occasional postural instability, asthenia, and depression. Neurological and cognitive assessments conducted at an outpatient clinic did not reveal any abnormalities. However, the Sniffing test confirmed the presence of hyposmia. Further investigations, including brain magnetic resonance imaging (MRI) and [18F]FDG PET scans as part of Neurocovid research, demonstrated millimeter chronic vascular lesions and bilateral moderate hypometabolism in the lateral temporal and posterior parietal lobes, respectively. Upon evaluation in a specialized Memory Clinic, the patient also reported insomnia, constipation, and a history of visual and auditory hallucinations. A slight visuospatial deficit and mild asymmetric parkinsonism with left-side predominance were detected. To explore the possibility of a LBD, additional diagnostic tests were conducted. DaT-SPECT revealed reduced dopamine transporter uptake in the putamen (predominantly in the right side), polysomnography showed REM sleep without atonia, and [123]I-MIBG myocardial scintigraphy demonstrated low uptake. These biomarkers were indicative of probable mild cognitive impairment with Lewy bodies (MCI-LB) based on current diagnostic criteria [3]. Therapy with Rivastigmine 4.6 mg/24h was initiated.

Discussion: The exacerbation of likely pre-existent hyposmia in association with Sars-CoV-2 infection led the patient to medical consult. The heightened awareness of hyposmia during the COVID-19 pandemic played a pivotal role in recognizing this symptom. Visiting a specialized center enabled a comprehensive evaluation of this non-specific symptom within the context of a complex disorder that could have otherwise been overlooked. The presence of cognitive impairment, depression, visual hallucinations, and subtle parkinsonism may suggest early-stage MCI-LB and should be considered in patients with hyposmia [3].

Conclusions: This case report serves as a reminder not to underestimate hyposmia, particularly in the post-COVID-19 pandemic phase when it is associated with cognitive or depressive symptoms. Improved recognition and thorough evaluation of hyposmia can contribute to the early detection and appropriate management of neurodegenerative disorders, including LBD. Clinicians should maintain a high index of suspicion for underlying neurologic conditions when assessing patients presenting with hyposmia.

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## CEREBRAL POLYOPIA/DIPLOPIA WITH ONSET DURING ACUTE SARS-COV-2 INFECTION

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Objectives: Cerebral polyopia (or cerebral diplopia) is a visual perceptual disorder where two or multiple images are perceived while fixating on a single object, even with one eye closed (monocular vision) [1]. It is important to differentiate cerebral polyopia/diplopia from other causes of monocular diplopia, particularly ocular refractive abnormalities. Cerebral polyopia/diplopia is extremely rare and is usually due to lesions involving the associative visual cortex, such as multiple sclerosis, stroke, trauma, encephalitis, brain tumors, epileptic seizures, and migraine [2]. The infection by SARS-COV-2, and its related COVID-19 disease, has been associated with many neurological and ophthalmological manifestations. Herein, I describe the first case of cerebral polyopia with onset during SARS-CoV-2 infection.

Materials and methods: Case report.

Results: The patient was a 50-year-old right-handed colorblind man without relevant medical history. Six months earlier, during a Sars-COV-2 infection (confirmed by nasopharyngeal swab with rapid antigen test) he experienced headaches, associated with high fever and diplopia. The diplopia was present and remained unchanged both when either one eye was closed (monocular vision) and when both eyes were open (binocular vision). The two images had equal characteristics in terms of visual resolution, size, and color; they were separated from each other by the same amount of space and with the same angular degree. The diplopia persisted unchanged after the infection had resolved. An extensive ophthalmological evaluation excluded primitive eye causes of monocular diplopia. The neurological examination was unremarkable. Serology for EBV, CMV, HIV, tick-borne encephalitis, Toxoplasma gondii, and Borrelia burgdorferi was negative. Serum autoimmune screening was unremarkable, acetylcholine receptor antibodies were negative, and cerebrospinal fluid examination yielded normal results (no oligoclonal bands or neurotropic viruses were detected). The serological test for COVID-19 confirmed prior infection. Ocular optical coherence tomography, visual field testing, visual evoked potentials, and electroencephalogram were normal. A contrasted brain MRI showed several subcortical T2-hyperintense blurry lesions in frontal and parietal white matter, without involvement of occipital region.

Discussion: The symptoms suggest that polyopia could have arisen within the context of a viral SARS-CoV-2 encephalitis. This hypothesis is supported also by the lack of any further etiological explanation and by the subcortical lesions seen on MRI, compatible with previous multifocal encephalitis.

Conclusion: Although extremely rare, cerebral polyopia/diplopia should be promptly differentiated from monocular diplopia due to refractive disorders. It can be the symptom of an acute brain lesion or dysfunction, including viral encephalitides, such as that due to SARS-CoV-2 infection.

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## RELAPSING DOUBLE SERONEGATIVE NEUROMYELITIS OPTICA SPECTRUM DISORDER POST-COVID VACCINATION

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Introduction: In this report we will discuss a rare case of relapsing double seronegative neuromyelitis optica spectrum disorder (DN-NMOSD) post-Covid vaccination.

Case-report: A 28-year-old man presented with diplopia, vomiting and hiccups within one week from the first jab of Pfizer vaccine (January 2021) persisting for longer than 10 days. Blood tests, abdominal ultra-sounds and MRI did not find signs of gastrointestinal tract infections. The symptoms regressed spontaneously. In February 2021, two days after the second jab of Pfizer vaccine, the patient complained again diplopia associated with dizziness, asthenia, and a skin rash in the right hemiface, interpreted as a VZV reactivation. While the skin rash improved with famciclovir treatment, the diplopia worsened, and the patient was admitted in the Neurology Unit. Bilateral gaze-evoked nystagmus and drowsiness were found. Brain MRI showed a T2/FLAIR hyperintense area at the medulla-cervical spinal cord junction and at the pavement of the IV ventricle. Serum anti-myelin oligodendrocytes glycoprotein (MOG)-IgG and aquaporin4(AQP4)-IgG were negative as well as cerebrospinal fluid (CSF) standard exam, film arrays for viral and bacterial infections and oligoclonal bands. He was treated with high-dose intravenous steroids (methylprednisolone 1g for 5 days) with a complete recovery. In December 2021, he suffered from a sudden right optic neuritis (visual acuity 1/10) and high-dose intravenous steroids were administrated with complete recovery of the right eye vision. MOG-IgG and AQP4-IgG were again negative. Oral steroids tapering off was started. In February 2022, few days after the oral steroids suspension, the patient experienced a left optic neuritis (visual acuity 4/10). CSF analyses were repeated and OCB and film Array on CSF as well as serum AQP4-IgG and MOG-IgG were found negative. MRI showed a new T2/FLAIR hyperintense swelling of the right optic hemichiasm, while PEVs showed bilateral slowing in conduction speed (left>right). This time the patient was left with reduction of the left eye visual acuity after high-dose steroids. DN-NMOSD was diagnosed, and rituximab treatment was started empirically without additional relapses.

Discussion: DN-NMOSD is a rare condition requiring the exclusion of both AQP4-IgG and MOG-IgG [1]. In this case AQP4-IgG and MOG-IgG were tested before the steroid therapy was started, confirming the double-seronegative phenotype of NMOSD. Five cases of DN-NMOSD after Pfizer vaccine were reported recently [2], however none of these cases presented with brainstem syndrome nor with a relapsing course and requiring rituximab treatment. The greater autoreactivity may be attributed to the viral vector of the vaccine [3].

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## ESSENTIAL TREMOR WORSENING AFTER SARS-COV-2 INFECTION: A SECOND CASE REPORT

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Aim: Neurological manifestations following SARS-CoV-2 infection are widely recognized. However, the potential effects of SARS-CoV-2 infection on essential tremor (ET) have not been extensively studied. We previously reported a case of ET worsening following SARS-CoV-2 infection1. In this report, we present a second case showing a substantial worsening of tremor in a 63-year-old woman diagnosed with ET after contracting SARS-CoV-2 infection.

Materials and Methods: We conducted clinical and kinematic assessments to evaluate various tremor features, including postural, kinetic and rest tremor. Additionally, cognitive and psychiatric evaluations were performed using clinical scales at two time points: 2 months (T2) and 1 year (T3) after the infection. The data were compared with the measurements taken 1 month before the infection (T1). Blood laboratory exams were also conducted before and after infection.

Results: At T2, we observed a significant increase in postural tremor amplitude in the upper limbs compared to T1 (average percent variation: +45%). Furthermore, there was a substantial increase in head tremor amplitude (average percent variation: +284%). At T3, we observed a reduction in both postural tremor amplitude (-24%) and head tremor amplitude (-48%) compared to T2. However, the values remained higher than those at T2 (+11% in upper limb postural tremor amplitude; +99% in head tremor amplitude). There were no significant variations in tremor frequency (Hz) or differences in rest and kinetic tremor features. The trends observed in the kinematic analysis were consistent with the clinical evaluation, as indicated by the total score obtained on the Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS). In T3, the score was 32, whereas it was 41 in T2 and 28 in T1. Additionally, there were no changes in cognitive and psychiatric status compared to the previous evaluation. Lastly, the results of blood laboratory exams did not significantly differ among the three evaluations.

Discussion: The observations overall indicate that the initial worsening of tremor is not solely attributed to the natural course of the disease, but rather to infection. It is plausible to hypothesize that the SARS-CoV-2 virus induced long-lasting neuroinflammation in the structures involved in the pathophysiology of ET, particularly the cerebello-thalamic network, resulting in a significant deterioration of tremor symptoms.

Conclusion: To the best of our knowledge, this is the second reported case of tremor worsening in ET following SARS-CoV-2 infection. Longer follow-up and measurement of neuroinflammation biomarkers could provide a better understanding of the causal role of SARS-CoV-2 infection in patients with ET.

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## FATAL POSTERIOR REVERSIBLE ENCEPHALOPATHY AS THE ONLY MANIFESTATION OF COVID 19

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Background: The novel human coronavirus disease (COVID-19) infection has been associated with many neurological complications vascular and thrombotic complications, some of which may result from endothelial dysfunction, including the posterior reversible encephalopathy syndrome (PRES). We describe a case report of a PRES a solely manifestation of COVID 19 and one week after first dose of COVID 19 vaccination.

Materials and Methods: We report the case of a 79 years-old caucasian woman, who was evaluated at the emergency department of our hospital due to malaise, dull and gravative headache, fever, cognitive impairment from three days. She had received administration of first dose SARS-COV2 vaccine (Spikevax) seven days before. At evaluation patient presented generalized tonic-clonic seizures (bilateral seizure foci at electroencephalogram) responsive to intravenous infusion of levetiracetam. She was clearly confused, with global aphasia, cortical blindness without motor or sensory defects or meningeal signs. Body temperature was 38°C while arterial pressure resulted 130/80 mmHg. Nasopharyngeal swab revealed COVID 19 infection. Chest tomography excluded respiratory involvement or pulmonary embolism. Oxygen saturation levels resulted normal. Her medical history was unremarkable, especially for cognitive impairment or psychiatric disorders. She suffered from arterial hypertension, stable and well-controlled. Lumbar puncture with film - array resulted normal. Blood exams resulted all normal except for high levels of ferritin (1278 ug/l), reactive C protein 44.6 mg/l (0-5), D dimer 1380 ug/l, Interleuchin 6 16.67 pg/ml. Autoimmune panel and paraneoplastic markers resulted normal.

Results: She performed brain magnetic resonance imaging showed 2/fluid-attenuated inversion recovery (FLAIR) symmetrical hyperintensities areas involving both occipito-frontal -parietal hemisphere with vasogenic edema and without contrast enhancement or haemorrage lesions. She was diagnosed with PRES. Despite intravenous steroid therapy, levetiracetam, empirical antiviral treatment, hydratation patient conditions worsened (state of coma) and she died after 2 days. Blood pressure and renal function remained normal until death.

Discussion: Final diagnosis was PRES due to COVID 19 infection in an old patient who had been exposed and infected either through the end-to-end or shortly after process of vaccination rather than a vaccine adverse event. PRES resulted the only clinical manifestation of COVID 19 (respiratory parameters and chest evaluations and remained normal, repeated chest radiography excluded pulmonary involvement) and the main cause of death.

Conclusion: We report a fatal PRES case due to COVID 19 infection, expanding current literature. Especially in the first wave of

pandemic prompt evaluation of neurological symptoms and treatment was necessary in order to save lives.

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## PREDICTORS AND IMPACT ON DISABILITY OF DELIRIUM IN COVID-19: AN OBSERVATIONAL STUDY ON 2288 CONSECUTIVE HOSPITALIZED PATIENTS

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Backgrounds: Delirium is a common event among Covid-19 hospitalized patients. In this work, we aim at evaluate the predictors of delirium and its impact on in-hospital mortality and disability in a large population of consecutive patients hospitalized for Covid-19.

Methods: Two thousand two hundred eighty-eight Covid-19 patients were admitted to single tertiary COVID-19 hospital from March 2020 to May 2022. Premorbid conditions, severity of COVID-19, incidence of delirium, mortality and disability at discharge were extracted from digital medical records. Univariate and multivariate regression analysis were implemented to evaluate predictive factors associated with delirium, mortality and disability at discharge.

Results: Out of 2288 patients, 223 (9.7%) experienced delirium (Del+). Compared to patients without delirium (Del-), Del+ subjects were older, exhibited more comorbidities and worse premorbid conditions, worse COVID-19 severity and higher mortality rates (31.4% vs 12.9%, p p<0.001) and discharge outcomes (mRS 2.78+1.3 vs 1.57+1.3 - p<0.001). Age, premorbid disability and Covid-19 severity were the strongest predictors of both delirium and poor outcomes. Patients with delirium appeared to be at higher risk of mortality and poor outcomes regardless the COVID-19 severity at variance with COVID+ patients.

Discussion and Conclusion: The study highlighted those elderly and frail patients, hospitalized for Covid-19, are at higher risk of delirium, which is an important predictor of in hospital mortality and poor outcomes, independently from COVID-19 severity.

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## POST-COVID19 AND POST-SARS-CoV2 VACCINATION MYELITIS IN COMPARISON: A CASE SERIES

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Introduction: The incidence of acute transverse myelitis (ATM) associated with Sars-CoV2 is not clear, ranging from 0.5 per million to 1.4%. We can distinguish two forms of ATM based on the latency period from the Sars-CoV2 infection to the first neurological manifestation: para-infectious cases (15 hours to 5 days) and post-infectious cases (10 days to 6 weeks). Furthermore, many cases of ATM post-Sars-Cov2 vaccination are described. The exact pathological mechanism that correlates infection or vaccination with myelitis is debated, considering viral neurotropism or immune-mediated reactions through molecular mimicry, epitope spreading, bystander activation or polyclonal B-cell activation. We report six cases of patients who developed myelitis correlated to Sars-CoV2 infection or vaccination admitted to our ward. The aim of this work is to compare clinical, neuroimaging, CSF pattern, response to therapies and outcomes in these patients, distinguishing three subgroups: para-infectious, post-infectious and post-vaccination.

Results: We observe that patients who developed SARS-CoV-2 para-infective myelitis showed a more severe clinical course refractory to several therapies and developed clear spinal lesions on MR study. The post-infective group seems to respond better to therapies and showed a mild illness compared to the first ones. Post-vaccination cases exhibited an even more benign course.

Conclusions: The differences recorded between the three groups suggest that there may be different pathogenic mechanisms underlying them. Moreover, it points out the importance of recognizing the type of ATM related to Sars-Cov2 in order to start promptly the more effective therapy.

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## SMALL FIBRE NEUROPATHY IN POST COVID-19 SYNDROME: A CASE- CONTROL STUDY

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Objectives: Patients with a post COVID-19 condition often complain of sensory symptoms and pain. Previous retrospective clinical observations raised the possibility that small fibre neuropathy may underlie these post COVID-19 related disturbances [1]. In this case-control study, we aimed to definitely diagnose small fibre neuropathy in patients with painful post COVID-19 condition.

Materials and Method: To definitely diagnose small fibre neuropathy, we collected clinical data (e.g., pain and autonomic symptom questionnaires) and investigated quantitative sensory testing (QST) and skin biopsy in 26 selected patients with painful post COVID-19 conditions. We also screened 100 previously ill COVID-19 survivors and selected 30 control participants without any post COVID-19 symptoms. Then, we compared the main demographic and clinical variables between groups.

Results: Of the 26 patients with painful post COVID-19 condition, 12 had skin biopsy and/or QST abnormalities, compatible with a small fibre neuropathy. In patients with post painful post COVID-19 condition (with and without small fibre neuropathy), demographic and clinical data (including COVID-19 severity) were comparable to those of previously ill COVID-19 survivors without any post COVID-19 symptoms.

Discussion: This case-control study shows that approximately 50% of our patients complaining of sensory symptoms and pain after the acute phase of COVID-19 received a diagnosis of small fibre neuropathy. In patients with small fibre neuropathy demographic and clinical data were comparable to those in previously ill COVID-19 survivors without a post COVID-19 condition. Of the 100 unselected participants with a previous SARS-CoV-2 infection, five suffered from a painful post COVID-19 condition; these five patients were eventually diagnosed with a small fibre neuropathy, expanding previous data on post COVID-19 small fibre neuropathy prevalence [2]. We found that our patients with small fibre neuropathy had a mechanical hyperalgesia (8 patients) and a sensory loss QST phenotype (4 patients). These findings are in line with previous studies showing that mechanical hyperalgesia and sensory loss are the most frequent QST phenotypes in patients with small fibre neuropathy. We therefore hypothesize that in our patients with small fibre neuropathy, pain might predominantly reflect central sensitization phenomenon; nevertheless, in some patients, pain might be also triggered by second order neuron deafferentation [3].

Conclusion: Our case-control study showed that small fibre neuropathy is relatively common in patients suffering from painful post COVID-19 condition; in our patients, however, this specific post COVID-19 complication was unrelated to demographic and clinical variables (e.g., COVID-19 severity or the duration of hospitalization) related to COVID-19.

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## CLINICAL CHARACTERISTICS OF SMALL FIBER NEUROPATHY FOLLOWING SARS-COV2 INFECTION OR VACCINATION: RESULTS FROM SKIN BIOPSY AND MULTIPLE SCALE ASSESSMENT

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Objectives: The study aims to characterize patients reporting with symptoms compatible with Small Fiber Neuropathy (SFN) temporally related to either SARS-CoV2 infection or vaccination, as already suggested by reports [1].

Materials: Patients were selected if they presented with a clinical picture compatible with SFN in close temporal connection ($\leq 2$ months) with either SARS-CoV2 infection or vaccination.

Methods: Skin biopsy was performed in all patients to assess intraepidermal nerve fiber density (IENFD). Large fiber neuropathy was excluded by neurological examination and nerve conduction studies. Clinical data, comprising time from infection or vaccination to symptoms, pain characteristics and localization, type of vaccination and response to therapy were collected. Additionally, the Douleur Neuropathique-4 Questionnaire (DN4) was administered to characterize the pain, as well as the Composite Autonomic Symptom Score (COMPASS) in order to assess autonomic fiber involvement and Short Form Health Survey-36 for assessment of quality of life.

Results: 66 (33 post-vaccination, 33 post-COVID) patients were enrolled (42 females, 33 males). Onset from event to clinical presentation was on average 248 hours (range 1-1440) in post-vaccination and 445 hours (range 24-2880) in post-COVID patients. Skin biopsy revealed reduced intraepidermal nerve fiber density compatible with SFN in 25/33 post-vaccination (75%) and 31/33 post-COVID (94%) patients. When assessable (28/33 post-vaccination, 31/33 post-COVID, total 59), DN4 was positive in 50/59 patients) and mean COMPASS score was 40.86 post-vaccination, 56.09 post-COVID.

Discussion: The majority of patients, moreso in the post-COVID category, showed reduced IENFD compatible with SFN. Moreover, clinical scores characterized pain as likely neuropathic, associated to autonomic symptoms.

Conclusions: In line with other studies, these results suggest a link between SFN and SARS-CoV2 infection or vaccination. A possible explanation could be the immune response against the Spike glycoprotein of SARS-CoV2 causing small fiber damage.

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## SMALL FIBER NEUROPATHY AFTER ANTI-COVID VACCINATION OR COVID INFECTION: A CASE SERIES

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Objectives: The aim of this case series is to describe two cases of Small Fiber Neuropathy (SFN) diagnosed by a congruent clinical picture and reduced intraepidermal nerve fiber density (IENFD), one occurring after anti-COVID vaccination and the other after COVID infection, as already suggested by reports [1].

Materials: Patient 1 is a 33-year-old female who first presented with severe back and lower limb burning pain 4 weeks after treatment with botulinum injections. Lumbosacral MRI, as well as blood exams for autoimmune disorders, was negative. Pain did not respond to gabapentin 100 mg/die, but slowly remitted over time. A first skin biopsy was negative. Successively, 4 days after the second dose of anti-COVID vaccination, she presented with burning pain localized to limbs and trunk. Skin biopsy was then repeated, showing reduced IENFD

compatible with SFN. Patient 2 is a 31-year-old male who presented with burning pain localized to both calfs, 4 days after the first dose of anti-COVID vaccination. Skin biopsy was negative; subsequently, around 2 months after COVID infection, he presented with burning paresthesia affecting both hands and forearms. Skin biopsy was then repeated, indicating reduced IENFD.

Methods: Clinical data of the 2 patients were collected concerning medical history, treatment and clinical examination, as well as skin biopsy results.

Results: Patients without previous SFN, as shown by negative skin biopsies, developed neuropathy, the first after vaccination and the second after infection.

Discussion: While studies concerning post-COVID/vaccination SFN cannot usually exclude previously reduced IENFD at skin biopsy, these two cases show a stronger correlation between these two events and SFN.

Conclusion: SFN is a potential complication of either COVID infection or vaccination and a coherent clinical picture should prompt assessment of small fibers.

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## EFFICACY OF INTRAVENOUS IMMUNOGLOBULINS (IVIG) ON COVID-19-RELATED NEUROLOGICAL DISORDERS OVER THE LAST 2 YEARS: AN UP-TO-DATE NARRATIVE REVIEW

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Introduction: IntraVenous Immunoglobulins (IVIg) are a preparation of human antibodies. They represent a consolidated therapeutic tool for the treatment of various immune-mediated neurological diseases. SARS-CoV-2 infection has been reported to determine several clinical manifestations, including neurological disorders. In recent years, the use of IVIg in these conditions has gradually increased, with an impact not only on the treatment of neurological complications, but even on the comprehension of their causal mechanisms.

Methods: We openly explored the available topic-specific indexed medical literature in order to answer the question of whether IVIg could be considered a valid tool to address the clinical management of COVID-19-induced neurological disorders. We collected the found studies in an extensive table, by indicating for each of them details about the subjects treated, the IVIg regimen employed and the therapeutical results obtained.

Results: In the first part of this narrative review, the mechanisms both of interaction of SARS-CoV-2 with the nervous system and of IVIg action were discussed. In the second part, we collected scientific literature data over the last years to discuss the use of IVIg therapy in different neuro-COVID conditions, in order to provide a critical summary of the possible strategies of treatment. As concerns our experience, we have dealt with and published cases of COVID-19-related Guillain-Barré and new onset refractory status epilepticus. They turned out to respond to IVIg treatment, even when disease-specific and other immunomodulating treatment had failed, without the appearance of side effects. In all cases we used the classical dosage regimen of 0.4 g/kg/day for 5 days. Virtually all reviewed studies are in agreement to detect an acceptable to great efficacy of IVIg employment in COVID-19-related neurological diseases, with no or mild adverse effects.

Discussion: IVIg therapy is a versatile tool with multiple molecular targets and mechanisms of action that might contribute to explain some of the underlined processes of Sars-CoV-2 infection, indeed its efficacy has to be linked with its immunomodulatory effects. As such, IVIg therapy has been used in several COVID-19-related neurological diseases, including polyneuropathies, encephalitis, and status epilepticus, reaching an improvement of symptoms even in the most severe cases, without the development of important side reactions, thus suggesting IVIg treatment can be both effective and safe.

Conclusion: In most treated cases, sometimes even when other medications had failed, IVIg proved to be simultaneously an effective, safe and often decisive therapy against several COVID-related neurological conditions, virtually without provoking adverse effects.

## COVID-19 MULTI-ORGAN PATHOLOGY: A SPECIAL FOCUS ON AGING BRAIN

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Objective: We describe COVID-19 pathology across different tissues to clarify the disease's pathophysiology, focusing on the brain.

Materials: Clinical and pathological data from COVID-19 cases.

Methods: Lung, kidney, heart, and brain from nine COVID-19 autopsies were compared by using antibodies against SARS-CoV-2, macrophages-microglia, T-lymphocytes, B-lymphocytes and activated platelets. Alzheimer's Disease pathology was also assessed. PCR techniques were used to verify the presence of viral RNA in the brain.

Results: COVID-19 cases had a short clinical course (0–32 days) and a mean age of 77.4 y/o. Hypoxic changes and inflammatory infiltrates were present across all tissues. The lymphocytic component in lungs and kidneys was predominant over that of other tissues ($p < 0.001$), with a significantly greater presence of T-lymphocytes in the lungs ($p = 0.020$). Microthrombosis was significantly higher in COVID-19 lungs ($p = 0.023$) compared with controls. The heart showed scant SARS-CoV-2 traces in the endothelium–endocardium, foci of activated macrophages and rare lymphocytes. All COVID-19 brains showed non-SARS-CoV-2-specific changes including hypoxic-agonal alterations, a variable degree of neurodegeneration and/or pre-existent small vessels disease. The neuroinflammatory picture was dominated by ameboid CD68 positive microglia, while only scant lymphocytic presence and scarce SARS-CoV-2 traces were detected. Microglial activation in the brainstem was significantly greater in COVID-19 cases ($p = 0.046$). Microglial hyperactivation in the frontal cortex and hippocampus was clearly associated to AD pathology ($p = 0.001$), regardless of SARS-CoV-2 infection. In COVID-19 cases complicated by delirium (all with neurocognitive disorders), there was a significant enhancement of microglia in the hippocampus ($p = 0.048$). The pons exhibited the highest microglial activation ($p = 0.017$).

Discussion: The most characteristic pathological features of COVID-19 were an abundance of T-lymphocytes and microthrombosis in the lung and microglial hyperactivation in the brainstem. Although higher in cases with both Alzheimer's pathology and COVID-19, cortical neuroinflammation is mostly related to pre-existing neurodegeneration. COVID-19 brains seem to manifest a boosting of innate immunity with microglial reinforcement, and adaptive immunity suppression with a low number of brain lymphocytes probably related to systemic lymphopenia. No neuropathological evidence of SARS-CoV-2-specific

encephalitis is detectable. Probably, the microglial hyperactivation represents the neuropathological basis of the "COVID-19 encephalopathic syndrome" in the elderly, favored by the microglial priming due to neurodegeneration. The prominent neuroinflammation in the brainstem is as a specific topographical phenomenon.

Conclusions: The long-term consequences of COVID-19 seem to represent a complex phenomenon arising from persistent inflammation, rather than persistent viral replication.

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## INVESTIGATING THE IMPACT OF SARS-COV2 INFECTION ON ESSENTIAL TREMOR: A SURVEY-BASED STUDY AND RETROSPECTIVE ANALYSIS OF CLINICAL AND KINEMATIC DATA

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Objectives: Over the past three years, SARS-CoV-2 infection has had a significant impact on people's health. Apart from the well-known manifestations, some individuals have experienced new neurological symptoms or worsening of existing neurological conditions. However, there is a lack of studies investigating the effects of SARS-CoV-2 on tremor in a large sample. This retrospective study aims to analyze longitudinal data from patients diagnosed with Essential Tremor (ET) to investigate the impact of SARS-CoV-2 infection on tremor features. The objective is to examine how the infection may have influenced the progression or changes in tremor over time.

Materials: This study consisted of a cohort of forty patients diagnosed with Essential Tremor (ET), with 21 females and a mean age of 69±12,25. A survey was conducted to assess the clinical progression of SARS-CoV-2 infection, identify any new neurological symptoms, and evaluate changes in tremor experienced by the patients.

Methods: The clinical features of tremor collected with the Fahn-Tolosa-Marin Clinical Rating Scale for Tremor (FTM) and The Essential Tremor Rating Assessment Scale (TETRAS) were retrospectively evaluated. Additionally, we retrospectively analyzed kinematic data, including rest, postural, and kinetic tremor, which were collected using an optoelectronic motion system.

Results: Out of the twenty-five patients who reported a SARS-CoV-2 infection, eleven (44%) experienced a subjective worsening of tremor. Only one patient reported the emergence of tremor in a previously unaffected body part. Among those who reported subjective worsening of tremor, a significant number (72%) also reported experiencing "Long-Covid" symptoms such as brain fog, fatigue, and myalgia, whereas this prevalence was much lower (7%) in those without worsening (P=0.002). However, when considering clinical and objective kinematic measurements, a notable worsening of tremor was confirmed in only two cases (18%) among those who subjectively reported worsening symptoms.

Discussions: While a considerable number of patients reported subjective worsening of tremor following the infection, objective measurements only confirmed this change in a minority of cases.

Conclusions: These findings suggest that significant tremor worsening may occur in a limited number of patients. Further research is needed to gain a clearer understanding of the impact of SARS-CoV-2 infection in patients with ET.

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## POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME AND REVERSIBLE CEREBRAL VASOCONSTRICTION SYNDROME IN PATIENTS WITH COVID-19 INFECTION. IS THERE A LINK? A SYSTEMATIC REVIEW AND CASE REPORT ANALYSIS

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Aim: During the SARS-CoV-2 pandemic, several cases of PRES and RCVS have been reported in patients with COVID-19, but the link between these clinical-radiological syndromes and COVID-19 has not yet been defined. This review aims to investigate whether SARS-CoV-2 infection or the therapies used to treat COVID-19 can be potential risk factors for the development of PRES or RCVS.

Methods: A systematic review was conducted on PubMed, Scopus, and Web of Science for case reports concerning patients with COVID-19 who developed PRES and/or RCVS. The clinical characteristics of the two populations were analyzed separately, and statistical analyses were performed to identify additional risk factors beyond those already known.

Results: 70 articles concerning 105 patients (85 with PRES, 20 with RCVS) were found. Our analysis revealed a lower incidence of common risk factors for PRES and RCVS in patients with COVID-19, suggesting that COVID-19 may be an independent risk factor for both conditions. This could be due to the ability of SARS-CoV-2 to cause endothelial dysfunction, which is the common pathophysiological mechanism for both RCVS and PRES. Additionally, our analysis found a statistically significant increase in antiviral therapy with ritonavir or darunavir in individuals without known risk factors for PRES. Since antiviral drugs can also cause endothelial damage by reducing the bioavailability of nitric oxide, they too may act as independent risk factors for the development of PRES.

Conclusions: In conclusion, a correlation has been found between PRES, RCVS, and COVID-19, as well as between PRES, COVID-19, and antiviral therapy used to treat SARS-CoV-2 infection. Further research is needed to confirm these results using larger sample sizes and randomized control groups.

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## AN OBSERVATIONAL STUDY OF PAINFUL POST COVID-19 CONDITION

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Studies now show that about 10-20% of people previously infected by SARS-CoV-2 may develop a post COVID-19 condition, manifesting with a collection of different physical and mental health symptoms, including pain. In this observational study, we aim to identify frequency and risk factors for painful post COVID-19 conditions. We consecutively screened 100 previously ill patients referred to a COVID-19 unit for the routine follow-up visit. The participants underwent a detailed neurological examination, and we collected the main demographic and clinical data, including information about any painful condition, regardless whether previously diagnosed or newly developed. We distinguished patients into three categories: patients without pain, patients with a pre-existing pain condition, patients with pain triggered by COVID-19. All patients with possible or probable neuropathic pain grading system for neuropathic pain underwent Quantitative Sensory Testing (QST) and skin biopsy. Of the 100 participants, 49 had chronic pain (i.e. pain persisting in the last 30 days). In 26 patients chronic pain followed the COVID-19. Conversely, 23 patients suffered from a previously diagnosed chronic pain condition; the severity of pain, nevertheless, increased after COVID-19. Of the 26 patients with painful post COVID-19 condition, five had possible neuropathic pain and seven probable neuropathic pain. Five patients were eventually diagnosed with a small fibre neuropathy. Unexpectedly, we found that our patients with painful post COVID-19 condition had similar demographic and clinical data compared to previously ill patients without a painful post COVID-19 condition. This study extends current knowledge about the frequency of neuropathic pain in previously ill COVID-19 patients. Previous systematic studies indicated that the overall frequency of possible neuropathic pain due to COVID-19 infection is 10%. Our study, showing a 5% frequency of definitely diagnosed small fibre neuropathy in unselected participants with a previous SARS-CoV-2 infection, now suggests that a considerable proportion of post COVID-19 neuropathic pain is due to small fibre neuropathy.

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## MULTI-DIMENSIONAL ASSESSMENT OF COGNITIVE AND PSYCHIATRIC BURDEN IN PEOPLE WITH LONG-COVID: A CROSS-SECTIONAL OBSERVATIONAL STUDY

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Cognitive and psychiatric symptoms have been increasingly reported after SARS-CoV-2 infection. These sequelae develop soon after infection and persist for several months. We aimed to study this syndrome and start implementing strategies for their objective assessment. One-hundred-thirty-five consecutive patients (mean age 55.4±12.3, 62% females), referred to the neurologist by the infectious disease department because of cognitive complaints after COVID-19, were evaluated. Neurological evaluation including a cognitive screening test [Montreal Cognitive Assessment (MoCA)] was performed; patients were also invited to answer a general symptom questionnaire and a self-administered multidimensional assessment of psychiatric symptoms, which was then followed by full psychiatric assessment if scores resulted above validated cut-off. Ninety-nine patients completed the cognitive screening and self-administered psychiatric questionnaire. Subjects were referred after a mean of 13.5±5.6 months from acute infection, which was of low severity for most patients (56% treated as outpatients, only 9.1% requiring ICU). The most common persisting symptoms were fatigue (92%), sleep problems (69.5%), and headache (52.4%). MoCA outlined cognitive deficits in at least one cognitive domain in 34% of patients, mainly in memory and attention. About 60% presented depressive, anxiety, or stress-related symptoms. Psychiatric scales scores correlate significantly with overall symptom burden and MoCA score. No significant correlation was found between cognitive scores at MoCA and overall symptom burden. Cognitive complaints after COVID-19 were confirmed by cognitive screening tests in only one third of cases and were associated with high levels of psychiatric symptom burden. While MoCA scores and overall symptom burden correlated significantly with psychopathological burden, no reciprocal correlation between these two variables was found. We hypothesize that persistent cognitive complaints after COVID-19 might be the reflection of a concomitant or reactive psycho-pathological condition, possibly coupled with an infection-related impact on cognitive functions. The application of a combined neurological and psychiatric assessment of patients who have suffered a COVID-19 patients seems crucial.

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## BICKERSTAFF ENCEPHALITIS PRESENTING WITH A STROKE-LIKE ONSET IN COVID-19 INFECTION

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Objective: Description of a particular case of Bickerstaff encephalitis (BBE) in Covid-19 infection.

Materials: Neurological manifestations of Covid-19 infection are observed frequently, in more than one third. [1] Headache, nausea, and vomiting, for example, are mild neurological symptoms. Other syndromes such as ADEM, meningo-encephalitis, GBS are described.

Methods: Here we describe the case of C.A., a 55-year-old man with an acute onset of ptosis in the left eye and dizziness. Cranial CT scan as well as brain MRI showed no abnormal results, given the partial occlusion left Cerebral Posterior Artery's P1 trait, the patient was treated as a stroke. At neurological examination, consciousness, language and speech were normal; limitation of vertical eye movements and impairment of smooth pursuit eye movements and accomodation were present, with bilateral ptosis; severe ataxia was present. The following day, the patient developed four limbs weakness and confusional state. PCR to SARS-CoV-2 was positive but he did not develop any respiratory symptoms. A second brain MRI showed hyperintense lesions in brainstem and basal ganglia. Electroencephalogram test showed right high-amplitude theta waves. CSF exam showed a leukocyte count of 5/mm3, glucose level of 50 mg/dl, protein level of 40 mg/dl, sterile cultures, and absence of oligoclonal bands. Anti-Hu, anti-Yo, anti-Ri, and anti-amphiphysin antibodies were absent in serum and CSF. Blood HIV test, IgM for Varicella-zoster virus, Epstein Barr virus, Cytomegalovirus were negative. Antithyroid, antinuclear antibodies were negative. Electromyography showed rieduced frequency of F-wave with no denervation. The patient received IVIG therapy without substantial improvements of clinical conditions while administration of high dose corticosteroids induced rapid and full recovery.

Results: Our case is an example of BBE (with a particolar onset) in Covid-19 infection.

Discussion: The coronavirus enters the nervous system either through the blood or via the olfactory nerves. Pathogenesis of neurological manifestations of human coronavirus infection includes direct neuronal damage, apoptosis, production of pro-inflammatory cytokines, immunopathological mechanisms. [1] GBS, Miller Fisher syndrome, acute necrotizing encephalitis, myelitis, acute disseminated encephalomyelitis (ADEM), and myasthenia gravis have been reported [2]. As in our patient, corticosteroids seemed to have a beneficial effect on several of these cases.

Conclusions: Recent evidence suggests that a wide range of neurological complications of SARS-CoV-2 infection could be explained by enhanced immune response [2]. Successful management of BBE is dependent upon a high clinical index of suspicion and early diagnosis. BBE widens the spectrum of para-infectious neurological disorders related to COVID-19.

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## COVID-19 HAS NO IMPACT ON DISEASE ACTIVITY, PROGRESSION AND COGNITIVE PERFORMANCE IN PEOPLE WITH MULTIPLE SCLEROSIS OVER TWO YEARS

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Objectives: We explored whether COVID-19 is associated with an increased risk of disease activity, disability worsening, neuropsychological distress and cognitive dysfunction during the 18-24 months following SARS-COV-2 infection.

Materials: We enrolled 174 PwMS with history of COVID-19 (MS-COVID) between March 2020 and March 2021 and compared them to an age, sex, disease duration, EDSS, line of treatment-matched group of 348 PwMS with no history of COVID-19 in the same period (MS-NCOVID). We collected clinical, MRI data and SARS-CoV2 immune response in the 18-24 months following COVID-19 or baseline evaluation. At follow-up, PwMS also underwent a complete neuropsychological assessment with Brief Repeatable Battery of Neuropsychological Tests, and optimized scales for fatigue, anxiety, depression and post-traumatic stress assessment.

Methods: Descriptive statistics and univariate logistic regression analyses were employed to evaluate the association between the group (MS-COVID and MS-NCOVID) and a change in clinical characteristics. Comparison of neuropsychological variables: Continuous variables were compared between the two groups by using the Mann-Whitney test, while categorical variables with the Fisher's exact test. P-values were adjusted with Bonferroni's correction to account for multiple testing.

Results: 136 MS-COVID and 186 MS-NCOVID accepted the longitudinal evaluation. The two groups did not differ in terms of EDSS worsening (15% vs 11%), number of relapses (6% vs 5%), need to change DMT (7% vs 4%), new T2 lesions (9% vs 11%) and gadolinium enhancing lesions (7% vs 4%) on brain MRI (p values range: 0.18-0.68). 22% of MS-COVID and 23% MS-NCOVID were cognitively impaired at follow-up, with no between-group difference in the prevalence of cognitive impairment (p=1.000). The z-scores of global and domain-specific cognitive functions, and the prevalence of neuropsychiatric manifestations were also similar between the two groups (p values range: 0.19-1.00). No difference was seen in term of SARS-CoV2 immune reactivity.

Discussion: Based on these findings, it may be appropriate to suggest that PwMS can begin to return to their normal lives with less fear of COVID-19. Of course, caution and good hygiene practices should still be encouraged, as the virus can still pose a risk to anyone, regardless of their immune status.

Conclusion: COVID-19 has no impact on disease activity and cognitive performance among PwMS 18-24 months after infection.

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## STROKE IN COVID-19 PATIENTS FROM 2020 TO 2022 IN CIRIE' NEUROLOGY UNIT

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Objectives: Sars-cov2 can cause multiorgan disease due to altered coagulability and microangiopathy. Patients have an increased risk of cerebrovascular events both ischemic and hemorrhagic [1]. The aim of our study was to compare clinical characteristics of Covid-19 stroke patients with data of larger metanalysis reported in literature [2].

Materials and Methods: Data of 1599 patients with Sars-cov2 infection admitted to our Hospital from 2020 to 2022 were collected. In 42/1599 stroke patients we analyzed the incidence cardiovascular risk factors (hypertension, coronary artery disease - CAD, atrial fibrillation, diabetes), stroke etiology (large vessel disease - LVD, small vessel disease - SVD, multiple embolic stroke - ME or intravascular bleeding - IB), ischemic stroke treatment (intravenous thrombolysis and/or endovascular treatment) and concomitant respiratory involvement.

Results: The annual incidence of stroke in Covid-19 patients was similar to the one reported in literature (2,5%). Our patients were older with a median age of 78.9 years versus 65.3 [2] and mostly female. Cardiovascular risk factors in Covid-19 patients developing acute cerebrovascular disease were hypertension in 76,2% of cases versus 62,2% in literature, CAD in 11,9% versus 15.9%, atrial fibrillation was more frequent in our population (33,3% versus 13.9%) and diabetes less represented (16,7% versus 36.7%). Considering stroke etiology, LVD was found in 57% of patients and SVD in 23,8% versus 10.6% and 3.3% respectively. ME strokes were 9,5% versus 21.9%. IB was described in 9,5% of cases compared to 11.6% in metanalysis data [2]. Acute stroke treatment was intravenous thrombolysis in 26,3% versus 19.1% while endovascular treatment was performed in 7,8% versus 25.9%. Stroke patients with Covid-19 and mild respiratory symptoms were 58,3% in 2020 and 2021, 54,5% in 2022; patients with severe respiratory symptoms were 65% in 2020, 36,4% in 2021 and 45,4% in 2022; cases of death were 60% in 2020 while in 2021 and 2022 no deaths were registered. In literature, severe Covid-19 disease was reported in 60.5% [2].

Discussion and Conclusions: Stroke incidence in our Covid-19 patients was the same described in metanalysis but our patients were older and prevalently female. Hypertension and CVD were similarly represented but we found more LVD and SVD related strokes and less ME events, probably due to gender difference [1] and milder Sars-cov2 respiratory disease in 2020-2022 compared to 2019-2021, after vaccination campaign, triggering lower prothrombotic activity [1,3]. Endovascular treatment was less performed probably due to longer timing to Hospital access in early pandemic phase.

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## A CASE OF PARSONAGE-TURNER SYNDROME AFTER COVID-19 VACCINATION IN A PATIENT AFFECTED WITH PARKINSON'S DISEASE AND A BRIEF REVIEW OF THE LITERATURE

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Objectives: We aimed to describe a case of Parsonage-Turner syndrome (PTS) in a patient affected with Parkinson's disease (PD) following COVID-19 vaccination. We also analyzed PTS cases reported in the literature so far.

Materials and Methods: Cases of PTS following COVID-19 vaccination were reviewed, and epidemiological, clinical and electrophysiological features were collected.

Results: A 69-year-old man affected with PD presented to our department due to acute and intense pain in the right shoulder and arm two weeks after the booster dose of mRNA COVID-19 vaccine (Pfizer-BioNTech BNT162b2) inoculation into the right deltoid. He did not benefit from treatment with non-steroid anti-inflammatory drugs. A few days later, he developed weakness on abduction and elevation of the right upper limb. He denied previous vaccine adverse reactions, trauma, or infections. Neurological examination showed muscular atrophy of the proximal right upper limb, and severe weakness of the shoulder rotation and abduction, elbow flexion and forearm supination. Biceps tendon reflex was decreased. Hypoesthesia of the right shoulder was present. Nerve conduction study revealed reduced bilateral sensory responses of median, ulnar and radial cutaneous nerves. Needle electromyography showed fibrillations, positive sharp waves and decreased motor unit recruitment in deltoid and brachial biceps muscles. As it had been more than a month since the onset of symptoms, only physical therapy was recommended. Six months later, the upper limb weakness and the hypoesthesia dramatically improved. Until now, forty-two cases of PTS following immunization with all types of COVID-19 vaccine have been reported. Most cases were male (69%) aged between 15 and 84 years (49.6 $\pm$ 16.3 years). Time of symptoms onset ranged from 13 hours to 8 weeks after the vaccination. The symptoms were ipsilateral to the side of inoculation in 29 cases (50%) and bilateral in two patients (4%). Pathological findings compatible with PTS have been described in all the cases that underwent electrophysiological study. All patients had amelioration of the symptoms, independently of treatment with corticosteroids.

Discussion: The pathophysiology of PTS is unknown, but it may involve genetic, environmental, and immune-mediated components. The mRNA vaccines may be associated with increased risk of autoimmune diseases, triggering type I interferon responses. As the patients can develop symptoms contralateral to the injected side, it is unlikely that INA is secondary to direct nerve insult from inoculation.

Conclusion: PTS may be associated with COVID-19 immunization. Electrophysiology is a useful to rule out other diseases. There is no specific treatment available, but it may resolve independently of pharmacological treatment.

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## LONGITUDINAL EVALUATION OF SERUM MARKERS OF NEURONAL AND GLIAL DAMAGE AFTER FULL CLINICAL RECOVERY FROM MILD COVID-19 INFECTION

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Objectives: Neurofilament light chain (NfL) [1] and glial fibrillar acidic protein (GFAP) [2] have been demonstrated to increase in the peripheral blood of patients during the acute phase of COVID-19, regardless of the presence of neurological manifestations. [3] In this 10-month longitudinal study, we assessed the trend of serum levels of biomarkers of neuronal and glial damage in a cohort of patients after mild COVID and investigated their associations with cognitive and working performance.

Material and Methods: 147 previously healthy university workers were recruited after SARS-CoV-2 infection (T0, one week after negative swab). The Cognitive Failure Questionnaire (CFQ) was administered and sNfL and sGFAP concentrations were assessed. 49/147 patients experienced the persistence of at least one symptom of long-COVID syndrome 10 months after swab negativization (T1). For all these patients the CFQ, sNfL, and sGFAP were repeated. In addition, a cohort of 82 age- and BMI-matched healthy controls (HCs) was recruited.

Results: Age and BMI-corrected sNfL and sGFAP concentrations at T0 were higher in patients after COVID-19 than in HCs (median sNfL 22.8 vs 7.2 pg/mL; median sGFAP 146.3 vs 63.5 pg/mL; $p< 0.001$ for both). 11/147 patients had an impaired CFQ (score < 43) at T0, showing higher levels of sNfL and sGFAP than those with normal CFQ (median sNfL 45.0 vs 22.4 pg/mL; median sGFAP 194.0 vs 131.3 pg/mL; $p=0.005$ for both). The 49 patients examined also at T1 had significantly reduced levels of sNfL and sGFAP at T1 (median sNfL 18.3 pg/ mL; median sGFAP 77.2 pg/mL; $p<0.001$ for both) compared to T0 and their mean CFQ values were significantly higher than the values observed at T0 (18.1 vs 27.1; $p<0.01$, 6/49 patients had impaired CFQ score). However, sNfL and sGFAP levels at T1 remained significantly higher than in HCs ($p<0.001$). No difference was found in sNfL and sGFAP levels when patients with normal and impaired CFQ at T1 were compared.

Discussion and Conclusions: In sum, inflammatory-related neuronal and glial degeneration characterizing the acute phase of COVID still persists months after full clinical recovery and is more pronounced in patients with cognitive difficulties during the period immediately after swab negativization. Moreover, these two biomarkers significantly decrease but do not return back to normal levels in those patients with at least one symptom suggestive of long COVID syndrome.

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## MBL LEVELS IN PATIENTS EXPERIENCING "BRAIN FOG" AS LONG-COVID SYMPTOM

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Objectives: To evaluate the potential relation between the long-COVID syndrome "brain fog" (BF) and the complement pathway; in particular between BF and Mannan-Binding Lectin (MBL) levels and activity.

Materials: Patients referring to the Neuro-Long-COVID ambulatory service were screened for the presence of neurological symptoms that were persistent or occured ex novo at least after 4 weeks from acute COVID-19 manifestations. Patients without previous history of cognitive deficits, who reported persistent inattention, lack of concentration, short-term memory loss or impaired cognition were included in the BF group (BF+ve), patients who reported only persistent hyposmia/hypogeusia were included in the "without BF" group (BF-ve). Volunteers without persistent symptoms but with history of COVID-19 were included in the BF-ve group, volunteers without history of COVID-19 were included in the control group (CTRL). General anamnestic data, including comorbidities, were collected. An extensive neurological assessment of the patients was performed, including the Montreal Cognitive Assessment (MoCA) for BF+ve. All participants underwent a blood sample.

Method: Commercial ELISA kits were used for the determination of serum levels of MBL and of the activation of classical, alternative and lectin pathways of all participants. T-test was used to evaluate the differences between the groups (BF+ve, BF-ve, CTRL).

Results: A total of 66 subjects were included in the study: 32 BF+ve, 16 BF-ve, 18 CTRL. Significantly lower levels of MBL were observed in the sera of BF+ve patients compared to BF-ve group ($p<0.01$). Sera belonging to the BF+ve group presented a lower percentage of lectin pathway activation compared to BF-ve patients, whereas no differences were found for classical and alternative pathways.

Discussion: The pathogenic mechanisms of BF remain still unknown. The complement system could have an ambivalent role: enhancing virus elimination in the early stages of infection and leading to hyperinflammation and endothelial injury as a consequence of an excessive or aberrant activation. MBL act, in the innate immune defense system, as an opsonin and as a recognition molecule in complement activation via lectin pathway. Reduced MBL levels in BF+ve group could suggest a reduced capacity to inhibit SARS-CoV-2 infection in this group of patient and could suggest a predisposition to long-Covid BF in patients with lower levels of MBL.

Conclusions: MBL level is significantly lower in patients experiencing BF in the post-acute phase of COVID-19. Long-COVID-associated BF can be considered as one of the manifestations of increased susceptibility to infections and diseases induced by MBL deficiency.

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## A MULTI-RELAPSING SERONEGATIVE AUTOIMMUNE ENCEPHALITIS TRIGGERED BY SARS-COV-2 INFECTION: A CASE REPORT

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Background: In recent decades, autoantibodies with high specificity for autoimmune encephalitis (AE) have improved diagnosis [1,2,3]. However, AE diagnosis in seronegative patients is challenging, and treatments are potentially harmful, emphasizing the importance of accurate clinical history, examination, and supportive paraclinical diagnostic tests. SARS-CoV-2 infection has been reported to trigger limbic encephalitis and anti-NMDA receptor AE, but the mechanisms are still poorly understood [1]. Moreover, due to AEs low frequency, their long-term prognosis and relapse risk is still unknown. Here we report the case of a multi-relapsing seronegative AE with onset after paucisymptomatic SARS-CoV-2 infection.

Case Presentation: A 60-year-old man with a negative medical history experienced paucisymptomatic SARS-CoV-2 infection (fever and sore throat, no hospitalization needed) in December 2021. He reported anxious behaviors and paranoia weeks later, progressively worsening despite psychiatric treatments. In March 2022, generalized seizures and cognitive impairment occurred. Brain MRI, lumbar puncture (LP), CSF Tau, p-Tau, beta-amyloid, and serum and CSF AE autoantibodies were negative. Brain PET revealed severe hypometabolism in bilateral temporal lobes and steroids and antiepileptic drugs were started. A diagnosis of possible AE according to 2021 diagnostic criteria was formed [2,3]. Six months later, we observed a partial improvement in cognitive and psychiatric manifestations while he continued to experience seizures despite the administration of different antiepileptics drugs. Brain PET was stable. Steroids were tapered, and he clinically relapsed with psychiatric manifestations and cognitive and memory deficits. LP and autoantibodies resulted once again negative. IVIG and rituximab were started. Cancer screening was negative. In February 2023 a third relapse occurred one month after the second semestral rituximab infusion. CSF 14.3.3 was negative at LP, CSF Tau was increased, and serum and CSF AE autoantibodies were analysed in a third-level expert laboratory. immunohistochemistry revealed a mild positivity on vessel walls and cytoplasmatic Purkinje cells, further supporting a possible autoimmune pathogenesis. Cyclophosphamide was started with clinical improvement.

Discussion: AE diagnosis and treatment in seronegative patients is challenging. Our case highlights the long-term difficulties in disease control despite the administration of high-efficacy therapies. SARS-CoV-2 infection, particularly severe infection, can trigger AE, which is usually seronenegative for well-known antibodies.

Conclusions: Seronegative AE is still underdiagnosed, but properly recognizing this condition has important consequences for patients' prognosis and treatment.

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## PLASMA BIOMARKERS OF NEUROLOGICAL DISORDERS: FROM ACUTE STAGE TO POST-ACUTE SEQUELAE OF COVID-19

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Background: We examined biomarker levels of brain injury (GFAP and NfL) and monocyte/macrophage activation markers (sCD163) with the presence of neurological symptoms (NS) during the acute phase of the disease (baseline) and after three months from hospital discharge (postCOVID, Tpost)

Materials and Methods: Hospitalized COVID-19 patients were enrolled. Plasma samples were collected for the evaluation of NfL and GFAP and sCD163 levels at both time-points. According to COVID-19 severity at acute stage of the disease, patients were stratified into severe and non-severe groups as well as based on the NS presence at both time-points into with and without NS groups.

Results: Study population included: 144 hospitalized COVID-19 patients and 53 heathy donors (HD). At baseline, higher NfL, GFAP and sCD163 levels in severe compared to the non-severe group were observed ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively). At baseline, higher NfL and GFAP levels in patients with NS on hospital admission compared to those without in both groups were observed (severe group: $p=0.0575$ and $p=0.0051$, respectively; non-severe group: $p=0.0427$ and $p<0.0001$, respectively). At Tpost, a significant reduction in NfL, GFAP and sCD163 levels compared to baseline was observed ($p<0.0001$, $p<0.0001$ and $p=0.0413$, respectively) although levels were almost higher compared to HD ($p<0.0001$, $p=0.0045$ and $p=0.0418$). At Tpost, higher NfL levels in both severe and non-severe groups compared to HD was observed ($p<0.0001$ and $p=0.0046$, respectively) while GFAP and sCD163 levels were still higher compared to HD only in the severe group ($p=0.0040$ and $p=0.0003$, respectively). At Tpost, patients with NS in the severe group showed higher NfL and GFAP levels compared to those with NS in the non-severe one ($p=0.0357$ and $p=0.0351$, respectively) as well as patients without NS in the severe group compared to patients without NS in the non-severe one ($p=0.0464$ and $p<0.0001$, respectively). Conversely, a higher sCD163 levels in patients with NS in the severe group compared to patients with NS in the non-severe one was observed ($p<0.0001$).

Conclusion: High NfL and GFAP plasma levels in COVID-19 could be due a proinflammatory systemic and brain response that involves microglial activation and sub-sequent neuronal damage. Our data highlight the association between myeloid activation and CNS perturbations. The recognition and diagnosis of these neurologic complications at both acute stage and post-COVID are challenging, particularly in the context of overstrained medical systems, where an under recognition or delays in diagnosis may contribute to poor outcomes.

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## NEUROEPIDEMIOLOGY

### POSITIVE PREDICTIVE VALUE OF ACETYLCHOLINE RECEPTOR AUTOANTIBODY TESTING BY RADIOIMMUNOPRECIPITATION ASSAY


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Background and Objective: Antibodies against the acetylcholine receptor (AchR-IgG) confirm a diagnosis of autoimmune myasthenia gravis (MG) when detected in serum of patients with compatible clinical phenotypes. Radioimmunoprecipitation assay (RIPA) is the gold standard for AchR-IgG detection with a reported specificity of ≈99%. However, its accuracy in large, unselected populations has not been fully elucidated. We determined the positive predictive value (PPV) and risk of false AchR-IgG positivity in a real-life setting.

Materials and Methods: We retrospectively identified patients consecutively tested for AchR-IgG by RIPA at the University-Hospital of Sassari between January 2003-March 2022 (n=4795). Medical records of patients with AchR-IgG positivity (antibody titer of ≥0.5 nmol/L) were independently reviewed by two neurology investigators to determine true vs false antibody positivity, based on clinical phenotype and/or presence of clear alternative diagnoses at last follow-up. AchR-IgG-positive patients with insufficient clinical information were excluded (n=84). Diagnostic performance was summarized with point specificity, positive predicted values and their 95% confidence intervals (CIs). Results: Of 362 AchR-IgG-positive patients included in the study, 50 (13.8%) were designated as false positives. Specificity and PPV were 98.9% (95% CI, 98.5-99.2) and 86.2% (95% CI, 82.2-89.6), respectively. Alternative diagnoses in patients with false AchR-IgG positivity included ocular diseases (n=8), rheumatic diseases (n=7), pseudoptosis (n=5), myopathy (n=4), isolated cranial nerve palsy (n=2), parkinsonism (n=2), migraine (n=2), demyelinating diseases (n=2), and others (n=18). Main reasons for antibody testing included isolated diplopia (n=18), nonspecific asthenia (n=16), isolated eyelid ptosis (6), or others. Compared to patients with true AchR-IgG positivity, false positive patients were younger (median age, 65 [range, 7-91] vs 38 [range, 5-80] years), more frequently female (155/312 [49.8%] vs 37/50 [74%]), and had a lower antibody titer (median, 6 [range, 0.5-28] vs 0.7 [range, 0.5-5.5] nmol/L); $p<0.01$. After stratification by AchR-IgG titers of ≥1 nmol/L, specificity and PPV increased to 99.8% (95% CI, 99.6-99.9) and 96.6% (95% CI, 94-98.3), respectively.

Discussion and Conclusions: Despite the high specificity of AchR-IgG testing by RIPA, the risk of false antibody positivity is not negligible in clinical practice (14% in this study). Caution is needed when low titer AchR-IgG positivity (0.5-0.9 nmo/L) is detected in patients with symptoms that are nonspecific for MG or explainable by more common alternative etiologies.

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### EPIDEMIOLOGY OF LATE-ONSET MULTIPLE SCLEROSIS: A POPULATION BASED-STUDY


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Background: Multiple Sclerosis (MS) is defined as Late Onset Multiple Sclerosis (LOMS) when the onset occurs after 50 years. LOMS patients might be underdiagnosed or misdiagnosed because they usually display a different disease phenotype compared to classical MS with a higher prevalence of Progressive forms (either primary or secondary), a more frequent motor or sensory symptom of onset and a faster disease progression. Across MS cohorts, the prevalence ranges from 0.6% to 12%, however little is known on the incidence of LOMS in the general population.

Aim: To study the annual incidence of LOMS in a population-based cohort.

Materials and Methods: Case ascertainment was conducted using as main sources the registries of all the MS centers of the province of Catania. Inclusion criteria were MS diagnosed according to McDonald criteria (2005) or subsequent revisions (2010, 2017); patients older than 50 years at the disease onset; onset between 2005-2020; resident in the province of Catania at the time of the onset. Incidence rates (IR) have been calculated for all the study period, according to sex, age classes and five years interval. Incidence rate ratios (IRR) have been computed to compare incidence rates.

Results: During the study period, 171 patients with LOMS were identified (104 women; 60.8%). The mean age at onset was 56 ± 6 years and the main phenotype was Relapsing Remitting MS (n=110; 64.3%), followed by Primary Progressive (n=34; 19.9%). The average annual crude IR was 2.7/100,000 person-years (pyar) (95% Confidence Intervals, CI 2.31-3.13). IR was 3.0/100,000 (95% CI 2.45-3.64) for women and 2.34/100,000 (95% CI 1.81-2.96) for men, with a female to male ratio of 1.29 (95% CI 0.94-1.77; p value = 0,11). Overall incidence risk was quite stable during the entire study period 2005-2020 (2.7/100,000 pyar). Nonetheless we observed an increased risk in the group aged 60-69 from 1.12/100,000 pyar during 2005-2010 to 3.12 during 2016-2020. When comparing the last quinquennum 2016-2020 to the first 2005-2010 the IRR was 2.79 (95%CI 1.13-7.81; p-value 0.01).

Conclusions: This is the first Italian population-based study exploring the incidence of LOMS. An increased IR over the time was observed in the age-group 60-69, possibly reflecting an increased age at onset of MS over the time. Although this increasing incidence in older people may be due to a better accuracy in diagnosis as well as to the aging of the general population, possible role of environmental factors cannot be excluded.

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## INCIDENCE OF MULTIPLE SCLEROSIS IN THE CITY OF CATANIA: A 45-YEARS OBSERVATIONAL POPULATION-BASED STUDY

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Background: Incidence of Multiple Sclerosis (MS) has been progressively increasing in Europe, with values ranging from 1.9/100,000 person years (pyar) in the fifties to 8.5/100,000 pyar in the years 2003/2007. However, in the last decades differences in temporal trends across European countries, especially considering high incidence areas, have been described. We have previously analyzed the incidence rates of MS in the city of Catania for a 30-years period (1975-2005), finding an increasing incidence.
Aim: To describe the incidence rates and temporal trends of MS in the city of Catania from 1975 to 2020.

Materials and Methods: Incident cases of MS have been ascertained using the registries of the main MS centers of the municipality of Catania. To be enrolled patients had to be diagnosed either with the Poser's criteria (cases between 1975 to 2001) or McDonald's criteria and subsequent revisions (cases between 2001 to 2020) and had to be resident in the city of Catania at disease onset. The onset adjusted annual incidence risk was based on the year of the clinical onset. Age and sex-specific annualized incidence rates have been calculated.

Results: From 1975 to 2020 a total of 718 incident cases were diagnosed in the city of Catania. Incidence steeply increased from 1.3/100.000 during 1975-1979 to 7.0/100.000 pyar during quinquennium 2000-2004 and showing a plateau soon after with substantially stable rates from 2004 to 2020 with an average annual crude incidence risk of 7.3/100,000 pyar. The average female to male ratio was 1.6 (95% CI 1.4-1.8, p value<0.0001) ranging from 0.8 (95% CI 0.35–1.61) in 1975-1979 to 1.8 (95% CI 1.2-2.8 p value<0.003) in 2016-2020. The mean age at onset increased steadily over the incidence study-periods from 23.9± 8.6 during 1975–1979 to 36.0±11.4 during 2016-2020.

Conclusions: MS incidence increased over time, reaching a plateau after 2004, possibly reflecting the effect of improvements in diagnosis and consequently a reduction in the time interval between clinical onset and diagnosis. The observed increasing age at onset might be the result of either improvement in diagnosis (through the use of MRI) or due to the effect of several environmental risk factor, whose relevance has changed over the years.
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## DISPARITIES AND INEQUALITIES FOR NEUROLOGICAL PATIENTS IN ITALY (DIS-NE-I)

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Objective: Health disparities and inequalities are important and a too long overlooked public health concern worldwide. These differences in health and health care can affect people with any disease, including neurological disorders. The aim of this systematic review was to provide an overview of the main health inequalities faced by neurological patients in Italy and identify the modifiable determinants of health injustice.

Methods: The main databases (PubMed, EMBASE) were searched systematically. Quality was assessed with the Mixed Methods Appraisal Tool. This review followed the standard guidelines of Preferred Reporting items for Systematic Reviews and Meta-Analyses (PRISMA).
Results: 1797 records was obtained with the search string and, after the title and abstract screening, we have included 215 studies eligible for the full-text screening. The studies included in the final round, of the review, will be subjected to quality appraisal. Finally, the results will be analysed and clustered by topic.

Conclusions: The expected results could highlight the current inequalities in neurological care in Italy. This information's can contribute to implement specific interventions to reduce differences and injustice and can be a useful start point for supporting policy maker in decision process.
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## DRUG USE IN PRESENCE OF CONTRAINDICATIONS IN MYASTHENIA GRAVIS: A REAL-WORLD COHORT STUDY IN ITALY - THE CAESAR STUDY

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Aims: To evaluate the use of pyridostigmine (Py) in presence of contraindications, and the use of concomitant potentially contraindicated drugs in a cohort of patients affected by Myasthenia Gravis (MG) in the Italian Regions of Lazio, Tuscany, and Umbria.

Materials: Administrative healthcare data were used to identify adults affected by MG (period 2013-2019). Among incident users of Py, the presence of contraindications (mechanical gastrointestinal/urinary obstruction, obstructive respiratory diseases, cardiovascular diseases, and mechanical ventilation) in the 2 years before the first prescription was evaluated. Among MG patients, the use of drugs with potential contraindications in the first year after enrolment was evaluated.

Methods: This is a retrospective cohort study. A multivariate logistic regression model was used to evaluate the determinants of Py and of potentially contraindicated drugs use in MG patients.
Results: Among 591 incident Py users affected by MG, 91 (15.4%) reported at least one of the contraindications considered at the first prescription of Py. Patients prescribed with Py in presence of contraindications were more frequently affected by diabetes, obesity, and renal diseases ($p<0.05$). Age 75+ years (odds ratio, OR 4.94, 95% confidence interval, CI 1.60-15.22 for Latium; OR 3.78, 95%CI: 1.26-11.34 for Tuscany; OR 5.83, 95%CI 1.19-28.52 for Umbria), the presence of at least one specific comorbidity (OR 3.93; 95%CI 1.68-9.17 for Latium), and polytherapy (6+ drugs, OR 4.90, 95%CI: 1.35-17.85 for Tuscany) were found to be significantly associated with Py use in presence of contraindications. Among patients affected by MG, 1,483 (62.6%) were treated with potentially contraindicated drugs in the first year of follow-up (66.9% in Latium; 59% in Tuscany; 57.6% in Umbria). Patients aged 75+ years, those with at least one specific complication or comorbidity, and those exposed to polytherapy were more likely to be treated with a potential contraindicated drug.

Discussion: The analysis of the determinants of Py use in presence of contraindications, and the use of concomitant potentially contraindicated drugs highlighted indicators of greater frailty, in particular for the covariates older age, comorbidities, and polytherapy.

Conclusion: Among incident users of Py, more than 15% of patients have at least one of the contraindications considered, and among patients diagnosed with MG, in the first year of follow-up >60% of subjects were treated with potentially contraindicated drugs.
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## POINT PREVALENCE OF EPILEPSY IN DEMENTIA: A "REAL WORLD" ESTIMATE

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Background: Several studies have demonstrated a higher frequency of seizures and epilepsy in Alzheimer's disease and other forms of dementia as compared with healthy elderly individuals [1,2]. However, incidence and prevalence of epilepsy in the general population of dementia are unknown since most previous studies were performed in secondary-tertiary referral centres. In addition all prior studies but one provided "period" rather than "point" prevalence estimates [3].

Materials and Methods: We assessed point prevalence estimate of epileptic manifestations requiring antiepileptic medication in patients Alzheimer's disease, vascular dementia, and frontotemporal dementia from a secondary clinical setting.

Results: Point prevalence estimates were 6.4% in Alzheimer's disease, 8.9 % in vascular dementia, and 6% in fronto-temporal dementia ($p=0.8$), rates that were greater than those observed in the healthy elderly population. Regardless of the etiology of dementia, epilepsy was characterized by unprovoked seizures that lacked distinguishing clinical features.

Discussion and Conclusions: These findings support epilepsy as part of the spectrum of dementia. The similar point prevalence of definite epilepsy requiring anti epileptic treatment in Alzheimer's disease and non-Alzheimer dementias raised the possibility of similar underlying mechanism of epileptogenesis. Although this was not a population-based study, accurate point prevalence data from clinic setting would be important to better define the burden of epilepsy in dementia and the demands on health services to manage the condition.
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## COVID-19 PANDEMIC IMPACT ON STROKE MANAGEMENT IN TRIESTE: A LOOK IN 2020, 2021 AND 2022 EMERGENCY EVOLUTION

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Background and Aims: COVID-19 pandemic has been the most impactful health event of the last century. Most worldwide studies have focused on the pandemic consequences on stroke management during first infection wave (spring 2020). In Italy COVID-19 pandemic went through various management phases adopted by Italian government following the infection waves, and emergency measures lasted until March 31st, 2022. Our aim was to expand the epidemiological investigation to the whole pandemic period.

Materials: We selected all patients admitted to Trieste Stroke Unit from January 1st, 2018 until December 31st, 2022.

Methods: We divided all the patients into seven groups, according to COVID government restriction measures: pre-COVID-19 phase (2018/01/01-2020/03/08), 1st COVID-19 wave (2020/03/09-2020/05/03), post-lockdown phase (2020/05/04-2020/06/14), phase of easing measures (2020/06/15-2020/11/05), 2nd COVID-19 wave (2020/11/06-2021/04/25), "green-pass" phase (2021/04/27-2022/03/31), post-emergency phase (2022/04/01-2022/12/31).

Endpoints were admission, treatments, and outcomes at various stages. We evaluated differences using Kruskal–Wallis test for numeric or Chi-square test for nominal variables. A level of $p < 0.05$ was considered statistically significant.

Results: We collected 1694 patients, 757 thrombolysis and 221 thrombectomies. The number of patients hospitalized per day reached the minimum during most restrictive measures (0,68 in 1st and 0,77 in 2nd wave vs 0,97-0,98 in pre-/post-emergency). Treatment was preserved all over the pandemic's various stages (p=0.415). Compared to pre-pandemic situation, 1st COVID-19 wave showed a decrease of patients with mRS 0-2 at discharge (34% vs 52%): functional independence returned to usual frequency in 2nd COVID-19 wave (47% vs 52%) but the amount of patients with mRS 5-6 increased (36% vs 26%, p=0.001).

Discussion: COVID-19 pandemic changed stroke management far beyond 2020: after a first decrease in admission, the following phases showed gradual recovery to a classical contest even if the pre-emergency situation is still returning. Nevertheless, neurological emergency treatment was preserved all over the pandemic: dedicated protected rooms, specific training for operators and quick Swab tests for each new stroke patient didn't affect the possibility of reperfusive therapies. As shown by mRS score, 1st COVID-19 wave showed a decrease in the percentage of patients with functional independence at discharge: this frequency returned to pre-pandemic condition in 2nd COVID-19 wave but the amount of totally dependent or dead patients increased.

Conclusions: Stroke management experienced other changes beyond the shocking first impact of the pandemic in 2020: although in different ways in its two main waves, the COVID-19 Era had an important impact on stroke patients' health in Trieste.

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## AN 8-YEAR, POPULATION-BASED STUDY IN CENTRAL ITALY: INCIDENCE OF ALS IN MARCHE REGION BEFORE AND DURING THE COVID-19 PANDEMIC


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Objectives: We sought to conduct a population-based longitudinal study in the Marche Region of central Italy to estimate Amyotrophic Lateral Sclerosis (ALS) incidence in this region, evaluate its trend between 2014 and 2021, and look for any variation during the COVID-19 pandemic (2020-2021).

Materials and Methods: We designed a longitudinal, population-based study of adults residing in Marche and listed in the regional registry as beneficiaries of the National Health System. Patients hospitalized for the first time with an ALS diagnosis (code 335.20 ICD-9 CM) or tagged with the disease-specific exemption code (RF0100) between 2014 and 2021 were considered incident cases. ALS cases residing for less than 3 years before the index date in the Marche Region, with a hospitalization for ALS, or with an exemption for ALS active in 2011-2013 were excluded. We used secondary sources to identify new diagnoses of ALS, in patients meeting the revised El Escorial criteria. The accuracy of secondary sources in identifying ALS incident cases was tested against the information included in the clinical database of the regional referral center for ALS. ALS mean incidence was computed as the ratio between the total incident cases and the regional population (12,223,809 p-y). A heatmap served to show the distribution of incidence rates according to the municipality of cases' residence. Incidence rate trend adjusted by sex and age was evaluated using Poisson regression model. ALS incidence in Marche Region was compared to that reported in similar studies conducted in other Italian regions.

Results: 425 new ALS cases (median age: 70y) were detected in the entire 2014-2021 period. The mean ALS incidence in the study period was 3.5 per 100,000 py (95%CI: 3.2-3.8; M:F = 1.22). No significant trend was observed during 2014-2019 period, but a significant mean decrease of 5.8% (95% CI 2.0%; 9.5%, p = 0.003) was observed after adding the 2020-2021 period to the Poisson regression model. ALS incidence in Marche was significantly higher compared to most similar studies conducted in other Italian regions.

Discussion and Conclusion: This observational study revealed a higher incidence of ALS in Marche, compared to other Italian regions, whose factors should be better investigated considering the role of environmental factors, occupational exposures and genetic features. We describe a significant decrease in ALS incidence over time. The understanding of the causes underlying this finding warrants a longer follow-up looking into ALS incidence trends after the pandemic.

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## MOVEMENT DISORDERS IN THE EMERGENCY ROOM: A NOT SO RARE OCCURRENCE FROM A PROSPECTIVE, OBSERVATIONAL STUDY


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Objectives: Although management of Movement Disorders (MD) is primarily outpatient, the recent identification of several dysimmune conditions mainly showing MD as a clinical phenotype has raised attention towards the association between Emergency Room (ER) and MD. This is a single-center, prospective, observational study exploring the acute MD occurrence and their associated clinical phenotype.

Subjects and Methods: Over a six-month-period (June-December 2021) data concerning subjects attending the ER for a new-onset MD or for worsening of a pre-existing MD were collected and analyzed. A pre-set questionnaire exploring: demographic data, information on past and present medical history (using Charlson Comorbidity Index) and therapy, MD-phenotype (hypokinetic, hyperkinetic, mixed), MD-severity (mild, moderate, severe), MD-distribution (generalized, axial, appendicular), MD-development pattern (acute, subacute, chronic); MD-duration (<24h; 24-48h; >48h); MD-awareness (anosognosic,

moderately anosognosic, fully aware) were utilized. Information about MD-fluctuations, MD-associated pain, ability to walk and indication for subject's hospitalization were also prospectively collected. Etiopathogenetic hypotheses on MD were also formulated according to the more common etiologies: vascular, dysmetabolic, infectious/inflammatory, worsening of pre-existing MD, epileptic, iatrogenic, lesional, functional, other. A Fisher's exact test was used to test the differences in proportions for categorical variables.

Results: Over a 6-month period, 1651 subjects admitted in ER were referred for an urgent neurological evaluation. Of these, 37 subjects (2.24%) had a new onset MD (n=25, 1.5%) or showed a worsening of a preexisting MD (n=12, 0.7%). Over two-thirds of acute MD were hyperkinetic in nature, tremor and corea being the most represented phenotypes (30% and 27% respectively). Autonomous gait was impaired in 62% of patients with acute MD, often leading to hospitalization (43% of acute MD-subjects). The iatrogenic, dysmetabolic and inflammatory origin were the most frequently hypothesized etiologies (in 27%, 10% and 10% of cases, respectively).

Discussion: Previous studies described a very low frequency of MD emergencies, ranging between 0.2% [1] and 0.073% [2]. According to our study, the occurrence of MD in emergency setting should not be considered rare, as it ranges between 1.5 and 2.24% of all subjects requiring urgent medical attention. Hyperkinetic movement disorders are undoubtedly the hallmark of acute MD and a particular sensitivity to detect hyperkinetic phenomenology should be encouraged also among ER personnel, to not miss severe and treatable conditions.

Conclusion: This study highlights that acute MD represent an important clinical entity in emergency settings despite the fact that literature on the frequency and underlying etiologies of acute MD is very scarce.

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## CLINICAL COURSE AND DEMOGRAPHIC FEATURES OF VEGETATIVE STATE/UNRESPONSIVE WAKEFULNESS SYNDROME PATIENTS IN A LONG-TERM RESIDENTIAL FACILITY


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Objectives: We aimed to characterize the clinical course and demographic features of Vegetative State/Unresponsive Wakefulness Syndrome (VS/UWS) patients in a long-term residential facility (RSD San Pietro, Monza).

Materials: Clinical registries of resident patients in a long-term facility with a diagnosis of VS/UWS from January 2014 to December 2021.

Method: Monocentric retrospective cohort study.

Results:113 patients with a new diagnosis of VS/UWS in the study period were included. The mean age at admission was 61,3 ± 16,2 years (range 18,7 – 88,3); 51,8% were female. According to ICD-9 codes, etiologies were cerebral hemorrhage (42,3%), including intraparenchymal, subarachnoid and traumatic mechanisms; trauma without hemorrhage (19%); anoxic brain injury (9,5%); ischemic stroke (6,9%); others including epilepsy, hydrocephalus, metabolic encephalopathies (22,3%). The Coma/Near Coma scale (CNC) categories were extreme coma (2,8%); marked coma (31,8%); moderate coma (39,3%); near coma (25,2%); no coma (0,9%). The Glasgow Coma Scale (GCS) at admission was 8 in 46,3% of cases, following a gaussian distribution of values in the interval 4 – 12. Survival probability by Kaplan-Meier curves at the maximum available follow-up was 12,6%, with a median survival of 100,7 months, grossly following a linear decrease.

Discussion: Compared to similar studies in other countries, we found hemorrhages to be the most common etiology of VS/UWS in our cohort. Pichler and Fazekas analyzed data from 19 VS/UWS patients in a single year and found anoxic brain injury to be the most frequent cause (63%), followed by hemorrhages (21%), and brain trauma (16%); a single case was due to ischemic stroke, while they did not report about other etiologies. This was in contrast to older studies, conducted in a timeframe between the late 1970s and the early 1990s, which indicated a predominance of traumatic brain injuries as causes of chronic disorders of consciousness (DoC). Both our and Pichler's findings could possibly reflect changing attitudes towards the withdrawal of life sustaining treatments in the acute stage after devastating brain injuries, as well as substantial advances in intensive care practices. Of note, our study was not designed to accurately stratify DoC patients into VS/UWS and minimal conscious state, due to the retrospective nature of the data.

Conclusions: Available epidemiological estimates show contrasting results about the predominant causes of VS/UWS. This knowledge gap would require future studies to follow a prospective, population-based design, to better inform stakeholders about resource allocation and care organization.

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## EPIDEMIOLOGY OF AQUAPORIN-4-IGG-POSITIVE NMOSD IN SARDINIA


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Objective: The Italian region of Sardinia (population, 1,587,413 people on December 2022) is a high-risk area for multiple sclerosis (MS), with an estimated prevalence of 330 per 100,000. It is unknown, however, whether the epidemiological burden of other demyelinating diseases of the central nervous system (CNS), such as aquaporin-4-IgG positive neuromyelitis optica spectrum disorder (AQP4-IgG+NMOSD), is similarly higher compared to other geographical settings. In this

study we aimed to determine the incidence and prevalence of AQP4-IgG+NMOSD in Sardinia.

Materials and Methods: Incidence was calculated between January 1, 2013, and December 31, 2022; whereas the prevalence day was December 31, 2022. Patients with a diagnosis of AQP4-IgG+NMOSD based on 2015 international diagnostic criteria were retrospectively identified using two different sources: 1) Archives of the MS Center Laboratory in Cagliari (reference and only laboratory for AQP4-IgG testing in the island); and 2) medical records of the four Sardinian reference units for treatment of MS and other CNS demyelinating disorders. Serum AQP4-IgG positivity was assessed by cell-based assay.

Results: A total of 45 cases were included in the study (incident, 30; prevalent, 41). The median age (range) at disease presentation was 51 (6-78) years and 96% were Caucasian. Female/male ratio was 9:1. The crude (95% CI) incidence and prevalence were 1.9 (1.3-2.6) per million person-years and 2.6 (1.9-3.5) per 100,000, respectively. Crude prevalence significantly increased from January 2013 (1.1 per 100,000; 18 cases over 1,640,379 people) to December 2022 (2.6 per 100,000; 41 cases over 1,587,413 people); p=0.002. After age-standardization to the world population, incidence and prevalence (95% CI) estimates decreased to 1.3 (0.8-1.9) per million and 1.8 (1.2-2.5) per 100,000, respectively. Among incident cases, the clinical syndromes at disease onset were longitudinally extensive myelitis in 21 (70%), optic neuritis in 4 (13%), brain/brainstem dysfunction in 3 (10%), or combinations in 2 (7%). Coexisting autoimmunity (either neurologic or systemic) were reported in 50% (mostly autoimmune thyroiditis). One incident case (4%) presented before 18 years of age.

Conclusions: Incidence and prevalence of AQP4-IgG+NMOSD in Sardinia are comparable to those reported in other Caucasian populations (≈1 per million and 0.8-3.3 per 100,000, respectively). The higher geographical MS risk in the island seems disease-specific and not associated with a higher risk of other CNS demyelinating disorders.

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## NEUROGENETICS AND RARE DISEASES

### APOLIPOPROTEIN E (APOE) HAPLOTYPES IN HEALTHY SUBJECTS: A WORLDWIDE POPULATION GENETICS AND SEX-BASED PERSPECTIVE FOR ANCESTRY-INFORMED GENDER MEDICINE


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Human APOE is a 299-amino acid long protein expressed and secreted in several tissues and body districts, where it exerts different functions mainly related to lipid metabolism, with specific activities around cholesterol transport and absorption/elimination. It has three main isoforms, determined by the pair of mutations rs7412-C/T and rs429358-C/T, which gives rise to the functionally different APOE variants ε2, ε3, and ε4. These have a distinct impact on lipid metabolism and are differentially implicated in Alzheimer's disease and neurodegeneration, cardiovascular disease, and dyslipidaemia. A plethora of other single nucleotide variants along the sequence of the APOE gene have been studied in cohorts of affected individuals, where they also modulate the influence of the three main isoforms to determine the risk of developing the disease. However, no contextual analysis of gene-long haplotypes has been carried out so far, and never extensively in cohorts of healthy individuals from different worldwide populations. Leveraging a rich, publicly available population genomics dataset, this study elucidates the distribution of APOE variants and haplotypes that are shared across populations and specific to macroareas, revealing a variety of risk-allele associations that distinguish peculiar ancestral backgrounds and can be leveraged for specific ancestry-informed screenings in medicine and public health. Moreover, when a dichotomous sex-based analysis is performed at a population and macroarea level, more subtle differences emerge in the distribution, frequency and sharing of haplotypes carrying protective and risk alleles that may be informative for a gendered approach to personalized medicine.

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### WORLDWIDE PARKINSON DISEASE RESEARCH: THE GLOBAL PARKINSON'S GENETICS PROGRAM (GP2)


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Background and Aims: The Global Parkinson's Genetics Program (GP2) is an international collaborative program that focuses on improving our understanding of the role of genetics in Parkinson Disease (PD) and on making this knowledge globally available and actionable. A substantial proportion of risk for PD is driven by genetics and these genetic links have advanced disease understanding and therapeutic development. Although much progress has been made, a majority of the heritable component of PD remains unknown. GP2 addresses these gaps, by working collaboratively and globally to collect and characterize hundreds of thousands of people representing diverse backgrounds and disease experiences. The three main scientific outcomes are: 1) enabling a dramatic expansion of knowledge on genetic PD risk 2) accelerating and improving genetic discovery of monogenic PD forms, and 3) making these findings globally relevant. Methods: Clinical data and blood/DNA samples of PD subjects and families, from existing global consortia and cohorts from around the globe are being collected and subjected to Neurobooster Array and, in a subset, to short and long-read whole-genome sequencing (WGS). For monogenic cases, we also developed the GP2 Monogenic Portal, an easy-to-use online electronic case report form (eCRF), to submit pseudonymized data of patients/families in whom a monogenic cause of PD is suspected. The collection of rich patient/family data will facilitate prioritization of samples for WGS, enable deeper analysis of genetic, clinical-demographic and environmental factors influencing disease expression. GP2 enables large scale data collection, production, analysis, and dissemination. Patients' genetic data generated in the project is returned to the referring clinician; moreover, harmonized data are made available to the scientific community at large for further research.

Results: To date, the GP2 has contacted ~150 potential contributors from >50 different countries. In Italy, 9 centers across the country are already registered to GP2. Array genotypes now consist of a total of 24,935 genotyped participants, while 722 individuals already underwent whole genome sequencing. More recently, GP2 is expanding to recruit at-risk populations for PD, such as individuals diagnosed with REM sleep behavior disorder or idiopathic hyposmia, as well as "atypical" parkinsonism cases.

Conclusion: GP2, with another seven years of project efforts ahead, will deepen and extend global understanding of the genetic basis of PD across diverse populations, including those currently underrepresented. Findings and data generated from GP2 will have wide implications for research and care of PD and other neurodegenerative diseases.

## CHARCOT-MARIE-TOOTH DISEASE 2C: A NOVEL MISSENSE MUTATION IN THE TRPV4 GENE

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Objective: With this study, we investigated the pathogenetic role of a novel heterozygous missense mutation (c.617G>A, p.Arg206His) in the TRPV4 gene, found in a Southern-Italy family with an axonal Charcot Marie Tooth disease (CMT). CMT type 2C is a peripheral neuropathy which is transmitted with an autosomal dominant manner caused by a mutation in TRPV4 gene, encoding for a Ca2+-permeable, nonselective cation channel.

Materials: Neurological examination, nerve conduction study, genetic analysis was performed in the proband and her family. Bioinformatic study of the mutation was also reported.

Results: We present a 32-year-old woman suffering from weakness of distal lower limbs, causing progressive walking disturbances and milder hand impairment. She underwent bilateral calcanear osteotomy and Achilles tendon lengthening (age 12 years). Neurological examination showed: mild pes cavus with hammertoes, stepping gait, positive Romberg sign, mild hypostenia of the intrinsic musculature of the hand (APB, ADM and FDI MRC 4/5) and more severe leg paresis (AT MRC=4/5; BDE and LAE MRC= 0/5), absence of deep tendon reflexes, bilateral needle hypoesthesia of the distal leg (CMTES= 10/28, CMTNS= 11/36). Electrodiagnostic studies showed an axonal, length-dependent sensorimotor polyneuropathy. The CMT panel showed a c.617G>A variant (p.Arg206His) in the TRPV4 gene. Family screening was performed: her mother and brother presented a milder clinical (CMTES 8 and 6, respectively) and electrophysiological phenotype. The same TRPV4 variant was identified in the affected family members.

Discussions: The c.617G>A (p.Arg206His) variant was never previously reported. Exome sequencing was negative for further pathogenetic known CMT genes. Its frequency in general population is lower than 0.01% (1/13,006 GO-ESP; 3/251,204 GnomAD). The CADD score is 19.69, predicting to be amongst the 1% most deleterious substitutions in human genome. Data collected about this gene seem to depose for a co-segregation familial model. Furthermore, this variant falls into the ARD2 (Ankyrin Repeat Domain) region, which is considered very important for regulation of cytoskeletal activity. Moreover, although the clinical and electroneurographic neuropathic phenotype is consistent with classical CMT2 cases, the affected members lack the auditory, vocal cord or respiratory system involvement, which are often reported in the disease [1].

Conclusions: According to ACMG guidelines [2], this variant is classified as probable pathogenetic in determining the disease.

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## SEIZURES, HYPOTONIA, MILD INTELLECTUAL DISABILITY AND DISMORFIC FACIAL FEATURES: A NOVEL MUTATION IN PRPS1 FOUND IN A 25-YEARS OLD MAN

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The PRPS1 gene codes for the enzyme phosphoribosyl-pyrophosphate synthetase-1 (PRS-1) that is a crucial enzyme in the de novo synthesis of purines and pyrimidine nucleotides. Mutations in PRPS1 may result in gain or loss of function for the protein. The spectrum of PRPS1-related disorders associated with loss-of-function mutations

includes Arts syndrome, Charcot – Marie – Tooth disease-5 and X-linked nonsyndromic sensorineural deafness. The phenotypes associated with gain-of-function mutations include PRPS-related hyperuricemia and phosphoribosylpyrophosphate synthetase superactivity. We report the case of a 25 years – old man who presented seizures, hypotonia, mild intellectual disability and dismorfic facial features, in which we identified a novel mutation in PRPS1. His pregnancy was characterized by prenatal growth restriction. At the age of 6 he presented a generalized epileptic seizure which was followed by other episodes. School support was needed from primary school. The patient experienced asthenia and muscle weakness even after minor efforts. In 2008 analysis of the karyotype and of the FMR1 gene was carried out, both reported within the norm. A EMG in 2019 showed mild signs of myogenic suffering in the lower limbs. When he referred to our department the neurological examination carried out during hospitalization showed bilateral distal weakness, loss of deep tendon reflex in the lower limbs and slight telekinetic tremor. The physical examination presented high and broad forehead, simplified ears, synophry, clinodactyly of the fifth toe bilaterally, sandal gap bilaterally, hollow left foot, kypho-scoliosis and stuttering. Consanguinity in the family was denied. The EEG showed episodic short sequences of theta activity at 5 hz in the left temporal region in the context of which sharper graphoelements are inscribed, without epileptiform abnormalities. Brain MRI were normal. A biopsy of quadriceps was within limits except for a predominance of type II fibers. A blood sample was acquired from the boy to perform analysis of genes associated with the clinical condition presented. The analysis carried out highlighted a hemizygous variant of uncertain clinical significance of the PRPS1 gene: c.307-3delT. The variant was inherited from the mother by a X – linked recessive condition. Mutations in PRPS1 is responsible of different effect in proliferating cells and postmitotic cells, resulting in an array of phenotypic presentations. The spectrum of recognized disorders caused by disruption of PRS-1 function is broad and more and more new mutations are being identified. With this novel mutation identified in our patient, we expand the already wide spectrum of PRPS1-related disorders.

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## DIFFUSE RADIOLOGICALLY ISOLATED LEUKOENCEPHALOPATHY (DRIL)


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Background and Aims: In adulthood, many (> 50%) leukoencephalopathies (LKENs) remain of unknown cause, despite extensive laboratory investigations [1]. In some cases, clinical and radiological findings can be sufficiently homogeneous to allow a classifying diagnosis useful for clinical practice. Objective of our work is to describe a condition we named "diffuse radiologically isolated leukoencephalopathy (DRIL)".

Materials and Methods: We reviewed the clinical and laboratory features of the asymptomatic adults with LKENs of unknown origin assessed from January 2004 to December 2018 in the Unit of Rare Neurological Diseases of Carlo Besta Neurological Institute, Milano, Italy, and in the Neuro-Metabolism Unit of Hôpital Pitié-Salpêtrière, Paris, France.

Results: We identified 19 subjects, 11 Italian (9 females) and 8 French (5 females), among 57 Italian (~20%) and 50 French (~15%) patients with unclassified LKENs assessed at our Institutions. These subjects underwent brain MRI at a mean age of 56 years (range 39-71) because of head trauma, headache, or nonspecific symptoms, and were referred to us for a supposed leukodystrophy. They all exhibited a supratentorial, diffuse, T2/FLAIR-hyperintense and T1-hypointense LKEN. There was evidence of neither brain injury at birth nor vascular risk factors. Neuropsychological assessment and neurophysiological testing were unremarkable. T2-star sequences, and, when performed, proton magnetic resonance spectroscopy, spinal cord MRI, gadolinium contrast-enhancement sequences, CSF analysis and muscle biopsy were normal. In the 15 followed-up patients no clinical sign or MRI change were observed after a median follow-up of 3 years (range 0.5-20). No mutation was identified using LKEN targeted-gene panels.

Conclusions: Our observations suggest the existence of a group of subjects, mostly middle-aged females, with a diffuse LKEN with stable demyelinating-like features on MRI that remains asymptomatic over the years. In all these subjects, LKEN was discovered when a brain MRI was performed for unspecific symptoms, likely unrelated to the widespread white matter abnormalities. The brain MRI findings lead to extensive, unsuccessful investigations, and cause anxiety to the patients by mimicking severe leukodystrophies, which were excluded by comprehensive next-generation sequencing testing. This condition could be referred to as "diffuse radiologically isolated leukoencephalopathy (DRIL)". As to the pathogenesis, myelin damage or neuronal loss seem unlikely based on lack of clinical abnormalities and unremarkable neurophysiological studies, and we speculated that the condition may reflect a brain water content increase due to blood-brain barrier permeability changes, as seen in the mitochondrial neurogastrointestinal encephalopathy syndrome TYMP-related (MNGIE) [2].

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## A NEW MUTATION DETECTED BY NGS IN MT-ATP6 GENE ASSOCIATED WITH MELAS AND IN SILICO 3D PROTEIN ANALYSIS


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Introduction: The possibility to utilize today tools for the 3D structural analysis of proteins based on artificial intelligence such as AlphaFold, allows to obtain with relative ease, very useful functional indications related to the modifications caused by gene mutations, comparable with those that can be obtained experimentally.
Objective: The aim was to understand the impact of mitochondrial gene mutations identified by NGS on protein stability by means of an in silico structural approach.

Materials and Methods: Thirdy DNA samples, previously analyzed for canonical diagnostic mitochondrial DNA mutations were deep sequenced in order to identify the possible mtDNA genetic determinants. The Precision ID mtDNA Whole Genome Panel was utilized and an Ion 318 Chip Kit v2 was subjected to the ION Torrent PGM sequencing machine. The sequences were reviewed by IGV, v2.1.13 software. The variants were annotated and filtered considering the type of pathogenic variants, the population frequencies and presence in database and an heteroplasmy >5%. Protein structures of interest were loaded as PDB files from UniProt on-line database ((www.expasy.org/). The PDB files by AlphaFold, were open and analysed using SPDBV viewer software version 4.1.

Results: After the alignment, the coverage analysis reported 100% of the on target reads, with a uniformity of the 99.9% and a mean coverage of 574x. We identified 27 non-synonymous variants with a MAF <1%. Among these variants, we focused our attention on the MT-ATP6 gene carrying the mutation m.9124A> G; p.T200A and associated with MELAS. The related protein belongs to the ATP sinthase intramembrane unit F0. The 3D structure of this protein with a polar non-polar variation (T200A) shows a loss of the intrachain H-bond at the H6 domain between residue 200 and 197.

Discussions and Conclusions: The new gene variant let us to suggest that at protein level the resulting alteration could distorce the H6 helical structure inducing an anomalous protein functionality related to Melas. Of interest is the observation that an analogous variant already identified, the A177T, on the H5 domain, associated with MELAS, determines also an H-bond alteration. Because the H5 and H6 alpha-helical are in a very near region, we therefore suggest that the protein functionality linked to this region (H5-H6) may be related to the MELAS phenotype.
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## ABNORMALITIES OF TRUNK ACCELERATION-DERIVED GAIT INDEXES IN SUBJECTS WITH GLUT-1 DEFICIENCY

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Objectives: Gait disturbances and movement disorders are frequent in patients with GLUT-1 deficiency, mostly represented by pyramidal, cerebellar, and extrapyramidal dysfunction. This study aimed to assess the ability of a set of trunk acceleration-derived gait indexes to identify gait unbalance in subjects with GLUT-1 deficiency, and to detect potential correlations with clinical and biochemical parameters.

Materials and Methods: We recorded a 30 meters gait of 10 subjects with GLUT-1 deficiency and of 10 age-, sex- and gait speed-matched healthy subjects (HS). Gait analysis was performed via an inertial measurement unit (IMU) placed at the lower back. Based on trunk acceleration patterns in the antero-posterior (AP), medio-lateral (ML), and vertical (V) directions, we calculated: spatio-temporal gait parameters, pelvic kinematics, harmonic ratios (HR), recurrence quantification analysis (RQA), stride length coefficient of variation (CV), the longest short term Lyapunov's exponent (sLLE), and the log dimensionless jerk score (LDLJ).

Results: When compared to the HS group, the GLUT-1 subjects showed lower values of HR AP, HR ML, single support (SS) phase, and cadence. Moreover, they showed higher values of CV, LDLJ AP, LLE AP, and double support (DS) phase duration. In the GLUT-1 group, HR AP negatively correlated with a positive history of recurrent falls ($r = -0.88$, $p = 0.03$), while CV negatively correlated with ketonemia ($r = -0.64$, $p = 0.04$).

Discussion: Subjects with GLUT-1 deficiency exhibited multiple alterations in the trunk acceleration-derived gait indexes. Interestingly some of these alterations correlated with clinical/biochemical features, such as history of falls and ketonemia.

Conclusions: IMU derived gait indexes are reliable in the detection of gait dysfunction in GLUT-1 deficiency syndrome. Hopefully we will be able to use these instrumental markers for the long-term follow up of patients and to monitor treatment response.
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## PHACE SYNDROME: CASE REPORT

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Objectives: PHACE syndrome (posterior fossa anomalies, hemangioma, arterial lesions, cardiac abnormalities/coarctation of the aorta, eye anomalies) is a rare condition whose etiology is still unknown, characterized by infantile large hemangiomas of face or neck and neurodevelopmental defects of heart, eyes, arteries and brain. Over 400 cases have been reported in scientific literature. Clinical trials are still open to consider a possible genetic involvement. We report the case of a 46 years-old caucasian woman who was diagnosed with PHACE.

Materials and Methods: She was evaluated at emergency department of our hospital due to epileptic seizure. Her medical history was positive for cerebral haemorrage at birth, epilepsy successfully treated with valproic acid and lamotrigine. She also underwent surgery due to infantile strabismus and was followed by psychiatrists due to persistent mood disorder. Her familial history resulted negative. She was unmarried and lived with her mother. She presented neurodevelopmental retardation (Wechsler Adult Intelligence Scale -WAIS IV score: 60). She attended compulsory education with support teacher and was right-handed.

Results: Neurological examination showed left moderate hemiparesis and sensory impairment. General examination showed short stature, left cheek cutaneous hemangioma extending to the left neck, bilateral proptosis. She performed brain computer tomography (CT) due to magnetic resonance imaging intolerance, which showed pontomesencephalic and right cerebral hemisphere hypoplasia, foramen Monroe colloid Cyst, right fronto-temporo-parietal lobes malacic area with ex -vacuo dilatation of right ventricle. Electroencephalography showed diffuse bilateral spike waves prevalent on the right hemisphere, consistent with neuroradiological pattern. According to 2016 revised diagnostic criteria (cutaneous hemangioma + 1 major criteria) diagnosis of PHACE syndrome was performed.

Discussion: PHACE syndrome is usually diagnosed during infancy, but also adult cases have also been reported (we recently described another adult caucasic patient with the same disease). Our patient has always been simply considered "mentally retarded" but a possible syndrome has never been taken into consideration. Unfortunately, she refused to perform brain magnetic resonance due to claustrophobia and psychosis while she is currently performing cardiovascular and ocular screening examinations. Sternal defects have been excluded such as thyroid disorders. We think that our case report can expand current literature.

Conclusion: We recommend to evaluate patients with segmental infantile hemangioma, expecially on the face, scalp and cervical region with clinical and imaging workup and considered PHACE among possible etiologies.

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## AUTOSOMAL DOMINANT SPG18: THE FIRST LARGE ITALIAN FAMILY


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Introduction: Hereditary Spastic Paraplegias (HSP) are clinically and genetically heterogeneous and are classified as "pure", when spastic paraplegia is the only symptom or "complex" when other clinical features are present. SPG18 is due to endoplasmic reticulum lipid raft associated protein 2 (ERLIN2) gene mutations. It was initially described as autosomal recessive HSP, but later two cases with an autosomal dominant (AD) inheritance were identified. Currently, 8 AR, 5 AD and 3 sporadic SPG18 cases have been reported.

Objectives: To describe clinical and molecular findings of a large Italian AD SPG18 family.

Materials and Methods: A detailed medical history inquiry, neurological examinations of the proband and family members were conducted. Patients underwent brain and cervical magnetic resonance imaging (MRI), electromyography (EMG), neuropsychological examination and whole exome sequencing. Sanger sequencing was performed to verify the genetic variation in the proband and family members. Velocity gradient assay on proband's fibroblasts was performed to investigate propensity of the mutated ERLIN2 to form oligomers.

Results: Five affected family members underwent neurological examination showing progressive spastic paraplegia. Age at onset ranged from four years old to 18. Brain MRI and EMG were unremarkable. Neuropsychological evaluation pointed out a borderline intellectual functioning in one patient. One patient reported generalized epilepsy. The proband's father died at 58 years old with a diagnosis of amyotrophic lateral sclerosis (ALS). Some of his siblings also died around 60 years old with an anamnestic history ascribable to ALS. Genetic analysis revealed the heterozygous missense mutation, c.502G>A (p.V168M), in ERLIN2 gene. It cosegregated with the disease in the affected patients and was not present in the healthy subjects. Velocity gradient assay indicated no differences in oligomerization between mutated and wild-type protein

Conclusion: We report a large Italian SPG18 kindred spanning three consecutive generations and supporting AD transmission pattern. While the AD SPG18 families, reported up to now, showed a pure phenotype, our kindred shows a complex phenotype characterized by intellectual disability in one and epilepsy in another patient. It came to light a broad intrafamilial phenotypic variability spanning from pure to complex HSP and to ALS. Our data strength p.V168M more frequent association to ALS. Biochemical assays unravelled that V168M does not affect the ability of erlin-2 to oligomerize, therefore, not supporting a dominant negative effect of the mutated protein. ERLIN2 mutations should be considered in Italian HSPs cases, particularly in patients with ALS positive familiar history.

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## A TREATABLE INHERITED METABOLIC DISEASE AS RARE CAUSE OF HEREDITARY SPASTIC PARAPLEGIA


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Severe 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency is a rare but treatable inherited metabolic disease associated with hyperhomocysteinemia leading to a neurological syndrome with variable age of onset and phenotypes including spastic paraplegia. We describe two unrelated adult males who presented to our Unit because of progressive gait disturbances with rigidity and mild weakness of lower limbs. The first case started to complain of stiffness at lower limbs and cramps at 33 years of age. He also suffered from depression. One year later he was

hospitalized because of generalized tonic-clonic seizures. Lab exams showed severe hyperhomocysteinemia, low folic acid and vitamin B12. EMG showed a sensorimotor neuropathy, Brain MRI showed cerebral and cerebellar atrophy and peritrigonal leukoencephalopathy. He underwent an NGS panel for HSPs and he was found compound heterozygous for the variants MTHFR c.1752+1G>T and c.1160G>A (p.Gly387Asp). The second case started experiencing gait difficulties since 16 years of age. One year later he was hospitalized due to a cerebral venous sinus thrombosis. Lab exams showed severe hyperhomocysteinemia, low folic acid and vitamin B12. Brain MRI showed periventricular leukoencephalopathy and a thin corpus callosum. He was affected by bipolar disorder and under treatment with lithium. The patient was found compound heterozygous for the variants MTHFR Arg345Cys and Asn483Ser. Both patients are currently under treatment with high dosage betaine, folic acid and vitamin B12 with stabilization of symptoms. MTHFR deficiency should always be considered as a possible cause of hereditary spastic paraplegias especially in the setting of an atypical, more accelerated clinical course and the presence of psychiatric disorders. Given the possibility of treatment, screening homocysteinemia should always be part of the diagnostic work-up of spastic paraplegias.

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## DELETION 15Q21.3-22.31 RELATED TO CEREBELLAR VERMIS HYPOPLASIA. A CASE REPORT


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Cerebellar vermis hypoplasia (Vm-Hyp) is characterized by an elective reduction of this portion of the cerebellum, which conserved its overall shape. Vm-Hyp is a rare malformative condition related to a wide variety of causes. Although, studies highlight a role of the cerebellum in not only sensory-motor functions, but also non-motor functions such as cognition, language and emotions. However, with difficulty, non-motor deficits are related to cerebellar malformations. In fact, Vm-Hyp is a rare and heterogeneous malformative condition which due to its etiological, clinical and neuroradiological characteristics is often overlooked and not considered. In fact, much more often Vm-Hyp is associated with clinical conditions in which there is a malformation of other portions of the central nervous system such as the brainstem or the basal ganglia. Here we report the clinical case of a young 29-year-old woman presenting an elective Vm-Hyp and a specific 15q21.3-22.31 deletion of about 7Mb. In fact, the neuroimaging investigation demonstrated the absence of malformations of other brain regions. In addition, other imaging analyses have evidenced the absence of malformative alterations in other regions of the body. The neuropsychological evaluation highlighted a serious impairment of practical-concrete skills, aimlessness, reduced social adaptation, medium-severe cognitive impairment. Although the correlation between the genetic deletion and Vm-Hyp is quite evident, further investigations are necessary to understand which cerebellar circuits are mainly compromised and which neuropsychological functions are most damaged.

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## CANVAS AND SLEEP DISORDERS: A PROSPECTIVE CROSS-SECTIONAL STUDY


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Objective: Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CAVANS) is a recessive late-onset ataxia caused by biallelic AAGGG expansions in the second intron of replication factor complex subunit 1 (RFC1) gene [1-2]. The aim in this study is to characterize, for the first time, sleep and its disorders in patients with genetically confirmed CANVAS.

Methods: Sleep was assessed by means of self-administered questionnaires and home-based polysomnography (PSG). Subjective sleep quality was assessed with Pittsburgh sleep quality index (PSQI), daytime sleepiness was assessed with Epworth sleepiness scale (ESS), and insomnia symptoms were assessed with Insonnia severity index (ISI). The presence of restless leg syndrome (RLS) was investigated with the administration of IRLS diagnostic clinical interview; in case of symptoms consistent with RLS, patients filled the IRLSSG severity scale. Symptoms of anxiety and depression were evaluated by means of Zung Self-Rating Anxiety Scale and Beck Depression Inventory short form, respectively.

Results: Eight patients with genetically confirmed CANVAS were enrolled (5 males, mean age: 64.1±7.3 years) with an average duration of disease of 13.9±7.2 years. Sensory axonal polyneuropathy and chronic spasmodic cough were present in all patients. Dysautonomia was reported in 5/8 patients. For what concern subjective sleep assessment, 5/8 patients complained poor sleep quality, 3/8 complained daytime sleepiness, 4/8 patients reported insomnia symptoms, 5/8 patients met the diagnostic criteria from moderate to very severe RLS. Four out to five patients with subjective poor sleep quality used sleep aids. The anxiety and depressive symptoms were present in 4/8 and 3/8 patients, respectively. PSG results showed a reduction of Slow Wave Sleep (N3/TST=15.2±13.0%) and REM (REM/TST=14.4±7.1%) and an increased wake after sleep onset (WASO=57.3±46.7 minutes). Obstructive sleep apnea (OSA) was present in 7/8 patients, ranging from moderate to severe (mean AHI=29.0±18.7), while 1/8 patients showed significant number of central sleep apnea; only one patient, with shorter disease duration (3 years from onset), did not show sleep-disordered breathing; only 2/7 patients with OSA reported daytime

sleepiness. Finally, 3/8 patients showed a periodic limb movement index over the cut-off.

Conclusions: Our data showed that patients with CANVAS have poor sleep quality, altered sleep architecture, and a high prevalence of sleep disorders, particularly of OSA, insomnia, and RLS. Although OSA is the most common disorder, daytime sleepiness was not reported in all patients [3]. Therefore, given the high prevalence of sleep disturbances, sleep assessment should be routinely performed in patients with CANVAS.

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## ERLIN 2 MUTATIONS IN AN ITALIAN SERIES OF PATIENTS: PHENOTYPIC AND GENETIC VARIABILITY

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Objectives: ERLIN2 gene mutations are associated to rare forms of hereditary spastic paraplegia (HSP) either autosomal recessive (AR) or dominant (AD), collectively known as type 18 (SPG18) [1]. The encoded protein is localized to lipid rafts of the endoplasmic reticulum and plays a critical role in inositol 1,4,5-trisphosphate signaling by mediating ER-associated degradation of activated IP3 receptors. About 13 families have been described worldwide (eight AR-SPG18 families, five AD-SPG18 families, and three sporadic cases have been reported) [2]. Clinical phenotype depends on the mode of transmission with AD-SPG18 as a juvenile-adolescent onset pure HSP, while AR-SPG18 is mostly a complicated HSP with earlier onset and more severe course. In rare cases, the initial spastic paraplegia could evolve to rapidly progressive motor neuron disease similar to amyotrophic lateral sclerosis (ALS) [3]. Brain MRI may display white matter alterations (WMA), thin corpus callosum. Herein, we report five patients with ERLIN2/SPG18, the largest series so far described in Italy.

Materials and Methods: Five patients were enrolled in 3 Italian centres, and underwent neurological examination, clinical cognitive assessment, brain MRI, and genetic analysis.

Results: Four subjects harboured a heterozygotic ERLIN 2 mutation (AD), with no family history in three, onset in childhood (1/4), 20-50 years (3/4). One patient harboured a double heterozygotic ERLIN2 mutation and infantile onset (AR). All showed a rather uniform phenotype including lower limb weakness and spasticity, mild impairment of vibration sense (2/4). One of the AD patients, the mother of another, after many years of spastic paraparesis developed rapidly evolving ALS-like with bulbar signs and lower motor neuron syndrome. Extra neurological manifestations included congenital cataract (1/5). Brain MRI showed WMA in 1/5.

Discussion and Conclusion: ERLIN2 was initially mapped in an autosomal recessive Turkish family with intellectual disability, motor impairment, and multiple joint contractures in 2011. Later ERLIN2 mutations were also identified in an autosomal recessive family with the complicated form of HSP in Saudi Arabia, which was designated as SPG18. Early reported families were all recessively inherited, complicated HSP. In 2018, two AD-HSP families caused by heterozygous ERLIN2 missense mutations [2]. This is the largest series of ERLIN2/SPG18 patients reported in Italy. In our series AD SPG18 seems to be more frequent than AR. The clinical phenotype ranges from early onset complicated HSP, both AD and AR, to mild adult onset HSP. In addition we observed one instance of HSP-ALS conversion phenotype. This confirms the wide phenotypic variability and raises the question of genetic counseling and prognosis.

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## USE OF LENADOGENE NOLPARVOVEC GENE THERAPY FOR LEBER HEREDITARY OPTIC NEUROPATHY IN EARLY ACCESS PROGRAMS

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Objectives: Lenadogene nolparvovec is a novel, as yet unapproved, gene therapy for patients with Leber hereditary optic neuropathy (LHON) due to the m.11778G>A MT-ND4 mutation. Through early access programs, patients with MT-ND4-LHON can benefit from lenadogene nolparvovec prior to marketing authorization.

Materials and Methods: Lenadogene nolparvovec was provided based on unsolicited requests and authorized for use by local regulations. Patients with confirmed MT-ND4-LHON received lenadogene nolparvovec as a unilateral or bilateral intravitreal injection at the dose of 9x1010 viral genomes/eye. Baseline characteristics, efficacy, and safety data were collected.

Results: Between August 2018 and March 2022, 63 MT-ND4-LHON patients received lenadogene nolparvovec in early access programs; 35 (55.6%) in France, 9 (14.3%) in Italy, 1 (1.6%) in the UK and 18 (28.6%) in the US. Overall, 42 (66.7%) patients were administered bilaterally; all but one received both injections on the same day. At first lenadogene nolparvovec injection, the mean (SD) age was 33.7 (16.6) years (median=31.0; range=13.0-74.0) and the loss of vision in the first affected eye had lasted for a mean of 11.30 (9.66) months. Idebenone therapy was ongoing in 81% of patients at the time of injection. Among the 63 patients, 45 patients have available data at one-year post-treatment. For these 45 MT-ND4-LHON patients, the mean (SD) change in BCVA from baseline to 1 year was 0.21 (0.69) LogMAR

(+10.5 EDTRS letters equivalent), and 29 were bilaterally treated and improved their BCVA at 1 year by -0.27 (0.76) LogMAR (+13.5 ETDRS letters equivalent). The safety of lenadogene nolparvovec was favorable with data comparable to those of the 189 patients treated in clinical studies.

Conclusion: Patients receiving lenadogene nolparvovec in the early access programs were predominantly European and received therapy mostly in both eyes. Preliminary efficacy and safety analyses show that lenadogene nolparvovec injection was associated with a clinically meaningful improvement of visual acuity and a favorable safety similar to that observed in clinical studies.

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## NEUROLOGICAL MANIFESTATION AND GENETICS OF PHACOMATOSES: A RETROSPECTIVE STUDY FROM UNIVERSITY OF PISA ADULT NEUROLOGICAL INSTITUTE

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Phacomatoses are a broad group of rare genetic multisystem conditions characterized by the development of slow-growing neoplastic formations of neuroectodermal and mesodermal origin. Tuberous sclerosis complex (TSC) and Neurofibromatosis (NF) (type I and type II) are among the most common types of phacomatoses and result from germline mutations in TSC1/2, NF1 and NF2 genes, respectively. Mutations can be de novo (most commonly) or familial with an autosomal dominant inheritance pattern. Intellectual/learning disability, seizures, sensorineural hearing loss and headache are among the most common neurological manifestations. In this study the aim was to assess the neurological manifestation and the genetic characterization of patients with phacomatoses referring to our adult neurological centre. A cohort of 39 patients (male 38.5%, female 61.5%) with a clinical suspect or a clinical/molecular diagnosis of TSC or NF was retrospectively studied. Genetic testing was performed using single gene or panel next-generation sequencing and Multiplex ligation-dependent probe amplification. Clinical and neuroradiological data were collected from the patients medical records. In our cohort a positive family history was present in 33,3% of cases. A clinical diagnosis was established mainly in adolescence (7 to 22 years old, 31.0%) or adult age (40 to 59 years old, 20.7%). A molecular diagnosis was reached in 27 cases, 5 resulted negative; 4 genetic testing are ongoing, in 2 cases molecular diagnosis performed in another center was unknown, 1 patient refused genetic tests. Mutations in NF1, NF2, TSC1, TSC2, and LZTR1 were found, establishing a molecular diagnosis of NFI (19), TSC (4), NFII (3) and Schwannomatosis (1). For NF1 mutations, the most represented were single nucleotide variants (68.4%), followed by deletions, duplications and insertions (6,9% each). NF1 most common mutation type were frameshift and missense (31.6% each) followed by stop codon, splicing and intronic variants (26.3%, 5,3% and 5.3% respectively). Neurological manifestations were present in about 50% of patients, the most common were epilepsy (35%), pediatric intellectual/learning disability (25%), headache (20%) and adult mood disorders (10%). A neuroradiological central nervous system involvement was present in 19/32 confirmed or suspected NF/Schwannomatosis and 7/7 confirmed or suspected TSC. Phacomatoses are complex genetic disease which commonly have neurological manifestations. Given the relative frequency of NFI (the most common autosomal dominant disorder of the nervous system) and the presence of recently approved drug able to control TSC-associated clinical manifestations, a deep understating of these conditions is needful for adult neurologists for a timely diagnosis and optimized management.

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## OCULODENTODIGITAL DYSPLASIA: DEEP NEUROLOGICAL PHENOTYPING FROM A TUSCAN PEDIGREE

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Oculodentodigital dysplasia (ODDD) is a rare congenital malformation syndrome characterized by craniofacial, ocular, dental, digital anomalies, and neurological symptoms with less than 300 cases described worldwide. ODDD is caused by mutations in the GJA1 gene (6q22-q23), encoding connexin-43, a gap junction protein. Inheritance is mostly autosomal dominant (AD) with high penetrance and variable expression. Neurological manifestations are thought to occur in approximately 30% of patients, including late-onset spastic paraparesis, ataxia, dysarthria, prominent bladder disturbances, hyperreflexia, seizures and developmental delay or mild intellectual disability. Brain MRI may show a mild hypomyelination leukodystrophy pattern and/or gray matter T2 hypointensity. The aim of this study was to describe the neurological phenotypes and neuroradiological features of 10 patients from a single Tuscan pedigree. We analyzed a large ODDD three-generations pedigree. Clinical and neuroradiological features were retrospectively collected from patients medical records. Brain MRI were performed in 5/10 patients (multiple time points from 2006), in 2 is scheduled. In June 2023 we performed a full neurological examination, collecting motor and cognitive scales. Patients harbored a heterozygous missense single nucleotide variant (c.416T>C, p.Ile139Thr) in GJA1 exon 2, classified as likely pathogenic (ACMG criteria). The pedigree was made up of 5 males and 5 females from three generations, 2 elderly patients (70 and 75 years old), 4 adults (from 43 to 55 years old), 3 adolescent (from 8 to 21 years old) and 1 infant (14 months old). Clear neurological symptoms were present in 5 of 10 patients. Neurological onset was characterized by late-onset slow-progressive gait disturbances (ataxia and spastic paraparesis) in 2 patients, neurogenic bladder (in the form of urinary urgency or urinary retention) in 2 patients, slight learning disability in 1 patient. The most common neurological features were spastic paraparesis/sign of lower limb pyramidal involvement (4/5), spastic ataxia (2/5), postural tremor (2/5), isolated ataxia (1/5) and mild cognitive decline (1/5). 2 adults had psychiatric disturbances (mild bipolar disorder and depression). Out of neurological features and typical syndromic characteristics, lower limb lymphedema was present in 3/5 females and bowel dysfunction (chronic diarrhea and fecal incontinence) reported in 3/10 patients. A

mild hypomyelination leukodystrophy pattern was recognized in 5/5 patients. ODDD diagnosis is often missed. Thus, the recognition of neurological manifestations, including lower limb slow-progressive pyramidal involvement and ataxia, and peculiar brain MRI patterns, in association with typical syndromic features should trigger the genetic evaluation of undiagnosed patients.

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## NOVEL PATHOGENIC VARIANTS INVOLVED IN AUTOPHAGY IN FRONTOTEMPORAL DEMENTIA: A WHOLE EXOME SEQUENCING STUDY

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Aim: Frontotemporal dementia (FTD) etiology has an important genetic component, the three most frequently involved genes, (MAPT, GRN and C9orf72) are implicated in about 5-10% of cases. The discovery of other causative genes opened new etiologic and therapeutic perspectives. Autophagy is one of the main intracellular mechanisms through which genetic alterations may converge on neurodegeneration. Beyond C9orf72, other autophagy associated genes mutations (in TBK1, OPTN, SQSTM1, UBQLN2, TDP43 and VCP) were demonstrated to cause FTD. The present study aims to identify gene variations by WES (whole exome sequencing) in a cohort of FTD patients with specific focus on genes involved in autophagy.

Materials and Methods: 78 patients (38 females, 40 males) were involved. They received a diagnosis included in FTD spectrum. The most frequent genetic variants known at the time of the diagnosis (MAPT, GRN and C9orf72) resulted negative. WES data were used to detect unknown variants in eight autophagy genes already associated with FTD and in twenty-three other autophagy genes. The American College of Medical Genetics and Genomics (ACMG) criteria were used to define novel variants as pathogenic, likely pathogenic or VUS (variants of uncertain significance).

Results: 4 novel variants classified as pathogenic were detected: three frameshift mutations (two in CHMP2B, one in UBQLN2) and one splice site variant of TBK1. Other two variants in UBQLN2 were classified as likely pathogenic. There were also 61 VUS affecting C9orf72, SQSTM1, TBK1, VCP, OPTN, CCNF, mTOR, ATG9, NDST3, AMPK, WDR41, TAX1BP1, WIPI2, YKT6, FIP200, STX17, ATG2A, ATG13, TMEM41B, TOLLIP, ULK1, BECN1, NBR1, NDP52 and STAU1. In five patients, we found the coexistence of pathogenic or probably pathogenic variants or VUS in autophagy genes already or not yet associated with FTD.

Discussion: Considering only autophagy genes, six patients are carriers of mutations classified as pathogenic or likely pathogenic. Five of them are oligogenic case, in which VUS and pathogenic variants coexist, involving gene products whit functional interactions. Together with subsequent confirmation by segregation and in vitro analysis, these novel variants will be reevaluated also considering the convergence on the same intracellular process and its effect on neurodegeneration.

Conclusions: Using WES in FTD cases not associated with the most frequent genetic variants could have an important clinical and research impact. Novel pathogenic variants will be further investigated to confirm their etiologic role. Moreover, this study deepens our knowledge about the association between FTD pathogenesis and autophagy, focusing on oligogenic cases.

## NEUROLOGICAL AND NEUROPSYCHOLOGICAL CORRELATES OF KLIPPEL-FEIL SYNDROME

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Background: Klipplel-Feil syndrome (KFS) is a rare congenital malformation characterized by the fusion of at least two cervical vertebrae. This condition leads to a classic triad of short neck, low hairline, and limited neck mobility, found in approximately half of all patients [1]. In KFS, neurological deficits are relatively common, primarily due to spinal stenosis, cervical spinal deformity, and vertebral instability [2,3].

Case presentation: A 66-year-old right-handed married man was referred to our neurological outpatient clinic. The man was a nurse and a drummer and only complained of dizziness after laughing. The neurological examination revealed multidirectional gaze-evoked nystagmus, more prominent on the left side, which was also inexhaustible. Hyperreflexia in the lower limbs was present and associated with an inconstant Babinski reflex. Ataxic gait was not evident, but he could not walk in tandem. At the inspection, the typical triad was found; thus, a diagnosis of KFS was hypothesized. Thus, an MRI scan of the brain was prescribed. The exam showed a complex cervical-occipital malformation, including the rise of the epistropheus above the line of Chamberlain, the fusion of the posterior arch of the atlas with the occipital squama, basilar impression, and downwards dislocation of the cerebellar tonsils. Platibasia (with the medulla and the pons compressed on the right lateral wall by a meningioma) was also evident. The fusion of multiple cervical vertebrae, associated with spinal canal stenosis and C4-C5 disc degeneration with myelopathy signs, were also present. A radicular cyst was finally reported. The patient also underwent neuropsychological evaluation, in which normal global cognition was found. However, borderline visuospatial scores emerged when performing the copy of the Osterrieth-Rey figure and the Trail-making tests.

Conclusions: Despite the extent of the underlying malformation, subjects with KFS may have a normal life and even perform complex motor tasks, as in the case of our patient, able to play drums at semiprofessional levels. Our patient's visuospatial functions showed borderline cognitive performance, but only follow-up will tell the possible evolution to full-course cognitive decline. The case demonstrates the remarkable levels of compensatory plasticity that the brain can set in motion even in the presence of major congenital defects.

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## HEREDITARY ATAXIAS: DIAGNOSTIC YIELD WITH NEXT-GENERATION SEQUENCING

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Hereditary ataxias (HAs) are a group of progressive monogenic rare neurodegenerative disorders characterized by a wide spectrum of ataxia-dominated phenotypes. Despite the identification of many causative genes, up to 50% of HAs cases still remain without a molecular diagnosis, mainly due to their vast clinical and genetic heterogeneity. Massive parallel next-generation sequencing (NGS) analysis broadened our knowledge of HAs genetic aetiology, consequently stimulating the trend toward genetically specific therapies. In this study, we aimed to assess the diagnostic yield of NGS panel and exome analysis in the clinical practice of our setting. A cohort of 111 patients with a clinical diagnosis of HA but no molecular confirmation was studied. In 7 patients the segregation analysis was performed to determine the genetic diagnosis. NGS panel (26 genes) and/or clinical exome sequencing (CES) were performed in the case of inconclusive first-line genetic tests for spinocerebellar ataxias (SCA1-3, 6-8,12,17), DRPLA, Friedreich's ataxia (FRDA) or phenotype-guided specific single gene sequencing ("traditional genetic tests"). By means traditional genetic tests a molecular diagnosis was achieved in 35,3 % of patients. 86,1% were short tandem repeats and the three most common were FXN (35,5%), ATXN2 (25,8%), and RFC1 (12,9%). Of 61 patients with HAs of indeterminate genetic origin, 43 underwent new molecular evaluation using NGS approach; for 2 patients NGS was performed directly. In 8 of 45 (17,8%) pathogenic or likely pathogenic variants were found. In 7 of these 8 patients, the diagnosis was made by CES. Genes mutations identified as causative of hereditary ataxia were found in SPG7 (1), CACNA1G (1), EEF2 (1), PRKCG (1), KCNC3 (1), ADCK3 (1), SYNE1 (1), ITPR1 (1). Finding ADCK3 and ITPR1 mutations by CES in two probands, allow us to identify the same mutations in other affected family members by Sanger sequencing. Furthermore, in 13,3% of patients (6/45) one or more heterozygous variants classified as VUS were detected in genes correlated with autosomal dominant form of HAs, particularly in FAT3 (1), FAT2 (1), STUB1 (1), ITPR1 (1), CTBP1 (1), IFRD1 (1) and CACNA1A (1). Overall, we present daily practice evidence that for about 20% of the patients with a clinical diagnosis of HA, but no molecular diagnosis on routine genetic testing, a definitive diagnosis can be reached with the NGS approach, especially using CES.

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## DNA APTAMER-BASED APPROACH: AN EMERGING TOOL TO FIGHT HUNTINGTON'S DISEASE

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Introduction: Aptamers, comprising single-stranded DNA or RNA, are molecular-recognition agents, predominantly emerged in the last years as valuable therapeutic candidates for several human diseases. Despite the exceptional advances made in Huntington's disease (HD) research, nowadays no definitive treatment is available for this invalidating progressive neurodegenerative disease, caused by elongation of CAG repeats in huntingtin (HTT) gene. Recently, a set of guanine-rich aptamers (named MS1 to MS4) able to preferentially recognize full-length HTT with an expanded polyglutamine tract has been identified, pointing out the use of these aptamers as promising approach in HD [1,2].

Methods: Biological characterization of MS3, which was emerged the best aptamer in this series, and its two truncated variants (named MS3-33 and MS3-17) was performed in SH-SY5Y cells, the widely used human neuronal cell line derived from neuroblastoma. Moreover, the biological impact of MS3 and MS3-17 aptamers was evaluated in the widely used immortalized striatal cell line model of HD stably expressing human expanded HTT (STHdhQ111/111) in comparison with wild-type counterpart (STHdhQ7/7) as well as on a well-established Drosophila melanogaster model for HD (Q128HD-FL).

Results: By confocal microscopy analysis we show a rapid, dose-dependent uptake of fluorescein-conjugated aptamers in SH-SY5Y cells, demonstrating their effective internalization with no general cytotoxicity. In addition, they are stable over time as evidenced by the presence of fluorescent signal 72 hrs after their wash out of medium, further supporting the feasibility of their in vivo use. Remarkably, these aptamers are readily taken up and persist even in STHdhQ111/111 cells, in comparable manner to STHdhQ7/7 cells. Since mitochondrial dysfunction seems to play a fundamental role in the pathogenesis of HD, by imaging and biochemical assays we have investigated the effect of the aptamer treatment on mitochondrial dynamics and functions. Interestingly, we observed that the tubular morphology of mitochondria was restored in STHdhQ111/111 MS3- and MS17- treated cells, indicating that the aptamer treatment promotes mitochondrial network organization Consistently, the expression of the mitochondrial fusion machinery was increased in treated cells. Finally, a significant improvement in the motor neuronal function and lifespan of transgenic flies fed with these aptamers was observed, proving their in vivo efficacy.

Conclusions: Overall, these data unravel the efficacy of these targeting mutant huntingtin aptamers both in vitro and in vivo. Thus, they highlight the relevant therapeutic potential of DNA aptamer-based approach for HD.

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## EFFECT OF GBA MUTATIONS AND GENDER ON NEUROPSYCHOLOGICAL FEATURES OF PARKINSON DISEASE AT DIFFERENT DISEASE STAGES

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Objective: To investigate the contribution of GBA mutations and gender on depressive and anxiety symptoms in patients with Parkinson Disease at different stages.

Methods: GBA-mutated (GBA-PD) and non-mutated (NM-PD) patients underwent a comprehensive clinical characterization (MDS-UPDRS I-II-III-IV, MOCA, SCOPAUT, UPSIT, RBDSQ, Pain, BDI and HADS-A). Clinical scores were compared between the two groups. To further investigate the neuropsychological profile of GBA-PD patients, subgroup analyses were performed upon stratification for disease duration (early stage: <6 years, intermediate: between 6 and 10 years, and advanced: > 10 years) and for gender. Correlation analyses were also investigated.

Results: 52 GBA-PD (56% males) and 84 NM-PD (64% males) were enrolled. Within GBA-PD, 9 subjects carried mild (17.31%), 18 severe (34.62%), 15 risk (28.85%) and 10 unknown (19.23%) variants. Overall, 45% (n=23) GBA-PD presented a clinically relevant depressive burden (BDI cut-off>13) compared to 19% (n=15) of NM-PD. BDI and HADS-A scores were also significantly higher in GBA-PD than NM-PD. Interestingly, when stratifying by gender, such higher BDI and HADS-A scores emerged only in GBA-PD males compared to their NM-PD counterparts, while scores were similar in females from both groups. Indeed, this observation was further substantiated when comparing genders within each group, as NM-PD males showed lower BDI and HADS-A scores compared to females, while no differences emerged in the GBA-PD group. The use of antidepressants and anxiolytics drugs was comparable between both PD groups and gender subgroups. When PD groups were stratified by disease duration, at early disease stage both BDI and HADS-A scores were significantly higher in GBA-PD than in NM-PD, while no differences were noted in intermediate and advanced stages. Moreover, differences in BDI and HADS-A scores between GBA-PD males and NM-PD counterparts were even more significant in the early stage while they were lost in the other disease stages. Finally, BDI and HADS-A scores in GBA-PD did not correlate with other clinical motor and non-motor parameters.

Conclusions: GBA-PD patients showed a greater burden of depressive and anxious symptoms, especially in the early disease stage. Noteworthy, this difference was mainly driven by GBA-PD males compared to NM-PD counterparts. This worse neuropsychiatric profile was unrelated to the severity of motor and non-motor symptoms. These data underscore the importance of early detecting and properly treating neuropsychiatric symptoms in GBA-PD, since GBA mutations confer a greater risk of mood disorders and male gender may affect this association.

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## EMERGING ROLE OF SERUM MIRNAS AS NOVEL LIQUID BIOPSY BIOMARKERS IN NEUROFIBROMATOSIS TYPE 1 AND RELATED CLINICAL COMPLICATIONS

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Aims: Neurofibromatosis type 1 (NF1) is a neuro-cutaneous genetic disorder caused by dominant mutations in the NF1 gene and characterized by heterogeneous clinical presentation with increased susceptibility to developing benign and malignant tumors. Dysregulation of gene expression can cause complex disease phenotypes. MicroRNAs (miRNAs) function in post-transcriptional gene regulation acting as both tumor suppressors and oncogenes in a wide variety of human cancers. Several studies have reported the potential role of circulating miRNAs to mirror physiological and pathophysiological conditions functioning as biomarkers for various diseases. To date, the role of circulating miRNAs in NF1 remains poorly investigated. We aimed to identify serum miRNAs profiling as novel diagnostic and prognostic biomarkers associated with NF1 phenotype and with disease severity. Material and Methods: The study included 126 NF1 patients, enrolled at Division of Neurology of AOU Luigi Vanvitelli and diagnosed based on the NIH Consensus Conference criteria of 1988. We stratified the patients into clinical severity progression groups (G1-G5), ranged from mild to severe phenotype, as reported in our recent NF1 genotype-phenotype correlation study [1]. To identify miRNA as circulating biomarkers of NF1 disease, small noncoding RNA sequencing (sncRNA-seq) for pooled serum samples, followed by qRT-PCR validation analysis for the best miRNA signature in independent samples were performed. miRNA-gene network analysis was investigated using IPA (Ingenuity Pathway Analysis) tool.

Results: sncRNA-seq results showed 87 deregulated serum miRNAs. A concordance expression pattern between sncRNA-seq and qRT-PCR data for seven miRNAs was found, suggesting their association with NF1 disease. IPA analysis revealed that the candidate miRNAs regulate multiple genes biologically connected to each other and mainly involved in the molecular signaling linked to development and progression of cancer, such as MAPK and PI3K/AKT/mTOR signaling, that are the most studied downstream pathways of neurofibromin, protein encoded by NF1.

Discussion: NF1 is characterized by a highly clinical variability. This study revealed for the first time the role of a panel of seven miRNAs as novel liquid biopsy biomarkers of NF1 and related clinical complications, paving the way for the exploration of their influence in the NF1 disease. Future studies should validate these results in a larger multi-centric cohort of patients.

Conclusions: Our findings highlight a role of circulating miRNAs in NF1 pathogenesis, thus representing future therapeutic targets of NF1disease.

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## A CASE OF MOG ANTIBODY DISEASE IN A PATIENT WITH HISTORY OF RECURRENT ADEM AND ATAXIN 1 GENE EXPANSION

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Introduction: Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) is an autoimmune disease of CNS. Here we describe a case of MOGAD in a patient with expansion of ataxin-1 gene (ATX-1).

Case presentation: A 29 year-old-girl was admitted to our hospital with paraesthesia in both feet, hypoesthesia of left limbs and gait ataxia, occurring few days after SARS-COV-2 infection. She inherited a 44-long CGG triplets expansion in ATX-1 gene from her father who had a diagnosis of spinocerebellar ataxia type 1 (SCA1). The patient had a history of recurrent acute disseminated encephalomyelitis (ADEM) and bilateral optic neuritis during childhood following infectious diseases. During each relapse, brain MRI showed typical post-contrast enhancing white matter lesions, completely disappearing after corticosteroid therapy. Repeated lumbar punctures revealed transient oligoclonal bands, while antibodies against MOG and Aquaporin-4 (AQP4) always tested negative, as well as genetic tests for LHON, MELAS and CADASIL. During the hospitalization in our department, brain and spine MRI showed a new lesion in right semi-oval center and a C3-C4 white matter lesion in the posterior columns without post-contrast enhancement as well as unchanged gliotic lesions and cerebellar atrophy. Laboratory tests showed IgM and IgG positive for Herpes Simplex virus 1. Intravenous methylprednisolone was administered, with progressive complete resolution of symptoms. Serum anti-MOG IgG was detected by cell-based assays (CBA) and confirmed by a second test. Based on the clinical history (ADEM, optical neuritis and transverse myelitis) and the anti-MOG antibodies positivity a diagnosis of MOGAD was made [1]. A 9-month follow-up showed the disappearance of spinal cord lesion at MRI and an unremarkable neurological examination with no relapses.

Discussion: To the best of our knowledge this is the first report of a patients with MOGAD and ATX-1 gene expansion. Even though gene ATX-1 is strictly related to SCA1, recent studies have suggested its role in other degenerative and autoimmune neurologic diseases. Indeed, ATX-1 seems to have an immunomodulatory mechanism by regulating B-cells functions and protecting from demyelination in animal models [2].

Conclusion: Since the genetic component in the pathogenesis of MOGAD is still unknown, future studies on patients with coexisting ATX-1 mutations could help elucidating this gene's possible role in the development and clinical course of the disease.

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## CALPAIN1-RELATED HEREDITARY SPASTIC PARAPLEGIA: NOVEL EVIDENCES FROM A SOUTHERN ITALIAN PATIENT

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Introduction: Hereditary spastic paraplegias (HSPs) are a group of clinically and genetically heterogeneous neurodegenerative diseases, characterized by progressive spasticity and weakness of lower limbs. More than 80 causal genes have been associated to HSP with all classical modes of monogenic inheritance reported. Clinically, HSPs are classified as pure when spastic paraplegia is the only symptom or complex when it is associated with other clinical features, such as ataxia, seizure, cognitive decline, extrapyramidal symptoms and peripheral neuropathy. Recessive mutations in the CAPN1 gene have recently been identified in spastic paraplegia 76 (SPG76), a complex hereditary spastic paraplegia (HSP) often combined to cerebellar ataxia [1].
Objective: To describe clinical and molecular findings of an Italian patient affected by SPG76.

Materials and Methods: Neurological, neuroradiological, neurophysiological and neuropsychological examination was conducted in a HSP patient from Southern Italy. Next generation sequencing-based HSP gene panel testing was performed and the causative variant was confirmed by Sanger sequencing. Furthermore, we investigated protein expression by Western blot analysis.

Results: The patient was a 43-years-old man born from first cousins. Onset was at 15 years old with running impairment and falls. Neurological examination disclosed sever spastic gait possible only with bilateral supports with increased muscle tone and weakness in lower limbs, brisk upper and lower limbs reflexes, bilateral ankle clonus and Babinski signs. No sensory alterations were detected, while cerebellar ataxia signs were present. Notably, the patient presented spastic dysarthria, urinary urgency and a cyclothymic disorder in a borderline personality. Nerve conduction studies were normal. Motor evocated potentials showed an impaired central conduction in the four limbs. Brain MRI showed thinning of the splenium of the corpus callosum. Genetic analysis revealed a homozygous truncating mutation in CAPN1 (c.1153C>T; p.R385*). As expected, at western blotting analysis the truncated protein was not detectable in patient fibroblasts.

Discussion: We describe a new Italian SPG76 patient with a complex form of HSP characterized by cerebellar signs less evident than pyramidal ones. Up to now, 50 families have been reported worldwide [2]. Only few Italian patients have been described; one of these with the same mutation as our case, suggesting a possible founder effect [2,3]. This patient showed an overlapping neurologic phenotype except of sensory deficit, not present in our patient, and absence of psychiatric disturbances.

Conclusions: Taken together, these evidences suggest an increasing role of CAPN1 in the pathogenesis of HSP, particularly in the Italian population.

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## HARMONIZING GENETIC TESTING FOR PARKINSON'S DISEASE: RESULTS OF THE PARKNET MULTICENTRIC STUDY

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Background and Objectives: Early-onset Parkinson disease (EOPD) commonly recognizes a genetic basis, thus EOPD patients are often addressed to diagnostic testing based on next-generation sequencing (NGS) of PD-associated multigene panels. However, NGS interpretation can be challenging in a diagnostic setting, and few studies have addressed this issue so far.

Methods: We retrospectively collected data from 648 PD patients with age-at-onset (AO) less than 55y who underwent NGS of a minimal shared panel of 15 PD-related genes as well as PD-MLPA in eight Italian diagnostic laboratories. Data included a minimal clinical dataset, the complete list of variants included in the diagnostic report. and final interpretation (positive/negative/inconclusive). Patients were further stratified based on AO≤40y (vEOPD, n=157). All variants were reclassified according to the latest ACMG criteria. For classification purposes, PD-associated GBA1 variants were considered diagnostic.

Results: In 186/648 (29%) patients, the diagnostic report listed at least one variant, and the outcome was considered diagnostic (positive) in 105 (16%). After reanalysis, diagnosis changed in 18/186 (10%) patients, with five shifting from inconclusive to positive and 13 former positive being reclassified as inconclusive. A definite diagnosis was eventually reached in 97 (15%) patients, of whom the majority carried GBA1 variants or, less frequently, biallelic PRKN variants. In 89 (14%) cases, the genetic report was inconclusive.

Conclusions: This study attempts to harmonize reporting of PD genetic testing across several diagnostic labs and highlights current difficulties in interpreting genetic variants emerging from NGS-multigene panels, with relevant implications for counselling.

## RETINAL VASCULOPATHY WITH CEREBRAL LEUKOENCEPHALOPATHY: A CASE WITH A NEW TREX1 MUTATION

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Aims: We report the case of a 46-year-old Italian man with a retinal vasculopathy with cerebral leukoencephalopathy (RVCL-S), initially misdiagnosed as glioma, and to underline the red-flags of this rare disorder.

Materials and Methods: A 46-year-old Italian man presented with a 5-day history of mild ideo-motor slowdown, subacute mild left hemiparesis and dysarthric speech. Brain MRI showed a right temporo-insular large lesion with surrounding edema and inhomogeneous enhancement that suggested cerebral lymphoma or glioma. He underwent cerebral biopsy revealing focal necrosis with reactive gliosis and modest perivascular lymphoid infiltrate. One month later he presented focal motor to bilateral tonic-clonic seizures and he started lacosamide. He repeated a brain MRI showing a dimensional increase of the lesion (restricted at diffusion weighted imaging and peripheral enhancement). Medical history included microvascular liver disease since 11 years before, microvascular kidney disease since 10 years before, anemia and a 13-year of scleroderma with Raynaud's phenomenon. Family history was negative (two healthy sisters, no children).

Results: Infective/autoimmune and tumoral screenings were unremarkable, and cerebrospinal fluid analysis negative. On oral steroids, a third brain MRI demonstrated volumetric reduction of the lesion with small nodular enhancement. Considering the pseudotumor onset and the multisystemic involvement, RVCL-S was suspected and confirmed by the identification of an heterozygous novel frameshift mutation (p.S267Qfs*57) in the C-terminal of the three-prime repair exonuclease (TREX1) gene.

Discussion: RVCL-S is a rare autosomal dominant vasculopathy caused by heterozygous C-terminal truncating mutations in TREX1 gene. The clinical spectrum includes vascular retinopathy, focal brain dysfunctions and other systemic manifestations, including Raynaud phenomenon, anemia with gastrointestinal bleeding, hypothyroidism, liver and kidney diseases. In our patient systemic symptoms developed several years before the onset of neurological manifestations. To date, there is no specific disease modifying treatment for RVCL-S. Our patient was treated with a course of intravenous methylprednisolone followed by oral glucocorticoids gradually tapered, anti-seizure drug, iron supplementation, blood transfusions for anemia and antihypertensive drugs. He started clinical and radiological follow-up: the last brain MRI, performed in May 2023, showed a severe dimensional increase of the lesion and the surrounding edema. Genetic counseling was discussed with family members (one healthy sister tested was negative for the mutation).

Conclusions: A pseudotumoral brain lesion might suggest RVCL in patients with ongoing systemic diseases. Recognition of this entity may help avoid unnecessary invasive examinations and therapeutic interventions.

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## JUVENILE ALEXANDER DISEASE: A CHALLENGING CASE OF A FAMILIAR PROGRESSIVE ATAXIA

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Case presentation: A 20 years old female came to our attention for gait ataxia and subtle involuntary movements. Moreover, she had scoliosis and history of enuresis and began some years before. The neurological examination evidenced difficulties in balance and walking, nystagmus in the horizontal gaze bilaterally, clonus at ankles with plantar cutaneous reflex in extension bilaterally and sporadic dystonic movements in her face and upper limbs. Her mother experienced since childhood ataxia with a rapidly progressive course, diagnosed as Primary Progressive Multiple Sclerosis. The similar phenotype, made an inherited cause highly probable. However, no other know relatives suffered from neurologic syndromes. Both autosomal dominant (AD) and autosomal recessive (AR) ataxic syndromes were considered, lacking a part of proband's pedigree, but not causative genetic alterations were found. Then, brain MRI evidenced T2 symmetric hyperintensities in medium cerebellar peduncles, basal ganglia, bilateral insula, and periventricular white matter, with thalamus sparing. Basing on these MRI findings and on the presence of cerebellar involvement and dystonia, we investigated Wilson Disease, a rare AR disorder of copper metabolism, which resulted negative too. Considering the strong suspect for an inherited condition, we performed a clinical exome sequencing (CES), that analyzes more than 4500 genes associated with diseases. CES evidenced the new heterozygous missense variant c.260T>A in exon 1 of glial fibrillary acidic protein (GFAP) gene (NM_002055.4), that causes the valine to aspartate aminoacidic substitution at codon 87 (p. Val87Asp) in the GFAP. The same heterozygous variant was detected in her mother.

Discussion: Damaging variants in GFAP are responsible for Alaxander's disease (AxD, MIM # 203450), a rare AD neurodegenerative disorder caused by the glial fibrillary acidic protein accumulation in astrocytes. AxD presents an age-related clinical spectrum with well-defined characteristics in both children (neurodevelopmental regression) and younger (seizure, ataxia, spasticity, scoliosis, autonomic dysfunction), with non-specific neurological manifestations in adults [1]. The c.260T>A in GFAP we found has never been described to date, either in general population or AxD cases. However, it it is in a mutational hot spot domain of the protein and is considered pathogenic by the most relevant pathogenicity scores (MetaLR 0.94; Revel 0.93). Moreover, different aminoacidic changes at the same codon (p. Val87Ile p.Val87Leu; p.Val87Gly) were previously described in late onset AxD patients [2]. This data, together with the maternal segregation and the phenotypes of the two women, are in favor of a pathogenic role of the p.Val87Asp substitution in determining the disease [3].

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## RILUZOLE IN SPINOCEREBELLAR ATAXIA TYPE 7: REPORT ON TWO FAMILIES

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Introduction: SCA7 is a very rare form of dominant cerebellar ataxia, caused by the expansion of a CAG repeat within the ataxin 7 (ATXN7) gene. Encouraging data on riluzole effects in patients with cerebellar ataxias [1,2] prompted us to try an off-label use of riluzole in an Italian and an American family with SCA7.

Methods and Results: A Peruvian-Algerian family had five members (4 female, 1 male) with progressive vision impairment and ataxia associated to abnormally expanded CAG repeat within the SCA7 gene in one allele. At baseline, before the onset of riluzole treatment, the SARA scores of Patients I-1, II-1, II-3 were respectively 20, 11, 9 while patient II-2 was 0; visual acuity was less than 1,0 logMAR in patients I-1 and II-1, equal or better than 1,0 logMAR in patients II-2 and II-3. It shows that after riluzole treatment the only patient treated before ataxia onset (patient II-2) had a significantly slowing of visual deterioration and no ataxia is yet occurring at last follow-up after 3,5 years. The remaining three patients, in whom riluzole therapy was introduced after ataxia onset, showed a clear stop of the pre-treatment steep increase of SARA

scores, showing decrease/stability of neurological deficit for 2-3 years, before the restart of ataxia worsening. No effect on visual function was observed in patients II-1 and II-3, while an improvement/stability was evident in patient I-1. Two female siblings (51 and 60 year-old), assessed at Tampa Center (US) reported visual disturbances and were diagnosed as SCA7 (39 and 40 repeats respectively). They were followed up by ophthalmological examinations and neurological examination for several years. In late 2010 they started riluzole After one year of therapy cerebellar and visual functions improved (respectively from 8 to 6 at SARA score and from 0.6 to 0.4 at logMAR) in both siblings. SARA score remained stable for 3 years and then started to increase (13 at the last evaluation - 6 years after the beginning of the treatment in both siblings), while ophthalmologic status remained practically stable in both siblings, since they started the drug. None of treated patients had adverse events or abnormal laboratory findings all over the follow-up.

Conclusions: Data from these families suggest some efficacy and safety of riluzole, even on long-term follow-up. A controlled trial is ongoing in Italy, and open to foreign Centers, that was granted by the Agenzia Italiana del Farmaco.

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## SPASTIC ATAXIA AND MOTORNEURON DISEASE AS POSSIBLE MANIFESTATIONS OF ATP13A2 VARIANTS

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Aim: To describe 5 late-onset sporadic cases carrying either biallelic or monoallelic variants in ATP13A2, showing either spastic ataxia (Spatax) or primary lateral sclerosis (PLS) as core phenotype.

Materials and Methods: Two Spatax patients (Patient 1 and 2) resulted negative for FXN, FMR1 and polyglutamine expansion-associated cerebellar ataxias and three patients with upper motor neuron features (Pt 3-5) underwent next-generation sequencing (NGS) targeted resequencing panels for ataxia and motor neuron disease, respectively.

Results: Spatax cases comprised two females with late-onset (63 and 52 years, respectively) gait difficulties. Neurological examination showed cerebellar and spastic signs in both patients, with more severe spasticity in Pt1, who was wheelchair-bound after 7 years from onset. Brain MRI showed cerebellar atrophy in Pt1, while was normal in Pt2. Pt1 carried the monoallelic p.Gln382Ter variant in ATP13A2, while Pt2 had the p.Met766Val variant. Pt3-5 had upper motoneuron features as core phenotype, with mean age at onset of gait difficulties at 57 years. Pt3 was a 72-year female showing PLS phenotype with mixed cerebellar and spastic dysarthria and cerebellar atrophy at brain MRI. Pt4 was a 56-year male with PLS and nystagmus, mixed cerebellar and spastic dysarthria and white matter abnormalities (WMA) at brain MRI, evolving to amyotrophic lateral sclerosis (ALS) in about 6 years. The last case, Pt5, was a 73-year female with HSP phenotype at onset, evolving to ALS after about 5 years from onset, with WMA at brain MRI. Pt3 carried the p.Arg1158Cys ATP13A2 variant, Pt4 was a compound heterozygous for p.Gly1115Cys and p.Pro1074=, whereas Pt5 carried the c.1039+6C>T and p.Gln1103Arg variants (segregation analysis was unavailable). Except for the p.Gln382Ter, which was predicted to be pathogenic, all the other variants in ATP13A2 were classified as variants of uncertain significance (VoUS).

Discussion: ATP13A2 is a lysosomal P5-type transport ATPase, whose transported substrate remains unidentified, with a pivotal role in both lysosomal function and mitochondrial network integrity. Biallelic pathogenic variants in ATP13A2 have been associated to Kufor-Rakeb disease, ALS, HSP, and neuronal ceroid lipofuscinosis. More recently, also a possible causative significance for monoallelic variants has been suspected, with a role as a risk factor for Parkinson's disease and Multiple System Atrophy.

Conclusions: Even in the heterozygous state, functional impairment of ATP13A2 might predispose to accelerated age-associated mitochondrial dysfunction. Functional studies on fibroblast-patient derived cells are needed to define pathogenicity of these VoUS in ATP13A2. If confirmed, this will expand spectrum of ATP13A2 variants associated phenotypes.

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## A NOVEL MUTATION IN MFN2 IS ASSOCIATED WITH ALS-FTD IN AN ITALIAN FAMILY

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Introduction: MFN2 gene encodes the protein Mitofusin 2, involved in essential mitochondrial functions such as fusion, trafficking, turnover, and cellular interactions. Mutations of MFN2 gene have recently been identified as the cause of approximately one-third of dominantly inherited cases of the axonal Charcot-Marie-Tooth disease (CMT type 2A) and of rarer clinical variants, including a severe, early-onset axonal neuropathy, in some instances associated with pyramidal tract involvement (CMT type 5), optic atrophy (CMT type 6), and, occasionally, alterations of cerebral white matter [1,2]. More recently, in a mouse model of ALS, MFN2 protein has been found to interact in complex with Transactive response DNA-binding protein of 43 kDA (TDP-43), involved in frontotemporal lobar degeneration (FTLD) and ALS [3].

Objective: We describe a family carrying a novel MFN2 mutation associated with an ALS-frontotemporal dementia (FTD) phenotype in the mother and a CMT2A in her son.

Methods: Patients underwent a multidimensional assessment including neurological and neuropsychological evaluation, structural and functional imaging, and genetic screening.

Results: The mother, a 67-year-old woman, referred to us for a three year-history of mood disturbance and gait impairment, and a more recent hypophonia, dysarthria, dysphagia, and diffuse muscle wasting. Family history was positive for psychiatric disorders and gait

disturbances. Brain 18F-FDG PET showed severe hypometabolism in the fronto-temporal brain cortex bilaterally. Electrodiagnostic studies (EDX) showed severe motor axonopathy in the bulbar, cervical and lumbosacral districts. Her 41-year-old son had a history of mood depression and sensory disturbances in the limbs, along with mild muscle wasting, weakness, and reduced reflexes. Nerve conduction studies revealed a moderate sensory-motor polyneuropathy, while brain MRI was normal. Whole exome sequencing of the patients' DNA identified a novel mutation in the MFN2 gene (NM_014874.4 c.581A>C p.(Asp194Ala).

Discussion: Our findings provide evidence for the significance of a newly discovered MFN2 mutation observed in two family members, each displaying distinct clinical manifestations. Additionally, we present the first documented case of ALS-FTD associated with an MFN2 mutation, thereby expanding the range of MFN-related disorders.

Conclusions: Further research involving larger cohorts of patients will be needed to better understand the role of MFN2 as a contributing gene in the development of ALS-FTD.

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## A NOVEL SPAST-MUTATION IN HEREDITARY SPASTIC PARAPARESIS SPG4

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Introduction: Hereditary spastic paraparesis (HSP) defines a wide variety of inherited neurological diseases affecting the upper motor neuron sustained by heterogeneous genetic mutations corresponding to diverse clinical phenotypes [1]. To date [1], over 100 loci/88 genes and 83 different clinical forms have been been associated to HSP. Nevertheless, SPAST (encoding for spastin) remains so far the most common gene mutated in HSP, identified in over 40% of cases. SPAST-associated forms (called SPG4) have usually an adult-onset result as a pure corticospinal degeneration. In this study, we characterize a novel homozygous SPAST mutation in an italian woman who presented a lower limb predominant spastic paraparesis and suspect but not characterized familiar history.

Materials and Methods: A 56-years-old italian woman was referred to our clinic for clinical and genetic evaluation. Molecular analysis was performed in 2022 by the means of a targeted massive sequencing panel (Illumina NextSeq).

Results: Patient's mother presented progressive difficulties in ambulation at 46 years old, one of mother's brothers was referred to walk "on toes' tip" since young age and one mother's female nephew (daughter of a brother) had multiple sclerosis. At 57 years old, the patient started to complain subtle onset of left lower limb weakness, specifically after an accidental fall. The symptoms became more pervading in 2019, when the patient started with the first exams (motor evoked potentials -MEP-, MRI), negative. In 2020 MEP resulted alterated and at the begin of 2021 the patient came at our attention. Neurological examination revealed a modest bilateral spastic paraparesis and diffuse brisk tendon reflexes. MRI studies resulted again negative while MEP resulted highly alterated. Therefore the patient was addressed to our genetic unit. Molecular analysis showed a novel c.1617-2A>C splicing variant in the SPAST gene, never reported on current databases.

Discussion: In this report, we described a novel SPAST-gene mutation. We assume an association to SPG4 since a single substitution of the same nucleotide was reported as pathogenic in a case of SPG4 [2], an adjacent variant is reported with low frequency [2] and patient's clinical presentation is consistent SPG4-phenotype. Nevertheless, our patient is the only affected member of the family that could be studied. We would then conclude that this novel SPAST variant is responsible for the clinical picture observed in the present case and could be classified as a novel pathogenic variant. However, further observations are needed.

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## MATERNAL UNIPARENTAL ISODISOMY IN A PATIENT WITH AUTOSOMAL RECESSIVE SPASTIC PARAPLEGIA TYPE 20

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Background: Hereditary spastic paraplegia (HSP) refers to a group of rare neurodegenerative disorders with the predominant clinical manifestation of spasticity in the lower extremities. A complicated form is identified by the presence of other neurological or non-neurological manifestations such as seizures, dementia, muscle atrophy, ataxia, intellectual disability, peripheral neuropathy, extrapyramidal disturbance, gastroesophageal reflux, Dupuytren's disease, or varicose veins. Autosomal recessive spastic paraplegia type 20 (SPG20) is a form of complicated HSP characterized by an onset in infancy of progressive lower extremity spasticity and weakness associated with distal amyotrophy, pseudobulbar palsy, motor and cognitive delays, mild cerebellar signs (dysarthria, dysdiadochokinesia, mild intention tremor), short stature and subtle skeletal abnormalities. SPG20 is due to mutations in the SPART gene (13q13), which encodes the protein spartin.

Objective: We studied a 10 years old boy with spastic paraparesis, dystonic movements, mild intellectual disability, speech impairment, multiple congenital anomalies, white matter abnormal signs and sensorimotor neuropathy. Array-CGH 60K showed a deletion in chromosome 17p12 including PMP22 gene, inherited from the father. This deletion, associated with hereditary neuropathy with liability to pressure palsies (HNPP), was not sufficient to explain the complex phenotype of the patient, therefore we extended molecular genetics studies.

Methods: We performed mutation analysis using whole exome sequencing (WES) and homozygosity mapping using SNPs-array.

Results: WES analysis showed the homozygous nonsense variant c.1120C>T (p.Q374X) in the exon 4 of the SPART gene. While segregation analysis in the mother, as expected, identified the SPART variant in a heterozygous state, it could not be displayed in the father. High resolution SNPs-array analysis provided evidence that the homozygosity of the SPART variant in the patient is due to maternal uniparental isodisomy (UPiD) in chromosome 13q.

Conclusions: Uniparental disomy (UPD) occurs when a person receives two copies of a chromosome, or of part of a chromosome, from one parent and no copy from the other. UPD can result in clinical conditions by producing either homozygosity for recessive mutations or aberrant patterns of imprinting in humans. Both UPiD and uniparental heterodisomy (UPhD) could result in imprinting disorders, while only UPiD or UPiD/UPhD could result in autosomal recessive disorders through the inheritance of deleterious alleles from a carrier parent. Our result highlights the importance of segregation analysis in both parents of a patient, especially in cases of homozygous recessive mutations, as UPD has significant implications for genetic counselling with a very low recurrence risk assessment in such families.
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## CEREBELLAR ATAXIA WITH OCULOMOTOR APRAXIA TYPE 1: CLINICAL AND GENETIC STUDIES


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Objective: To describe the clinical and genetic features of a family with a non-Friedreich progressive ARCA.

Design/Methods: Two brothers of a consanguineous marriage with progressive cerebellar ataxia were recruited in this study. After written informed consent a genome sequencing were performed.

Results: A 47 year old man was unsteady since the age of 10 years and three years later he developed cerebellar ataxia and ocular abnormalities. He presented with a slowly progressive gait impairment. Neurological examination was characterized by ataxia, oculomotor apraxia and dystonia. There was decreased deep tendon reflexes and neuropsychological tests were normal. Brain magnetic resonance imaging showed cerebellar atrophy. A genetic panel sequencing for AOA including APTX (aprataxin), SETX (senataxin), PIK3R5, PNPK genes was performeds and disclosed a pathogenic homozygous variant (p.Ala198Val, c.593C>T ) in the APTX gene, confirming the diagnosis of AOA1. The same APTX variation (p.Ala198Val, c.593C>T) and a heterozygous variation in SETX (p.Arg2098Ter, c.6292C>T) were identified in the brother of the proband. In the neurologic examination, dysarthric speech, dysmetria, dysdiadokinesis, instability and ocular apraxia were present. The symptoms began in adolescence and slowly progressed into adulthood. There was evidence of cerebellar atrophy on cranial magnetic resonance imaging.

Conclusions: This is the first report of an Italian family with c.593C>T mutation in APTX gene. In our patients, AOA1 typically manifests with gait ataxia in the first decade of life, followed by dysarthria and upper limb dysmetria and oculomotor apraxia. This description validate concept that the diagnosis of some movement disorders should rely on genetic testing and clinicians should consider this when reporting cases of inherited movement disorders.
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## COMBINING MT-TL1 AND MT-ND1 GENE MUTATION: CASE REPORT OF MELAS DURING PREGNANCY AND LITERARY REVIEW


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Objective: Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is one of the most frequent mitochondrial disorder [1]. We present a 36-year-old pregnant woman with stroke like episode (SLE) who received a genetic diagnosis of MELAS syndrome during hospitalization. The peculiarity of our patient consisted in presenting together the heteroplasmic m.3243A>G mutation in the MT-TL1 gene and homoplasmic mutation m.3394T>C in the MT-ND1 gene. Moreover, we reviewed the cases of pregnant women with MELAS present in the literature.

Methods and Materials: We performed a systematic review using keywords as "MELAS" or "mitochondrial disease" and "pregnancy".

Results: A 36-year-old woman at 6th week pregnant was admitted to our hospital for SLE, presented with migraine, followed by sudden acute onset of bilateral neurosensorial hearing loss, and bilaterally asymmetrical temporal cortico-subcortical hyperintensity in T2/FLAIR and DWI weighted sequences on brain magnetic resonance imaging (MRI). Arterial blood gas analysis presented elevated lactate levels. Genetic analysis showed both abovementioned mutations. At 10th week appeared coma, breathing failure and severe metabolic acidosis with spreading of cerebral lesions to parieto-occipital and cerebellar cortices on brain MRI. We identified 15 case reports (mean age 31.5±5.65, mean week of pregnancy 23.13±10.02) of pregnancy-induced worsening of MELAS. MELAS syndrome was diagnosed during pregnancy in 5(33,3%) cases due to abrupt worsening of clinical condition. The reason of hospitalization were obstetric complications in 7 cases (47%), neurological symptoms in 4 cases (27%), cardiovascular complications in 2, medical evaluation before childbirth and for chronic kidney disease in other ones.

Discussion: The physiological change of pregnancy, with its increased respiratory demands, suggests that women who already have mitochondrial dysfunction may be at risk of worsening symptoms [2]. Frequently, pregnant women with MELAS have obstetric complications and these are patients with a known diagnosis (40%). Among the women who received a diagnosis during pregnancy (n=5), as in our case, neurological symptoms are more frequent (60%) (2 had myopathy, 1 epilepsy). Therefore, despite the approach to patients with MELAS must be multidisciplinary, the neurologist plays a central role in the management. M.3394T>C mutation is a rarely associated with Leber's hereditary optic neuropathy, but the significance of this mutation is not fully understood [3].

Conclusion: Our findings suggest that m.3394T>C mutation may contribute to the MELAS phenotype. Furthermore, we confirm pregnancy is a risk factor for worsening of symptoms in MELAS.

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## QARS-RELATED EPILEPTIC ENCEPHALOPATHY CAUSED BY A NOVEL MISSENSE VARIANT: A CASE REPORT

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Aim: To identify the genetic cause of developmental and epileptic encephalopathy in a 5-year-old female patient.

Materials and Methods: Neurological exam, EEG, brain MRI, and trio-based whole-exome sequencing were performed.

Results: The patient was born 45.5 cm long (<3rd centile) at 41 weeks. At 11 months, she was 67.9 cm long (-2.2 SD). Head circumference and body weight remained around the 3rd centile. Brain ultrasonography showed two little subependymal germinolytic cysts around the left caudo-thalamic groove. At 3.5 years, she displayed focal epilepsy with occipital paroxysms and autonomic involvement (resembling Panayiotopoulos syndrome); recurrent occipital spikes and spike-wave were recorded during non-REM sleep EEG; brain MRI was normal. At 5 years, a viral pharyngitis triggered an acute encephalopathy with psychomotor slowing. EEG showed fronto-temporal θ activity and recurrent occipital spikes on a middle-high amplitude δ-rhythm background activity. Brain MRI showed subcortical white matter T2-hyperintensity and DWI restriction compatible with intramyelinic edema and hypomyelination, mild cerebellar-prevalent global atrophy, and minimal cerebellar tonsil elongation. She was treated with corticosteroids and improved within two weeks. She is currently seizure-free with carbamazepine and levetiracetam, displays a constitutional growth delay, and a mild language delay allowing her to pronounce simple sentences. Whole-exome sequencing revealed two compound heterozygous variants in the QARS gene (NM_005051.3): c.1304A>G (p.Y435C) and c.799C>T (p.R267W). The p.Y435C is a known pathogenic variant. The p.R267W is extremely rare (gnomAD allele frequency: 0.0000159), is predicted pathogenic in silico (MetaRNN: 0.9368) and affects a conserved aminoacidic residue (phyloP100: 9.206).

Discussion: Biallelic loss-of-function variants in QARS, encoding glutaminyl-tRNA synthetase, cause an autosomal recessive encephalopathy with 23 cases reported to date. Its clinical features include neonatal-onset pharmaco-resistant epilepsy, intellectual disability, constitutional growth delay, speech delay, brain atrophy with cortical structural abnormalities and hypomyelination. Phenotypic severity correlates with Qars enzyme aminoacylation activity, solubility, and affected domain: some missense variants allow a residual aminoacylation activity though lowering solubility, resulting in milder phenotypes. The p.Y435C affects the catalytic domain impairing the interaction between Qars and its tRNA. The p.R267W, also in the catalytic domain, has never been associated with disease, however, its rarity, the presence of supportive in silico predictions, and its combination with a known QARS pathogenic variant in a patient with a compatible phenotype, strongly supports its pathogenic role.

Conclusions: We expand the spectrum of QARS-related disease to a milder form displaying infection-triggered acute reversible encephalopathy in association with two missense variants, of which one is novel.

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## RARS2-RELATED ENCEPHALOPATHY: A CASE OF ATAXIA-EPILEPSY DUE TO A NOVEL SPLICING VARIANT AND REVIEW OF THE LITERATURE

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Aim: To identify the genetic cause of ataxia-epilepsy in a 16-year-old patient and draw a genotype-phenotype correlation for this rare disease.

Materials and Methods: The patient was evaluated by a pediatric epileptologist and movement disorders expert neurologists. Electroencephalograms and a brain MRI were performed. Whole-exome sequencing (WES) was followed by segregation analysis with Sanger sequencing. Functional analyses included cDNA sequencing, western blot, and mitochondrial respiratory chain activity assessment on peripheral lymphocytes.

Results: Disease appeared at 3 years with mild cerebellar ataxia and cognitive impairment. At 13 years, the patient was hospitalized for focal-to-bilateral tonic seizures with unresponsiveness. EEG displayed sharp waves and 3 Hz spike-wave discharges. Levetiracetam was started with complete seizure control. Brain MRI showed an isolated cerebellar vermis atrophy. At 15 years, neurological examination showed cerebellar dysarthria, gaze impairment, dysdiadochokinesia, dysmetria, postural and kinetic tremors, multidirectional oscillations at Romberg's test, gait ataxia with tandem gait inability. WES revealed two heterozygous variants of RARS2 (NM_020320.5), encoding mitochondrial arginyl-tRNA synthetase. Segregation analysis demonstrated their biallelic status: c.685C>T (p.Arg229*) is a known pathogenic variant, while c.972C>T (p.Thr324=), affecting the third-to-last nucleotide of exon 11, is extremely rare (gnomAD allele frequency = 0.000004), reported likely benign in ClinVar, but predicted in silico to likely impact splicing. cDNA analysis demonstrated that c.972C>T is a splice-disrupting variant excluding exon 11, though allowing the synthesis of some wild-type transcript, consistently with the patient's mild phenotype in comparison to other patients with RARS2-related encephalopathy. Mitochondrial respiratory chain activity was not significantly different from two healthy controls. Western blot in triplicate revealed a moderate reduction (~39%) of normal-length Rars2 protein in patient's lymphocytes compared to two healthy controls.

Discussion: A clinical phenotype compatible with a mild form of RARS2-related encephalopathy and the presence of the compound

heterozygous status with the p.Arg229*, led us to reclassify the c.972C>T splice-disrupting variant as likely pathogenic (ACMG criteria: PM2, PM3, PS3) and hypothesize that the phenotypic severity is negatively correlated with the amount of residual functional Rars2 protein. Hence, we reviewed scientific literature on RARS2-related encephalopathy delineating a genotype-phenotype correlation, as variant severity, including protein impact (e.g., missense, nonsense, splice-disrupt) and affected domain (e.g., catalytic core, anticodon-binding domain), is well correlated with disease onset, survival, neurological and systemic features, neuroradiological and biochemical profiles (e.g., respiratory chain activity).

Conclusions: A prompt genotypic characterization of RARS2-related encephalopathy is important to predict the phenotype, improving diagnostic counselling, follow-up, and assistance for patients and caregivers.

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## NEUROIMAGING

### CHOROID PLEXUS ENLARGEMENT AS MARKER OF CHRONIC INFLAMMATION AND NEURODEGENERATION IN MULTIPLE SCLEROSIS: A COMBINED 3- AND 7-TESLA IMAGING STUDY

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Aim: Choroid plexus (CP) enlargement has been recently evaluated in multiple sclerosis (MS) as a novel imaging marker of compartmentalized inflammation. We investigated, in a heterogeneous MS cohort, the association between CP enlargement and imaging metrics of neurodegeneration and compartmentalized inflammation, including cortical and paramagnetic lesions (CL, PRL) on 7T MRI, and neurological disability, measured by Expanded Disability Status Scale (EDSS).

Methods: One-hundred MS patients (74 relapsing-remitting, 26 secondary progressive MS, RRMS, SPMS) and 41 age and sex-matched healthy controls (HC) were recruited. Longitudinal clinical and MRI data were available respectively for 71 and 46 patients. All subjects underwent 3T anatomical imaging to obtain cortical thickness, thalamic and white matter (WM) volumes and 7T susceptibility MRI for PRL, leukocortical, intracortical and total cortical lesion (LCL, ICL, TCL) volume and count. Volumes of CP of lateral ventricles were extracted from Freesurfer segmentation, manually edited and normalized by total intracranial volume to estimate CP ratio (CPR). Univariate associations between CPR and neuroradiological/clinical measures were assessed by Spearman correlation. Forward stepwise regressions were performed to evaluate imaging metrics predicting EDSS, CL volume and PRL count at baseline and follow-up. A linear mixed effect model was built to explore time-dependent changes in CPR in a subgroup (n=26) of the longitudinal cohort, adjusting for age and sex.

Results: CPR was abnormally increased in MS patients, both RRMS and SPMS, relative to HC, also adjusting for ventricular volume, age, and sex ($p<0.001$). CPR inversely correlated with thalamic volume, cortical thickness, and WM volume ($p<0.05$). CPR positively correlated with non-rim WML volume, PRL and CL volume and count at baseline and follow-up ($p<0.05$). In the stepwise regressions non-rim WM lesions and ICL volumes were predictive of EDSS at baseline and follow-up ($p\leq0.001$), non-rim WM lesions and PRL volumes of CL volume at baseline and only WML-non rim at follow-up($p\leq0.001$), TCL volume and WM volume of PRL count ($p<0.008$). No time-driven CP enlargement was found ($p=0.76$).

Discussion: We confirm the finding of CP enlargement in MS compared to HC, and its correlation with measures of neurodegeneration and inflammation. We also report a new modest association with 7T CL and PRL volume and count. However, CPR does not seem to have a main role in predicting neurological disability or, indirectly, MRI metrics associated with disease progression.

Conclusion: Choroid plexus enlargement is a feature of MS but only marginally accounts for the complexity of the pathological processes underlying disease progression.

### CHARACTERIZATION OF FTLD SPECTRUM THROUGH ADVANCED DIFFUSION-WEIGHTED MRI METRICS: A CONNECTOME APPROACH

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Objective: To investigate structural alterations in brain network of FTLD spectrum using connectome analysis with advanced diffusion-weighted MRI metrics.

Materials: Thirty-four behavioral-variant frontotemporal dementia (bvFTD), 11 semantic variant primary progressive aphasia (svPPA), 11 nonfluent variant primary progressive aphasia (nfvPPA)

and 18 motor neuron disease (MND) patients and 48 controls were enrolled and underwent multi-shell diffusion MRI.

Methods: Fractional anisotropy (FA) maps were computed. Intra-cellular Volume Fraction (ICVF) maps were estimated using the NODDI model, providing a direct quantification of neurite morphology and its integrity. Graph analysis and connectomics assessed global and local structural topological network properties and regional structural connectivity. In particular, mean distance (MD), eigenvector centrality (EC), degree centrality (DC) and sum of node weights (SN) metrics were extracted.

Results: Overall, widespread structural changes were observed in bvFTD patients relative to controls, MND and svPPA patients. nfvPPA patients showed altered FA properties (higher DC, SN and EC and lower MD) at global level compared to controls and MND patients. This condition was also verified at a lobar level, in particular in frontal, basal ganglia, parietal, and temporal areas. In addition, ICVF graph analysis measures showed that svPPA had a lower DC and SN in the temporal lobe compared to healthy controls and MND patients. Considering the regional connectivity analysis, bvFTD patients showed widespread decreased FA compared to MND patients and controls in all brain areas. In addition, bvFTD patients showed marked decreased FA strength relative to svPPA patients particularly in the right hemisphere, involving frontal lobe, supplementary motor area, putamen, parietal and temporal areas. nfvPPA patients showed a decreased FA in the left hemisphere relative to controls and MND patients, in particular involving precentral gyrus, supplementary motor area, insula, putamen and temporal lobe. Considering ICVF, greater alterations were detected compared to FA maps, showing differences also between svPPA and nfvPPA patients.

Discussion: Conventional diffusion-tensor measures are sensitive to highlight connection damage along the FTLD spectrum. However, ICVF demonstrated to be a clinically relevant biomarker more specific to differentiate pathologies of FTLD spectrum. Specifically, the benefit emerged in the differentiation between svPPA patients and other groups.

Conclusions: Connectome-analysis based on advanced diffusion-weighted models is useful to evaluate structural brain disruptions with greater differentiation among FTLD syndromes compared to diffusion-tensor derived measures.

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## DECODING THE AGING PROCESS: UNVEILING AGING FEATURES THROUGH CONNECTOME ANALYSIS AND ADVANCED DIFFUSION-WEIGHTED METRICS WITH A MACHINE LEARNING APPROACH

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Objectives: To develop an advanced machine learning (ML) algorithm combining brain connectome analysis and advanced diffusion-weighted metrics to classify different features underlying aging process.

Materials: Forty-eight young healthy controls (YC), aged 20-31 years, and 21 middle-aged [MC] and 44 elderly healthy controls [EC], aged 41-85 years, were enrolled and underwent brain multi-shell diffusion MRI and cognitive evaluation.

Methods: Fractional anisotropy (FA), Intra-cellular Volume Fraction (ICVF) and Orientation Dispersion Index (ODI) maps were estimated. TBSS and connectomics were performed to estimate structural connectivity differences between groups (FA, ICVF and ODI). A feature selection algorithm, applied to a support-vector machine (SVM) model trained on mean FA, ICVF and ODI values of all connections that resulted different in TBSS and connectome analysis in the following comparison YC vs MC, YC vs EC, MC vs EC, was used for the identification of features (TBSS- or connectome-related) of the aging process. The features that better distinguished the three groups were then used as variables in a multivariate polynomial regression model to predict subject's age. Pearson's correlation coefficient was obtained to evaluate the association between the predicted age by the model and the actual age of the subjects.

Results: SVM models showed a 99.7% and 100% accuracy in the correct classification of YC relative to MC and EC with mean ODI values of TBSS-related connections as best selected feature. SVM models demonstrated an accuracy of 83.4% between MC and EC groups, identifying mean FA values of connectome-related connections as the most informative feature for classification. Mean ODI of TBSS- and FA of connectome-related connections were used in the construction of multivariate polynomial regression model to predict subject's age, utilizing a quadratic term to capture non-linear relationships. Correlation analysis indicated robust linear relationship between age predicted by the model and actual age of subjects ($r= 0.93$; $p<0.001$).

Discussion: SVM models, based on advanced diffusion weighted (ODI) measure and connectomics, provided strong discriminatory power in classifying different groups. Correlation analysis implies that the model's predictions align well with the true ages of subjects, providing evidence of effectiveness in estimating age based on the selected neuroimaging features.

Conclusions: Combination of SVM models with neuroimaging features achieved high accuracy in group classification and age prediction, highlighting the potential of these methods for understanding brain connectivity patterns and age-related changes. These findings pave the way for improved diagnostic and prognostic tools in neuroimaging research.

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## MODELING PATHOLOGICAL SPREAD THROUGH THE STRUCTURAL CONNECTOME IN THE FTLD SPECTRUM

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Objective: To explore the relationship between network vulnerability and longitudinal atrophy progression in patients within the frontotemporal lobar degeneration (FTLD) spectrum, using Network Diffusion Model (NDM) of pathology spread.

Materials: Thirty-four behavioural-variant frontotemporal dementia (bvFTD), 11 semantic-variant primary progressive aphasia (svPPA) and 11 nonfluent/agrammatic-variant primary progressive aphasia (nfvPPA) patients underwent longitudinal T1-weighted MRI. Forty-eight young healthy subjects (20-31 years) underwent multishell diffusion MRI scan.

Methods: NDM was developed to assess whether the progression of FTLD pathology might be modeled by a spreading process, originating from a seed and then proceeding through the healthy structural connectome. The connectivity measures used to create the structural connectome were fractional anisotropy (FA) and intra-cellular volume fraction (ICVF). Three disease epicenters were identified from the peaks of atrophy of each FTLD variant: right orbitofrontal cortex (bvFTD), left inferior temporal gyrus (svPPA), and left supplementary motor area (nfvPPA). Correlations were tested between longitudinal atrophic changes estimated by NDM and those empirically obtained in FTLD patients over a follow-up of 24 months.

Results: In the case of bvFTD, NDM showed an early spread to frontal lobe and basal ganglia (6 months) and to right sensorimotor, parietal, temporal and occipital lobes (12 months), with an involvement of the left hemisphere between 18 and 24 months. In svPPA, NDM predictive maps in young controls suggested an early spread of pathology to the left occipital (6 months) and inferior frontal lobe (12 months). At 18 months, left parietal lobe would be reached, whereas only few regions in the right parietal and occipital lobes would be affected at 24 months. In nfvPPA, NDM predicted a pathology spread through all brain regions, except for the occipital lobe, which would be involved after 12 months. NDM-predicted atrophy of each region was positively correlated to longitudinal atrophy empirically observed in all three FTLD variants. Overall, NDM applied on ICVF connectome provided higher correlation values relative to NDM applied on FA maps.

Discussion: The strong correlations that were found between the atrophy estimated by NDM and the real atrophy support the hypothesis that healthy structural architecture can influence the spatiotemporal atrophy progression in FTLD. The accuracy values of each model also showed that ICVF had a greater specificity than FA to model pathology spread.

Conclusion: The NDM implementation to cross-sectional structural connectome is a valuable tool to predict atrophy patterns and pathology spreading in FTLD variants.

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## THE ROLE OF MAGNETISATION TRANSFER RATIO IN EVALUATING THE PATHOLOGICAL MECHANISMS IN OPTIC NEURITIS

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Background and Aims: Acute optic neuritis (ON) frequently occurs in multiple sclerosis (MS) and can cause permanent neuroaxonal damage to the anterior visual pathway. Magnetisation transfer ratio (MTR) is a quantitative technique that measures the capacity of macromolecules to exchange magnetisation with the surrounding water, indirectly estimating tissue integrity. While MTR has been strongly associated with myelin content, it has also been suggested that axonal loss may play a role in its changes. The aim of our study was to investigate the pathological substrates of MTR evaluating the relationship between MTR values in the optic nerve versus visual evoked potentials (VEP) and optical coherence tomography (OCT) data.

Methods: We analysed data from the Phenytoin Neuroprotection Study, a randomized, placebo-controlled, double-blind phase 2 trial. Patients with acute ON aged 18–60 years, presenting within 2 weeks of onset, with visual acuity of 6/9 or worse, were randomly assigned (1:1) to oral phenytoin or placebo for 3 months. Measurements from 60 patients were included in this study (28 phenytoin, 32 placebo). MTR maps of the anterior visual pathway, OCT peripapillary retinal nerve fibre layer (pRNFL) and macular ganglion cell-inner plexiform layer (mGCIPL) thicknesses, and latency and amplitude VEP data were obtained at baseline and 6-months follow-up. Multilevel mixed models adjusted for possible confounders were built to evaluate the associations between VEP and OCT measures and the affected optic nerve MTR.

Results: At 6-months follow-up, anterior to the lesion (pre-lesion), greater MTR was associated with higher VEP amplitude (coeff = 0.434; p=0.001, 95%CI = 0.184 to 0.683) and thicker pRNFL (coeff = 0.797; p=0.024, 95%CI = 0.107 to 1.488). Within the lesion, greater MTR was associated with higher VEP amplitude (coeff = 0.195; p=0.048, 95%CI = 0.001 to 0.389), shorter VEP latency (coeff = -0.141; p<0.001, 95%CI = -0.201 to -0.081), and higher thickness in both pRNFL (coeff = 0.555; p=0.030, 95%CI = 0.054 to 1.055) and mGCIPL (coeff = 0.144; p<0.001, 95%CI = 0.064 to 0.223). Higher post-lesional MTR was associated with higher thickness in mGCIPL (coeff = 0.093; p=0.026, 95%CI = 0.011 to 0.173]).

Discussion: We found that myelination associations were localised to the lesion at 6 months, while neuroaxonal associations were more robust within the lesion, but also found pre/post-lesionally.

Conclusion: Our results demonstrate that MTR is a valuable technique for evaluating the pathological processes underlying optic nerve damage, and that it reflects both myelin content and axonal integrity.

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## TIME-VARYING CONNECTIVITY CORRELATES OF COGNITIVE PERFORMANCE DIFFER IN LATE-ONSET VS ADULT-ONSET MS: A STUDY OF THE PRECUNEUS AND POSTERIOR CINGULATE CORTEX

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Objectives: Around 5-20% of multiple sclerosis (MS) patients exhibit an age at onset after 45 years, a condition named late-onset MS (LOMS). Prevalence of cognitive deficits in LOMS vs adult-onset (AO) MS is still debated; also, resting state (RS) functional connectivity (FC) abnormalities of LOMS patients were never described. We explored abnormalities of static (sFC) and time-varying functional connectivity (TVFC) of precuneus and posterior cingulate cortex (PCC) in LOMS and AOMS patients, and their association with cognitive profile.
Materials and Methods: From three Italian sites, we enrolled 39 LOMS, 281 AOMS and 156 healthy controls (HC), divided into two groups (n=45/111) to match LOMS and AOMS patients, respectively, and perform disease-by-age interaction analysis. Subjects underwent neuropsychological (Rao's battery) and 3T RS fMRI assessment. TVFC was estimated through sliding-window correlation analysis using the bilateral precuneus and PCC as seeds. For this latter region, three seeds were placed in the dorsal (dPCC), ventral (vPCC), and retrosplenial cortex (RSC). sFC was assessed by standard seed-to-voxel correlation analysis.

Results: AOMS and LOMS patients showed similar global and domain-specific cognitive performances (p=0.07-0.5). Both AOMS and LOMS showed circumscribed fronto-temporal sFC decrease, and parietal, parahippocampal (PHG) and deep grey matter sFC increase, with limited disease-by-age effects. Conversely, pronounced disease-by-age effects were found for TVFC, indicating specific TVFC abnormalities for LOMS and AOMS patients. In particular, AOMS showed decreased TVFC between the precuneus and the left (L) lingual gyrus, as well increased TVFC of the RSC with the L middle occipital gyrus (MOG) and L precuneus. Conversely, LOMS patients showed significantly decreased TVFC between the vPCC and L precuneus, and between the RSC and L thalamus. They also showed increased intra-precuneal TVFC, as well as increased TVFC between the dPCC and right (R) precuneus, L MOG, L PHG and R inferior frontal gyrus. In AOMS, increased TVFC between the RSC and L precuneus correlated with better visuo-spatial memory (r=0.14, p=0.02), while in LOMS patients increased TVFC between the dPCC and L MOG correlated with better cognitive scores (r=0.4-0.6, p=0.001-0.02).

Discussion: Despite similar cognitive profiles, specific TVFC abnormalities characterized LOMS and AOMS. In both groups, higher TVFC was associated with better performance, suggesting the presence of compensatory mechanisms.

Conclusions: Altered TVFC of the precuneus and the PCC seems to have a role in the maintenance of an adequate cognitive performance in both LOMS and AOMS patients.

## FDG-PET AND ASL MRI DEMONSTRATE CORRESPONDING METABOLIC AND PERFUSION CHANGES IN LIMBIC AUTOIMMUNE ENCEPHALITIS

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Introduction: Metabolic abnormalities in autoimmune encephalitis (AE) can be detected using 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography ([18F]FDG PET), with relative hypermetabolism indicating disease activity. While evidence of pulsed arterial spin labeling (PASL) perfusion MRI to identify hyperperfusion changes in AE is still anecdotal, its potential to track the disease course relies on the close coupling of metabolism and perfusion. We compared PASL perfusion changes with [18F]FDG PET metabolic alterations in patients with definite AE to evaluate the correspondence between these metrics during the acute stage and after immunotreatment.

Material and Methods: Among 23 patients with confirmed autoimmune encephalitis (AE) admitted to our hospital in the 2018-2022 timeframe, a retrospective cohort of 5 patients with either antibody-associated AE (n=2 NMDAR, n=1 LGI1, n=1 Ma2) or seronegative AE (n=1) underwent both PASL-MRI and [18F]FDG-PET during the acute stage. In 4 out of the 5 patients, these scans were repeated after six months after initial immunotreatment. Scans were visually assessed by two independent raters. Following consensus, regions with hypermetabolism ([18F]FDG-PET) or hyperperfusion (PASL-MRI) were manually delineated, referencing the contralateral hemisphere, and their spatial overlap was evaluated by DICE analysis at either baseline or 6-month follow-up. Clinical assessment scale in AE (CASE) and modified Rankin Scale (mRS) scores were obtained at baseline and every 3 months, with an average follow-up duration of 15.8 months.
Results: At baseline, three patients demonstrated hypermetabolism on both [18F]FDG PET and hyperperfusion on PASL (DICE coefficient: Pt1, 0.2; Pt.2, 0.5; Pt.5, 0.35), while the other patients showed no abnormalities. After immunotreatment, the hypersignals decreased with a similar concordance Pt.5 (DICE=0.25) or completely solved (pts 1 and 2) in both modalities, paralleling clinical improvement (-4 points in CASE and -1.8 mRS score as a mean).

Discussion: We observed full concordance between negative scans in PASL and [18F]FDG-PET, while moderate spatial concordance was observed in regions exhibiting hypersignals. Following immunotreatment, metabolic and perfusion changes consistently demonstrated a decrease, aligning with clinical improvement. Although these techniques may identify slightly different underlying processes, leading to incomplete concordance, they are coupled in their ability to monitor the progression of the disease.

Conclusion: Although confirmation in larger cohorts is needed, PASL-MRI shows promise as an indicator of disease activity, treatment response, and recovery in AE, making it a favorable alternative to FDG-PET due to its concordance with metabolic abnormalities, cost-effectiveness, safety, and wide availability.
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## REGIONAL HIPPOCAMPAL ATROPHY REFLECTS MEMORY IMPAIRMENT IN PATIENTS WITH EARLY MS

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Objectives: Hippocampal atrophy is significant in multiple sclerosis (MS), especially related to memory impairment. Research has suggested that different hippocampal subfields are affected to varying extents during different disease stages. However, studies examining the functional consequences of subfield-specific hippocampal damage in early MS are limited. We studied a relatively large population of early RRMS patients (≤5 years from onset) to gain insights into the relationship between hippocampal atrophy and memory function by i) assessing whether there is global and regional hippocampal atrophy at this early stage, ii) investigating the correlation between hippocampal atrophy and memory performance in patients with different degrees of impairment.

Materials and Methods: From the Italian Neuroimaging Network Initiative (INNI) dataset, we selected 3D-T1W brain images acquired at 3T of 219 early RRMS (150 F, mean [±SD] age: 34 [±10] years, median [range] disease duration: 2 [0-5] years) and 246 HC (133F, mean age: 34 [±9] years). Patients underwent Selective-Reminding-Test (SRT) and Spatial-Recall-Test (SPART) and were classified as mildly (MMI-MS: n.110) or severely (SMI-MS: n:109) memory impaired, according to recently proposed cognitive phenotypes. We employed the EADC-ADNI protocol to segment hippocampus, and voxel-based morphometry to identify regionally atrophic areas within the hippocampus and to select voxels correlating with memory scores. We used Freesurfer to segment hippocampal subfields and identify the subfields containing the previously identified atrophic voxels. Finally, we used generalised linear models to compare volumes and Spearman test to correlate volumes with memory performance.

Results: Early RRMS showed lower volumes in the whole, right and left hippocampi compared to HC ($p<0.001$), while hippocampal volumes did not differ between MMI-MS and SMI-MS. In MMI-MS, lower hippocampal volumes correlated with worse memory tests ($p\leq0.01$, R from 0.23 to 0.37), while in SMI-MS, only a weak correlation was found between left hippocampal volume and SRT-LTS ($p=0.04$, $R=0.189$). Atrophic hippocampal voxels were detected in all subfields (from 79% in CA2-3 to 21% in tail). In MMI-MS, decrease subfield volumes correlated with decrease in memory performances, with the closest correlation with right CA1 volume (SRT-recall: $R=0.38$; SPART: $R=0.34$, $p<0.01$). In SMI-MS, no correlations were found between subfield volumes and memory tests.

Conclusion: Hippocampal atrophy is a distinctive feature of MS, spreading from the CA to the tail since the early stages. This seems to be associated with memory impairment in MMI-MS, while this correlation is lost in SMI-MS suggesting a limited adaptive functional reorganization of hippocampi in MS, even at early phases.

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## GENERALIZED SPINAL CORD ATROPHY: CASE REPORT

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Background: Spinal cord atrophy is a rare condition. Generally, spinal cord atrophy may be focal or generalized. Focal spinal cordatrophy may be due to Chiari malformation, previous CNS infection, trauma, radiotherapy, spinal surgery, immunological disorder, vascular abnormality or CNS tumour. Generalized spinal cord atrophy is rare and may caused by Chiari malformation, luetic CNS infection, and hereditary disorders like arthrogryposis multiplex congenita, Chediak-Higashi syndrome, adrenoleucodystrophy, Sjogren syndrome, familial spastic paraparesis, and hereditary motor and sensory neuropathy with pyramidal signs (HMSN-V), multiple sclerosis. We report the case of a 62 years old caucasian woman with generalized spinal cord atrophy in which all known causes have been excluded.

Materials and Methods: A 50 years-old caucasian woman has been evaluating due to persisting gait disorder started at the age of 20 and remaining stable over time without weakness or sensory symptoms. Her medical history was positive for arterial hypertension and familial history resulted unremarkable. Neurological exam showed brisk lower limb reflexes, paraparetic gait, lower liomb hypopallesthesia with distal apallesthesia, mild proximal lower limb weakness (3/5 medical research council). She denied bulbar or sphincter disorders. No fasciculations or muscle hypotrophy were obeserved; Babinski and Hoffman were normal and clonus of the ankles was absent.

Results: She performed spine magnetic resonance imaging (MRI) showing generalized and homogeneous spinal cord atrophy with marked lumbar spinal stenosis (L3-L4); brain MRI resulted normal. Both were superimposable on previous ones performed 10 years before in another hospital. Electromyography and electroneurography

resulted normal. Somatosensory evoked potentials resulted normal, while evoked motor potential showed four limbs prolonged central motor conduction time. Genetic evaluation of known spastic paraparesis resulted normal. Blood exams with immunological panel resulted normal. Syphilis was excluded.

Discussion: All known causes of spinal cord atrophy have been excluded. Gait disorders started at the age of 20 seems to exclude a congenital malformation (but two different MRI performed 10 years apart from each other were superimposable). Gait disturbance and paraparesis could be also related to marked lumbar spinal stenosis (for which she was recently surgically treated with mild benefit on both gait disorder and paraparesis).

Conclusions: To our knowledge this case of spinal cord atrophy is still idiopathic and can expand existing literature. Follow-up with neurological examination, neuroimaging exams can be helpful in excluding differential diagnoses and monitoring disease progression.

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## LONG-TERM ACCUMULATION OF SLOWLY EXPANDING LESIONS IS ASSOCIATED WITH GREY MATTER ATROPHY AND DISABILITY WORSENING IN MS: A 10-YEARS FOLLOW-UP STUDY


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Aims: Multiple sclerosis (MS) is associated with progressive tissue damage of the central nervous system and consequent clinical disability worsening. Recently, slowly expanding lesions (SELs) have emerged as a reliable MRI marker of chronic inflammation in MS. Long-term assessment of SELs and their relationship with measures of regional brain atrophy and disability progression has not been investigated yet. To assess SELs volume and number over a 10-year follow-up and explore the relationship between SELs, grey and white matter (GM/WM) atrophy and disability accumulation in patients with relapsing-onset MS.

Materials and Methods: Longitudinal MRI scans (acquired using a 1.5 T Philips scanner) of 97 MS subjects (number of females: 71; mean [SD] age: 34.21±7.66; median [range] baseline EDSS 1.5 [0-5.5]; median [range] follow-up: 10.1 [1.4-14.5] years) were retrospectively analysed. Using an in-house developed pipeline, SELs were identified as T2 lesions showing constant and concentric local expansion assessed by the Jacobian of the nonlinear deformation field between the T1- and T2-weighted scans across all the available timepoints. Normalized brain (NBV), GM and WM volume was obtained using SIENAX tool. General linear model with negative binomial regression was applied to investigate the relationship between SEL burden (volume and number) with both EDSS change and annualised regional GM and WM volume change assessed between baseline and the last available follow-up. Analyses were corrected for age, sex, baseline NBV and T2 lesion number and volume.

Results: A total of 138 SELs were found in 41 (49%) MS patients (mean [SD] SELs volume: 1.51±3.3; mean [SD] SELs number: 3.36±3.08). In this long-term study, a higher number of SELs was associated with increased EDSS over time ($p<0.01$, $B=0.41$) and with greater GM atrophy ($p<0.01$, $B=-1.72$). A greater volume of SELs was associated with increased GM atrophy ($p<0.01$, $B=-0.23$). A trend was found for the relationship between SELs' volume and EDSS change ($p=0.06$, $B=0.05$). No association was found between SELs and WM volume change.

Discussion and Conclusion: We showed here that SELs are associated in the long-term with GM volume changes and disease progression. This suggests that chronic inflammatory activity and sustained GM tissue loss are two related mechanisms, progressively leading to disability worsening.

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## METRONIDAZOLE-INDUCED CENTRAL AND PERIPHERAL NEUROTOXICITY. DIAGNOSIS AND 1-MONTH FOLLOW-UP


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Objectives: Metronidazole is an antibiotic widely used to treat protozoan and anaerobic bacterial infections. Although metronidazole is generally safe and well-tolerated, rare cases of neurotoxicity have been reported. Central nervous system involvement is usually characterized by highly suggestive abnormalities on neuroimaging. Herein, a case of metronidazole-induced central and peripheral neurotoxicity with encephalopathy, cerebellar ataxia, and sensorimotor polyneuropathy is described.

Materials and Methods: A 71-year-old man was admitted to our Emergency Department with a 3-week history of rapidly progressive gait impairment, somnolence, and speech disturbance. His past medical history was remarkable for a bladder and a colorectal tumor treated 15 years earlier. He was recently hospitalized for a suspected cancer relapse, associated with a purulent pelvic collection and received 3 months of antibiotic polytherapy, including metronidazole. On admission, neurologic examination revealed impaired arousal, moderate dysarthria, tetraparesis with severe distal muscle weakness, mild trunk and limb ataxia, deep tendon hyperreflexia, and severe sensory deficit.

Results: The head CT scan was negative for any acute findings. Blood tests, including metabolic, immunological, and infection screening were unremarkable. Electromyoneurography examination revealed subacute severe symmetric sensorimotor polyneuropathy, with predominantly axonal features. Lumbar puncture revealed no albuminocytological dissociation or oligoclonal bands in the CSF. Brain MRI detected T2/ FLAIR-hyperintensity of the dentate nuclei and splenium of the corpus callosum, whereas spine MRI didn't show any relevant findings. Based on the history and MRI findings, a diagnosis of metronidazole neurotoxicity was made. Stopping metronidazole therapy, the encephalopathy progressively improved over the following weeks, whereas the polyneuropathy showed no significant improvement. One-month MRI follow-up showed complete regression of the abnormalities.

Discussion and Conclusions: We described a patient with a long exposure to metronidazole, who suddenly developed encephalopathy and severe sensorimotor axonal polyneuropathy. The clinical history of the tumor complicated by recent superinfection led to a complex differential diagnosis including possible infectious, autoimmune, paraneoplastic, and toxic-dysmetabolic causes. The MRI findings, taking into account the anamnestic informations, prompt the diagnosis. Metronidazole is a little-known, but probably underestimated, iatrogenic cause of encephalopathy and neuropathy. The case we reported points out the need for neurological monitoring during metronidazole therapy and the diagnostic role of neuroimaging when neurotoxicity is suspected. Timely diagnosis is crucial to avoid extensive and futile treatment and to promote rapid drug discontinuation.

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## SPONTANEOUS SPINAL CSF LEAKAGE PRESENTING WITH ISOLATED MYELOPATHY


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Objective: Spontaneous intracranial hypotension (SIH) is characterized by postural headache and could be caused by cerebrospinal fluid (CSF) leak, mostly in thoracic spinal cord. We report on a case of a 33-year-old woman with CSF leak presented with rapidly progressive myelopathy causing right leg weakness, brisk reflexes, reduced superficial and pain sensation, and urinary retention. Patient complained of neither headache nor history of trauma.

Materials/Methods: Brain and whole spine MRI with and without gadolinium contrast and CT-myelography were performed. Neurophysiological assessment included transcranial magnetic stimulation and somato-sensory evoked potentials.

Results: Sagittal and axial T2-weighted MRI showed anterior displacement of the spinal cord due to epidural CSF longitudinal collection with dural detachment, likely from thoracic disc-osteophytic complex. Brain MRI was normal. Both transcranial magnetic stimulation and somato-sensory evoked potentials confirmed involvement of motor and somatosensory pathways of the right lower limb. The patient was hence immediately treated with methylprednisolone 500 mg/day for 5 days, showing clinical improvement. After 7 days from the end of steroids, a CT myelography study was performed and it did not show any CSF collection nor leakage. After 21 days from first MRI, CSF collection spontaneously disappeared on MRI. Further clinical improvements followed.

Discussion: CSF leakage from disrupted spinal meninges can cause epidural collections, usually leading to intracranial hypotension and postural headache. Accordingly, MRI frequently shows such CSF collections in association with brain abnormalities including pachymeningeal enhancement, subdural effusions and sagging brainstem. [1-2] Conversely, our case presented with compressive myelopathy caused by CSF dorsal epidural collection.

Conclusions: We report on a rare clinical presentation of CSF leakage characterized by isolated spinal cord clinical and MRI findings, suggesting that spinal epidural collection could be an uncommon cause of myelopathy.

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## NEUROPHYSIOLOGICAL CONSEQUENCES OF NETWORK DEGENERATION IN ALZHEIMER'S DISEASE


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Objective: The response to transcranial magnetic stimulation (TMS) of cortical networks captured by electroencephalography (EEG), i.e., the TMS-evoked potential (TEP), relies on the integrity of the cortex and its white matter (WM) connections to distant areas. [1] The network-specific gray matter and WM degeneration occurring in Alzheimer's disease (AD), may be depicted in changes of TEP amplitude and topography. Demonstrating that TEPs can track neurodegeneration within cortical networks would make TEPs a novel biomarker for AD and possibly for other neurodegenerative disorders.

Materials: In the present cross-sectional study, we collected TEPs, resting state functional MRI (rs-fMRI), diffusion tensor imaging (DTI), and an extended neuropsychological evaluation in healthy elderly individuals and patients with AD at various stages of the disease. TEPs were elicited by stimulating the parietal nodes of the default mode network (DMN) and the frontal nodes of the executive control network (ECN), as both networks are known to be affected by AD.

Methods: We tested for differences in cognition, WM microstructural tract integrity and early TEP amplitudes (<50ms) across groups. Finally, we verified if TEP components altered in AD pathology were associated with intrahemispheric and interhemispheric WM structural connections.

Results: Two early TEP components generated for DMN stimulation, i.e., P20P and N20F, showed significantly higher amplitude after left stimulation than after right stimulation in mild cognitive impairment (MCI) due to AD, and not in other groups. Moreover, the N20F following a left DMN stimulation was stronger in MCI patients compared to healthy controls and to AD patients in dementia stage.

Finally, these TEP components were associated with the WM integrity of healthy controls: the parietal component P20P was positively associated with the integrity of the corpus callosum (CC), and the frontal component N20F was positively associated with the integrity of the CC and the contralateral superior longitudinal fasciculus. Importantly, this association was absent in AD cases.

Discussion and Conclusions: In the early stages of the disease, AD is associated with asymmetric alterations of neurophysiological responses in the DMN, in line with previously reported vulnerability of this network and of the left hemisphere in AD cases. [2] The increased TEP responses only in the MCI group indicate that neurophysiological alterations within the DMN are not linearly related with the disease staging. Early TEP components from DMN stimulation have the potential to differentiate MCI due to AD from healthy individuals.

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## DIABETES IMPACT ON NIGROSTRIATAL VULNERABILITY IN PARKINSON'S DISEASE

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Objectives: Several studies suggested a possible association between diabetes mellitus (DM) and Parkinson's disease (PD) [1,2]. Aim of the study was to investigate in vivo whether diabetes mellitus influences motor function via its impact on nigrostriatal dopaminergic vulnerability in two independent cohorts of drug-naïve patients with early-stage Parkinson's Disease (PD).

Materials: The study included two independent prospective cohorts of drug naïve PD patients: n=54 patients from the single -center DNA-PD study and n=112 patients from the PPMI dataset (PD-PPMI cohort). Each cohort comprised two subgroups of patients with diabetes mellitus (PD-DM) or without diabetes mellitus (PD-noDM), which were matched 1:1 for age, sex, motor and cognitive impairment at baseline. All subjects underwent a neurological examination and Brain SPECT to measure dopamine transporter (DAT) density at baseline. A subset of the PD-PPMI cohort (n=46 PD-noDM; n=18 PD-DM) underwent a dopaminergic imaging follow-up after 12 months.

Methods: In order to test the impact of diabetes to nigrostriatal function, PD patients with and without diabetes were matched for motor severity, age, sex. The ANCOVA test was applied to test whether diabetes may enhance nigrostriatal vulnerability (i.e., differences in striatal binding) – adjusting for age, sex, handedness, and SSRI treatment. In the PPMI cohort, the annual difference in striatal binding was entered in an ANCOVA model – adjusted for age, sex, and handedness- to test differences in progression trajectories driven by diabetes mellitus.

Results: In both PD-BS and PD-PPMI cohorts, PD-DM and PD-noDM were matched for motor severity and comparable for non-motor symptoms. In both independent cohorts, PD-DM patients had higher dopamine uptake in left putamen, as compared to PD-noDM with the same disease severity. In PD-PPMI cohort, the follow-up evaluation revealed that PD-DM had a faster annual decline of left putamen binding than PD-noDM (-20% vs. -9%).

Discussion: Findings showed that diabetes mellitus may impact on motor presentation by increasing the vulnerability of the nigrostriatal systems. This result was further confirmed by the follow-up evaluation showing a greater annual difference in left putamen binding.

Conclusions: The diabetes mellitus has an impact on nigrostriatal vulnerability. Results were confirmed in both an Italian monocentric cohort and in the multicentric PPMI cohort.

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## DOPAMINERGIC DEFICITS ALONG THE SPECTRUM OF ALZHEIMER'S DISEASE: A 123I-FP-CIT STUDY

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Objectives: Both post-mortem and in vivo data suggested dopamine dysfunction in patients with Alzheimer's Disease (AD) [1,2]. However, the role and timing of dopaminergic systems alterations in AD is still under debate. Aim of the study was to evaluate in vivo dopaminergic changes using DATSCAN imaging in AD patients in prodromal and dementia stages.

Materials: 60 A+T+N+ AD patients (n=22 MCI-AD; n=38 AD-DEM) and n=60 age-matched controls (CG) entered the study and underwent DATSCAN imaging.

Methods: The occipital binding was used as reference region to obtain single-subject binding in different brain regions. Between-groups differences in 123I-FP-CIT binding were assessed using ROI-based and voxel-wise analyses-adjusting for the effect of centre, age and sex. Functional covariance analysis was applied to evaluate the covariance of a brain region- or "seed"- with other brain regions.

Results: In all AD patients, nigrostriatal imaging resulted negative according to cut-off used in clinical practice [3]. Compared to age-matched controls, the whole AD sample exhibited significant dopamine deficits within caudate, putamen, globus pallidus, amygdala and hippocampus in ROI-based and voxel-wise analyses. Specifically, MCI-AD showed alterations limited to caudate, putamen and globus pallidus, while AD-DEM patients also exhibited the involvement of amygdala and hippocampus bilaterally. Functional covariance analysis

using caudate as seed showed a related pattern of reduced dopamine binding in striatal, frontal and temporal regions progressively decreasing from CG to MCI-AD and dementia stages.

Discussion: This study indicate that subtle basal ganglia alterations are a common feature of AD already in prodromal stages, whereas hippocampal and cortical deficits were prominent in later stages of the disease. Further longitudinal studies are warrented to evaluate the clinical impact of dopaminergic deficits on cognitive and motor/behavioral progression over time.

Conclusions: We managed to find in vivo dopaminergic alterations in Alzheimer's Disease, both in MCI and dementia phases.

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## EXPLORING THE NEURAL BASIS OF MILD MOTOR IMPAIRMENT IN PRODROMAL ALZHEIMER'S DISEASE: INSIGHTS FROM [18F]FDG PET AND ENGINEERED GLOVE ASSESSMENT

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Objective: Mild motor impairment (MMI) often emerges in neurodegenerative diseases before cognitive decline[1]. Using an engineered glove enables objective assessment of motor performance, particularly during finger-to-thumb opposition movements, facilitating identification of individuals in the prodromal phase of dementia. However, the neural underpinnings of MMI remain inconsistent, with variable alterations observed in brain cortical areas and the cerebellum[2]. To enhance our understanding of the metabolic correlates of MMI in mild cognitive impairment due to Alzheimer's disease (MCI-AD), we employed [18F]FDG PET analysis during tasks involving the engineered glove. Our goal is to contribute to existing knowledge on MMI in this patient population.

Materials: We retrospectively identified 23 patients with MCI (age 78.13±8.05 years; education 8±4.6 years; MMSE 22.26±4.22) and an intermediate likelihood of AD who underwent [18F]FDG PET and performed finger-to-thumb opposition sequences at maximum velocity while wearing the engineered glove within 3 months from the baseline assessment.

Methods: Four main indices were extracted for each hand (dominant versus non-dominant, and their mean), including rate at maximum speed, number of correct sequences, tapping delay, and intertapping interval. Voxel-based analysis correlated these indices with cerebral metabolism values and identified hypometabolic areas in patients compared to 40 matched healthy subjects (nuisance: age). The statistical threshold was set at <0.001 at the voxel level, with less conservative thresholds explored additionally. Clusters with at least 100 voxels, family-wise error (FWE) corrected at the cluster level, were deemed significant.

Results: The dominant hand's intertapping interval negatively correlated with metabolism in an area primarily including the left pulvinar and bilateral thalamic ventral posterior lateral nucleus, and marginally left putamen and right parahippocampal gyrus (p=0.007 at voxel level). Importantly, these regions were separate from hypometabolism encompassing left temporo-parietal areas.

Discussion: Our findings suggest that dysfunctional visual and somatosensory integration should be accounted for MMI in prodromal AD. The posterior thalamic nuclei serve as relay regions for somatosensory pathways and contribute to visual attention and motor activities like saccades, reaching, and grasping. Previous research has indicated heightened thalamic activity with increasing movement complexity, highlighting its role in the integration of signals towards the association cortices to control hand dexterity. Early dysfunction of these thalamic areas may contribute to fine motor deficits of the dominant hand in prodromal AD, even in the absence of overt hypometabolism.

Conclusions: This research reveals some neural correlates of MMI in MCI-AD, aiding the development of objective measures for assessing motor impairments and predicting cognitive progression.

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## ASSESSMENT OF CNS DISEASE ACTIVITY IN SUSAC SYNDROME: INTRACRANIAL VESSEL WALL IMAGING (VWI) VERSUS STANDARD MRI SEQUENCES

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Aims: Evaluate the accuracy of three-dimensional (3D)-vessel wall imaging (VWI) compared to standard sequences and contrast enhancement-3D T2-fluid attenuated inversion recovery (CE-FLAIR) to assess central nervous system (CNS) disease activity in two cases of definite Susac Syndrome (SS).

Material and Methods: Brain magnetic resonance imaging (MRI) scan and retinal fluorescein angiogram (RFA) were performed at disease onset and at one, three and six months after induction therapy start. CE-FLAIR and VWI based on 3D black-blood proton density weighted with and without gadolinium were added to standard sequences on a 3 Tesla MRI scanner.

Results: Contrast enhancement-VWI (CE-VWI) detected an abnormal diffuse leptomeningeal enhancement (LME) in both cases at onset and during follow-up. Pathological enhancement on CE-VWI persisted at six-month brain MRI, despite absence of new lesions and disappearance of LME on CE-FLAIR. Follow-up RFA revealed new arterial wall hyperfluorescence (AWH) in both cases.

Discussion: SS is a rare immune-mediated vasculitis affecting retina, inner ear and brain. Currently, the following are considered as markers of suboptimal therapeutic response: the presence of new or persistently enhancing lesions on brain MRI scan, residual LME and

new branch retinal artery occlusion (BRAO) and/or AWH on RFA, being the latter the most sensitive exam to evaluate disease activity. In our two cases we demonstrated that the stability of lesion load is not enough accurate to establish absence of disease activity in the CNS, and that the use of VWI may add valuable information for SS monitoring. Despite absence of new lesions, or even a reduction in lesion number (Case 1) at standard examination, a pathological enhancement was detected with CE-VWI in both cases, and this was consistent with evidence of disease activity at RFA. LME assessment on CE-FLAIR is considered another tool useful to diagnosis and monitoring of disease activity in SS, but its regression did not seem sufficient to predict a complete suppression of CNS involvement, as suggested in case 2. Moreover, in our cases, CE-VWI seems to be at least as sensitive as CE-FLAIR in detecting LME compared to CE-T1.

Conclusions: VWI may represent a useful tool for diagnosing and monitoring CNS disease activity in SS, as confirmed by concordance with RFA, leading treatment's choice and timing. Moreover, CE-VWI seemed at least as sensitive as CE-FLAIR in detecting LME, possibly being superior to the latter in posterior fossa. LME remission might be not accurate in predicting suppression of CNS inflammation in SS.

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## NON-STENOSING INTRACRANIAL ATHEROSCLEROTIC LESIONS IN EMBOLIC STROKE OF UNDETERMINED SOURCE: A PROSPECTIVE VESSEL WALL MRI STUDY

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Background: Despite standard diagnostic approach, 30% of ischemic strokes remain cryptogenic, most of them being classified as embolic stroke of undetermined source (ESUS). Artery to artery embolization from non-stenosing complicated atherosclerotic intracranial plaques has been suggest being relevant in ESUS aetiology, possible more than occult atrial fibrillation but it is often undetected by conventional imaging. Vessel wall MRI (VWMRI) can identify high-risk atherosclerotic plaques and other culprit intracranial arterial lesions. However, prospective studies of VWMRI in ESUS patients are lacking.

Materials and Methods: We prospectively evaluated all consecutive patients with acute ischemic stroke admitted to IRCCS Mondino Stroke Unit from July 2022. All patients underwent standard diagnostic workup including CT angiography of intracranial and epiaortic vessels, transthoracic echocardiogram and 72 h ECG monitoring. All patients respecting ESUS criteria and with no contraindication to MRI were included in the study and underwent VWMRI with gadolinium contrast agent administration within 1 month from enrollment.

Results: We have enrolled 31 patients; one patient was not able to complete the whole MRI protocol and was excluded from the analysis. The mean (± SD) age was 64.5 (± 12.75) years, 16 (53.33%) patients were female. VWMRI revealed culprit intracranial vessels lesions in in 30% (n=10) of patients. Particularly, 9 patients had non-stenotic complicated atherosclerotic plaques with contrast enhancement; 1 patient had an intracranial vertebral artery dissection. Patients with symptomatic intracranial atherosclerosis were older (71 vs 63 years, p-value = 0,018), more likely to have hypertension (89 % vs. 38 %, p-value = 0.016), and more frequently smokers (78 % vs. 33 %, p-value = 0.046).

Discussion: VWMRI was well tolerated in acute stroke patients and was able to identify culprit intracranial arteries lesions undetected by luminal-based imaging in the 30% of our ESUS patients, in particular non-stenosing complicated atherosclerotic plaques. Clinical factors associated with symptomatic intracranial atherosclerosis were older age, smoke exposure and hypertension. These would be useful to select patients at higher risk of symptomatic intracranial atherosclerotic disease who would benefit more from the adjunction of VWMRI to the diagnostic workup.

Conclusions: Our preliminary data suggest a potential role of VWMRI in improving the diagnostic workup of ESUS, reducing the percentage of cryptogenic strokes. Particularly, VWMRI was able to reveal the presence of a culprit non-stenosing intracranial atherosclerotic lesion in a significant portion of ESUS patients. Clinical factors as age, smoking and hypertension may be useful to select patients at higher risk. Our data needs to be confirmed in larger samples before translating them to clinical practice.

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## A RARE CASE OF ASYMPTOMATIC TWIG-LIKE MIDDLE CEREBRAL ARTERY

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Objectives: Congenital middle cerebral artery (MCA) anomalies, including aplastic MCA or Twiglike MCA (T-MCA), are very rare.

Materials: We describe a case of congenital aplastic MCA in a patient with a history of hydrocephalus and brain trauma.

Methods: The patient underwent clinical evaluation, brain computed tomography (CT), CT angiography (CTA), brain magnetic resonance imaging (MRI) and MR angiography (MRA).

Results: A 48-year-old woman presented to the Emergency Department for acute onset of altered mental status and urinary incontinence. She had a positive past medical history for a brain trauma 4 months before. Neurological examination showed confusion and lethargy, without any focal neurological deficit. She underwent brain and spine CT which showed an odontoid process fracture and hydrocephalus. Subsequently a brain MRI was performed, that confirmed tetraventricular hydrocephalus; MRA showed absent left MCA signal. Either recent or chronic ischemic lesion in MCA

vascular territory were absent, and only some gliotic spots due to small vessel disease were present. To better characterize these alterations, the patient underwent a CTA, that confirmed the absence of MCA, which was replaced by a prominent network of dilated small arteries supplying M2 territory. No associated aneurysm or other vascular abnormality were seen. A ventriculoperitoneal shunt (VPS) was implanted, which resolved the hydrocephalus, with dramatic improvement of patient's mental status.

Discussion: These radiological findings were consistent with developmental T-MCA. It is a rare vascular anomaly characterized by replacement of the M1 segment of MCA by a plexiform network of small vessels. Few cases have been described in the literature so far, and it is detected in 0.11%–1.17% of people who undergo angiography. Nearly all cases are unilateral. The pathogenesis is unknown, but it has been hypothesized to result from an interruption of plexiform network fusion into MCA trunk during the embryogenesis. T-MCA can be asymptomatic, being an incidental finding, as the case described above. However, it can also be associated with intracranial hemorrhage, cerebral infarction, as well as epilepsy, vertigo, headache, or focal neurologic deficits. In our case the diagnosis was made with MRA and TCA; meanwhile, she did not perform a conventional angiography because of her poor clinical status.

Conclusion: T-MCA is a rare congenital MCA anomaly, which can be asymptomatic as well as being associated with ischemic and hemorrhagic complications. Because of its rarity, it can be easily confused with other pathologies. However, correct diagnosis is fundamental for prognostic and therapeutic implications.

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## STRUCTURAL BRAIN NETWORK CONNECTIVITY GRADIENTS IN STROKE: A LONGITUDINAL ANALYSIS


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Objective: Stroke is a major cause of death and disability globally, resulting in significant neurological impairments. Brain damage from stroke involves both local cellular changes and connectivity diaschisis affecting distant brain regions. While research has primarily focused on the former, understanding the latter is crucial for a comprehensive view of the mechanisms underlying recovery and disabilities. In this study, we conducted a cross-sectional and longitudinal analysis of structural connectivity patterns to unravel connectivity changes in stroke patients.

Materials: Multi-shell diffusion-weighted imaging (DWI) were acquired in a sample of first-stroke patients, from the Washington University in St. Louis. Data were preprocessed according to standard procedure. We employed a probabilistic tractography model to reconstruct the number of fibers passing through each brain voxel. These fibers were then projected onto a parcellation scheme (Schaefer 100 parcels) to create a symmetric connectivity matrix representing fiber counts between each parcel pair. We separately considered inter- and intrahemispheric fibers. The structural connectivity matrix was subjected to diffusion map embedding analysis, generating a low-dimensional connectivity axis where parcels with similar connections were grouped together. Parcels were categorized based on Yeo's network template to compute network-gradient patterns, which were compared between stroke patients and controls, as well as between baseline and 3-month follow-up measurements within stroke patients.

Results: We included 50 stroke patients followed at two-week and three-month intervals from the event. A total of 29 age-matched healthy controls (HC) were included. Three main connectivity structural gradients were identified. Network-gradient patterns exhibited differences extending beyond the lesional and perilesional regions to distal networks. These alterations worsen during recovery. Notably, we found that right-hemisphere lesions resulted in more pronounced network-gradient alterations compared to left-hemisphere lesions. Finally, network-gradient for inter-hemispheric structural connections were less disrupted than gradient patterns computed using intra-hemispheric connections, regardless of lesion location.

Discussion: Our findings demonstrate a broad reorganization of large-scale structural connectivity following stroke, extending beyond the immediate lesion site. Notably, right-hemisphere lesions showed more severe network-gradient alterations than left-hemisphere lesions. This information has implications for developing targeted interventions based on lesion location and severity.

Conclusion: This study provides valuable insights into the impact of stroke on the brain's structural connectivity, offering potential avenues for developing new treatments and interventions. By understanding the reorganization of connectivity patterns following stroke, we can enhance our ability to tailor therapies and improve outcomes for stroke patients.

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## COMPARATIVE ANALYSIS OF SUPRA AND INFRATENTORIAL ATROPHY IN CEREBELLAR ATAXIAS: UNVEILING DISTINCTIONS ACROSS DIFFERENT NEURODEGENERATIVE ATAXIAS


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Objective: This study examined structural alterations in gray matter (GM) and white matter (WM) in patients with different neurodegenerative cerebellar ataxias (CA).

Materials: Twenty-eight autosomal dominant (AD) CA patients (including cases of genetic spinocerebellar ataxia and patients without a known mutation but with an AD transmission pattern), 17 autosomal recessive (AR) CA patients (including cases of Friedreich's ataxia, CANVAS, ANO10 mutation, Oculomotor Apraxia Type 2, ARSACS, and patients with an AR pattern of inheritance without a known mutation), 29 sporadic cases of CA (including 16 idiopathic late-onset CA), 8 multiple system atrophy patients (MSAc) and 20 controls were included. MRI and clinical assessment were conducted.

Methods: Whole-brain Voxel-Based Morphometry (VBM) and cerebellar-optimized VBM (SUIT toolbox) were used to assess GM atrophy. Brainstem and superior cerebellar peduncles (SCP) volumes were estimated and compared between groups using Freesurfer.

Results: CA groups showed widespread GM cerebellar atrophy compared to controls. AD and AR groups showed significant supratentorial GM atrophy compared to controls in: (i) bilateral medial temporal gyri, insula, calcarine cortex, and right orbitofrontal cortex in AR; and (ii) right inferior orbitofrontal cortex, postcentral, and superior temporal lobe gyri, left superior temporal gyrus, and cingulate cortex in AD. No significant GM differences were found in whole brain, except for GM alterations in right calcarine cortex in AR relative to MSAc. Moreover, MSAc showed more involvement in the medial Crus-I and II compared to AD. Concerning brainstem analysis, AD, AR, and MSAc groups exhibited reduced whole-brainstem, pons, and medulla volumes compared to controls. Moreover, AD and MSAc groups demonstrated reduced whole-brainstem and pons volumes compared to sporadic cases. AD and AR groups displayed significantly reduced midbrain volume compared to controls, and only AD exhibited a reduction compared to sporadic cases. SCP volume was reduced in CA groups compared to controls. In addition, AD showed reduced SCP volume compared to sporadic cases.

Discussion: CA groups showed diffuse cerebellar atrophy, while AD and AR groups showed also distinct supratentorial patterns of atrophy, suggesting different underlying pathophysiology. The sporadic group showed less involvement in brainstem compared to CA groups, potentially aiding in distinguishing sporadic CA from inherited forms.

Conclusions: Our study provides evidence of distinct structural alterations involving both GM and WM in CA patients of different neurodegenerative ataxias, contributing to a better understanding of the underlying degenerative processes and having implications for diagnostics and future therapeutic approaches tailored to the specific CA causes.

## CEREBRAL SMALL VESSEL DISEASE LOAD AND PROGRESSION IN A COHORT OF OLDER PATIENTS WITH ATRIAL FIBRILLATION ON ANTICOAGULANTS: STRAT-AF STUDY

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Aims: In atrial fibrillation (AF), anticoagulants reduce the risk of thromboembolism at the cost of increased bleeding risk. Treatment decision should consider the estimate of such risk. Available risk stratification schemes rely on gross clinical information and attempts to refine them are under way. Unfortunately, none of such schemes are directed toward the most feared hemorrhagic complication, i.e. intracerebral hemorrhage (ICH). In AF, neuroimaging has led to increased detection of "asymptomatic" changes, particularly those related to small vessel disease (SVD), the main pathologic substrate of ICH. SVD might serve as surrogate marker of a bleeding-prone state. Despite this, debate is ongoing on how to consider such "brain" information in treatment decision-making. Our aims were to describe, in a cohort of older AF patients on anticoagulants, baseline SVD load and progression, and to evaluate predictors of such progression.

Methods: Strat-AF was a single center, longitudinal, observational study evaluating older (>/=65 years) patients with AF on anticoagulants. Patients were recruited from the outpatient clinic Center for Thrombosis at Careggi University Hospital and assessed by means of a comprehensive clinical evaluation and brain MRI, both repeated after 18 months. SVD was assessed according to visual scales: white matter hyperintensities (WMH; Fazekas, Scheltens scales), Microbleeds (MB; MARS), lacunar infarcts (LI; number), enlarged perivascular spaces (EPVS; 4-point scale). SVD total score was calculated (0-4 point). Face to face comparison between the baseline and follow-up scan was used to measure SVD progression: Rotterdam scale for WMH; incidence of new MB and LI; 1-point increase of EPVS scale. Predictors of progression were assessed by logistic regression.

Results: At baseline, 170 patients were enrolled (mean age 77.7+/-6.8, 110 males), of whom 114 had complete follow-up information (mean age 76.7+/-6.5, 77 males). At baseline, 67% of the cohort had moderate severe WMH, 60% had moderate severe EPVS, 22% and 17% had >/=1 LI and MB. SVD total score: 0=18%, 1=24%, 2=38%, 3=13%, 4=4%. At follow-up, two thirds of the study cohort progressed in at least one lesion type; 53% WMH, 17% EPVS, 5% LI, 12% MB. Baseline WMH (Scheltens score) and MB (number) were the independent predictors for their individual progression [OR1.09(95%CI,1.03-1.15) and OR1.76(95%CI,1.18-2.63) respectively].

Discussion: In Strat-AF, neuroimaging detected a considerable proportion of AF older patients on anticoagulants with high SVD burden, and confirms that baseline SVD load predicts future progression, corroborating the hypothesis of a useful surrogate marker.

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## POLIOMYELITIS-LIKE ACUTE FLACCID PARALYSIS DUE TO WEST NILE VIRUS 1 STRAIN: CLINICAL AND NEUROIMAGING FINDINGS

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Introduction: The West Nile virus (WNV) is an arbovirus than can infect human beings and caused neuroinvasive disease (WNND) in more than half of reported cases to CDC in past years (53% reported as encephalitis, 37% as meningitis, 7% as acute flaccid paralysis or AFP). Despite the low sensitivity of MRI (20 to 70%), lesions affecting basal ganglia, thalami, brainstem, cerebellum are often detected. In AFP anterior horns and/or anterior spinal nerves roots have been sometimes found affected.

Aim: To report clinical and imaging findings for neuroinvasive disease due to WNV lineage 1 during the outbreak occurred in Veneto in 20223.

Materials and Methods: Forty-seven patients with WNV infection diagnosed at our center, between 12/07/22 to 21/09/22 (45 definite WNND, 2 probable WNND; 29 males; mean age 71 +/- 14.1 years)

were collected. 38/47 patients underwent brain MRI and 19/47 a whole spinal cord MRI. Statistical analyses included descriptive statistics, Pearson's correlation, and chi-square tests (Bonferroni corrected for multiple comparisons). Three patients underwent brain and spinal autopsy.

Results: AFP was the most frequent clinical phenotype (42.6%), followed by encephalitis (34%), paucisymptomatic disease (12.8%) and meningitis (10.6%). The most common imaging finding was the diffuse gadolinium enhancement of anterior spinal nerves roots, especially those of cauda, in 10/19 of total cases and 10/14 of AFP cases. In fewer cases, MRI showed hyperintensity foci in T2-weighted sequences in cerebellum (5/38), brainstem (3/38), cranial nerves (3/38), thalamus (2/38), basal ganglia (1/38), mesial temporal lobe (1/38) and dorsal spinal cord (1/19), sometimes associated to alterations in diffusion-weighted sequences and/or gadolinium enhancement. The spinal nerves roots involvement, AFP phenotype and motor deficit severity were predictors for ICU admission, death, and correlates positively with post-event mRS and length of hospitalization. The overall 3- and 7-month mortality were 35% and 45% in AFP cases. Pathologic studies in three patients with AFP demonstrated extensive inflammatory infiltration in cerebral hemispheres, brainstem, anterior horns and in one case also in the anterior roots of the spinal nerves.

Discussion and Conclusions: The new WNV-1 strain appeared to be associated with an increased risk of severe AFP, worse prognosis, and higher mortality. MRI shows a sensitivity of 50-70%, especially in cases of AFP. Further studies need to define whether the WNV-1 can cause a more severe form of WNND due to major tropism toward anterior horns and/or spinal nerve roots, or maybe if damage at these levels is also due to reactive immune-mediated attack.

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## CLINICAL RELEVANCE OF SPATIAL CORRESPONDENCE BETWEEN REGIONAL GENE EXPRESSION AND GREY MATTER ATROPHY IN MULTIPLE SCLEROSIS


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Objectives: Heterogeneous pathological processes, possibly influenced by specific regional gene expression differences, may contribute to a non-random and clinically-relevant grey matter (GM) atrophy progression in multiple sclerosis (MS). In this study, we aimed to investigate the spatial associations between regional GM atrophy and gene expression in MS.

Material and Methods: Brain 3T magnetic resonance imaging (MRI), neurological evaluation and neuropsychological assessment were obtained from 286 MS patients and 172 healthy controls (HC). Patterns of regional GM atrophy in MS patients compared to HC and according to clinical disability and cognitive status were investigated using voxel-based morphometry (VBM) ($p<0.05$, family-wise error-corrected). Genes associated with MS were identified from Open Target Platform (n=2710). The spatial cross-correlations between VBM-derived GM maps and gene expressions provided by Allen Human Brain Atlas were explored using the MENGA platform. Using ToppGene Suite, enrichment analyses were performed to explore over-represented molecular functions and cellular components involving gene expressions significantly associated with VBM-derived GM maps ($p<0.05$, Bonferroni-corrected).

Results: Compared to HC, MS patients showed widespread GM atrophy being significantly associated with the regional expression of 74 genes, involved in synaptic GABA receptor functions and mitochondrial oxidoreductase activities and mainly expressed in neurons and astrocytes. Lower volume in bilateral deep GM nuclei and cerebellum, and left insula was significantly associated with a higher Expanded Disability Status Scale score and with the expression of 44 genes being enriched in the mitochondrial and cellular nucleoids of all central nervous system (CNS) resident cells. Cognitively-impaired (n=113) vs cognitively-preserved (n=173) MS patients had distributed GM atrophy being significantly associated with the expression of 64 genes, that are involved in protein heterodimerization and oxidoreductase activities of mitochondrial and organelle membranes/envelopes and are expressed by microglia and endothelial cells.

Discussion: A clinically-relevant regional GM atrophy occurs in MS patients, especially in those with a more severe disability and cognitive impairment. This regional GM atrophy pattern is non-random and is associated with different regional expressions of genes that are mainly involved in synaptic GABA receptor activity and mitochondrial oxidoreductase functions.

Conclusions: Specific gene expression differences may influence regional susceptibility to excitatory/inhibitory imbalance and oxidative stress not only in neurons, but also in other resident CNS cells. This may accelerate neurodegenerative processes and, ultimately, GM atrophy.

## DIFFERENTIATING BETWEEN COMMON PSP SUBTYPES USING STRUCTURAL MRI: A MACHINE LEARNING STUDY


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Background: Differentiating Progressive supranuclear palsy-Richardson's syndrome (PSP-RS) from PSP-Parkinsonism (PSP-P) may be extremely challenging [1-2]. In this study, we aimed to distinguish these two PSP subtypes using MRI structural data.

Methods: Sixty-two PSP-RS, 40 PSP-P patients and 33 control subjects were enrolled in the study. All patients underwent a brain 3T-MRI; cortical thickness and cortical/subcortical volumes were extracted using Freesurfer 7 on T1-weighted images. We calculated the Automated MR Parkinsonism Index (MRPI) and MRPI 2.0 and tested their classification performance. Machine learning (ML) models (eXtreme Gradient Boosting [XGBoost] and Random Forest) using different combinations of structural MRI data were also tested in differentiating between PSP subtypes.

Results: MRPI and MRPI 2.0 showed AUC >0.97 in distinguishing PSP patients from controls but had AUC of 0.88 and 0.81, respectively in differentiating PSP-RS from PSP-P. ML models demonstrated that the combination of MRPI and volumetric/thickness data was more powerful than each feature used alone. The best ML model in differentiating between PSP subtypes was XGBoost which showed AUC: 0.93(0.04) using a combination of MRPI, cortical thickness and subcortical volumes. Similar performance (AUC: 0.93[0.06]) were also obtained by XGBoost in a sub-cohort of 59 early PSP patients.

Conclusion: The combined use of MRPI and volumetric/thickness data was more accurate than MRI features used alone in differentiating between PSP-RS and PSP-P. Our study supports the use of structural MRI to improve the early differential diagnosis between common PSP subtypes, which may be relevant for prognostic implications and patient inclusion in clinical trials.

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## A CASE OF MARCHIAFAVA-BIGNAMI DISEASE

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Introduction: Marchiafava-Bignami disease (MBD) is a very rare disorder discovered in 1903 by Italian pathologists Ettore Marchiafava and Amico Bignami. It is caused by demyelination/necrosis of the corpus callosum and the near subcortical white matter and is especially predominant in ill-fed alcoholics. The clinical picture is characterized by dementia, dysarthria, spasticity, and walking inability. [1]

Clinical case: A 47 years-old man with severe alcohol use disorder (per DSM-5 criteria) presented to the Emergency Department of our Hospital for a tonic-clonic generalized seizure. He had a two-months history of severe impairment of attention, imbalance, postural tremor, and walk difficulties. At neurological evaluation he was awake, displayed disorientation in time and space, postural tremor of upper limbs, severe imbalance with impossibility to walk. Laboratory tests showed decreased hemoglobin (12.5 g/dL), increased mean globular volume (99.1 fL), increased γ-glutamyl transferase (71 U/L), and increased creatine-kinase (1666 UI/L). A brain CT scan demonstrated no pathologic finding, while a brain MRI showed bilateral ovaloid areas in the splenium of the corpus callosum and in the left-side of the genu of corpus callosum that appeared hyperintense on T2-weighted images and diffusion-weighted images and hypointense on T1-weighted images, consistent with MBD. B-complex vitamins were administered, and alcohol use was forbidden.

Conclusion: Alcohol consumption is the most relevant risk factor for MBD. However, its etiology remains unclear. The symptoms of MBD are nonspecific and common in other alcohol-related diseases, such as alcohol withdrawal syndrome, Wernicke's encephalopathy, delirium, and dementia, thus making the differential diagnosis wide ranging. The distinctive element of MBD lies on the MRI characteristic presentation consisting of T1-hypointense and T2-hyperintense bisymmetric lesions involving the corpus callosum. There is no specific therapy for this disease. Some case reports have shown a favorable response to high-dose parenteral thiamine and oral B-complex vitamins. An early diagnosis and adequate treatment may provide a favorable outcome for a potentially fatal disease. MBD should be considered in the differential diagnosis of patients with heavy alcohol consumption presenting with imbalance, memory and/or behavioral abnormalities, hallucinatory phenomena, and gait disturbances. Although therapy significantly overlaps with that of Wernicke-Korsakoff syndrome or alcohol withdrawal syndrome, one should always bear in mind that a high-dose thiamine course might be required.

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## ALTERED FUNCTIONAL NETWORKS IN CORTICOBASAL SYNDROME AND PROGRESSIVE SUPRANUCLEAR PALSY: A COORDINATE BASED ALE METANALYSIS

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Corticobasal Syndrome (CBS) and Progressive Supranuclear Palsy (PSP) are neurodegenerative diseases characterized by movement disorders and progressive cognitive decline, belonging to the Fronto-Temporal Lobar Degeneration (FTLD) spectrum. In this study, we analyzed these two diseases for their common underlying neuropathology and their concurrent evolution in dementia and movement impairment. To better define diagnostic and pathophysiological differences between them, we extrapolated their radiological traits through a neuroimaging coordinate based meta-analytic approach. Then, we used a functional connectivity (FC) analysis to identify altered brain resting-state networks (RSNs) associated with the resulting imaging maps. We selected 32 functional imaging studies using Fluoro-Deoxy-Glucose Positron Emission Tomography (FDG-PET) and Tecnetium-99 Single Photon Emission Computed Tomography (ECD-SPECT), following the Preferred Reporting Items for Reviews and Meta-analysis (PRISMA) statement, and analyzed them through the activation likelihood estimate statistical framework to identify syndrome-specific hypofunctional regions. Neurosinth software were used to determine FC maps of these areas. PSP is distinguished by much underactivated subcortical regions: Mid-brain, Putamen, Caudate Nucleus and Thalamus. Also cortical areas were found dysfunctional, precisely Anterior and Middle Cingulate Cortex, Anterior Insular Cortex and Superior Frontal Gyrus. CBS showed hypofunctional areas corresponding to Thalamus and left Inferior Parietal Lobule. Conjunction analysis between syndromes showed the Thalamus as the only region affected in both diseases. Subtraction analysis confirmed Mid-brain, Striatum and Fronto-Insular areas as abnormal in PSP, while Inferior Parietal Lobule characterizing CBS. Analyzing the RSNs implicated in each resulting underactivated region, it emerged that PSP have a remarkable involvement of the Basal Ganglia Network (BG), but also of cortical networks: Ventral Attention Network (VAN), Fronto-Parietal Control Network (FPCN) and anterior Default Mode Network (aDMN). The

RSNs associated with CBS were BG and Dorsal Attention Network (DAN). As expected, PSP demonstrated an abnormal functioning of the BG, predominantly associated with Mid-brain and Striatum. Furthermore, also VAN, FPCN and aDMN are involved, reflecting the executive and goal-directed behavior dysfunctions which characterize the disease. Interestingly, CBS did not show Striatum impairment, more commonly associated with movement disorders, but abnormal thalamic activity, although still belonging to the BG. The concomitant dysfunctional DAN suggests the possible presence of a complex attentional-perceptive deficit underlying the great variety of movement disturbances and dysexecutive symptoms featuring this syndrome. The present study identifies brain regions of hypofunctional activity in PSP and CBS, highlighting the related altered RSNs. The resulting maps could help to isolate brain target regions for future non-invasive brain stimulation applications.

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## CSF-IN GRADIENT OF THALAMIC AND CORTICAL DAMAGE IN MULTIPLE SCLEROSIS: A 3T MAGNETIZATION TRANSFER RATIO AND R2* STUDY

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Objectives: A cerebrospinal fluid (CSF)-in gradient in cortical and deep gray matter (GM) damage has been found in multiple sclerosis (MS). However, the combined evaluation of gradient of cortical and deep GM damage has not been explored yet. We analyzed the concomitant patterns of cortical and deep GM microstructural abnormalities in MS at progressive distances from CSF using a multiparametric MRI approach.

Materials and Methods: Brain 3T MRI scans were acquired from 52 MS patients (33 relapsing-remitting [RR], 19 progressive [P]) and 70 healthy controls (HC). From 3DT1-weighted, we sampled cortical layers at 25%-50%-75% depths from pial to cortical-white matter (WM) interface and thalamic and caudate bands at 2-3-4 voxels from ventricular- GM interface. We tested between-group comparisons of magnetization transfer ratio (MTR) and R2* layer-specific z-scores and CSF-in across-layers z-scores changes, as well their correlations with clinical and structural measures (linear mixed models).

Results: Compared to HC, RRMS patients showed significantly lower MTR values in the outer cortical layer (FDR-p=0.025) and lower R2* values in all three cortical layers (FDR-p≤0.027). Compared to HC, PMS patients had significantly lower MTR values in the outer and middle thalamic layers (FDR-p≤0.048), in the outer caudate layer (FDR-p≤0.024), and in the outer and middle cortical layers (FDR-p≤0.016). They also showed lower R2* values in the outer thalamic layer (FDR-p=0.046) and in the outer cortical layer (FDR-p=0.003) as well as higher R2* values in all three caudate layers (FDR-p≤0.031). A significant gradient of damage, with lower values closer to the CSF, was found for thalamic MTR in both RRMS and PMS patients (FDR-p≤0.042), thalamic R2* and caudate MTR only in PMS patients (FDR-p≤0.013), cortical MTR in both RRMS and PMS patients (FDR-p≤0.002) and cortical R2* only in PMS patients (FDR-p=0.005). Lower MTR and R2* values of outer thalamic, caudate and cortical layers and steeper gradient of damage towards the CSF were significantly associated with older age, higher brain WM lesion volume and lower brain volume (absolute β≥0.08, all FDR-p<=0.040). No correlations with choroid plexus volume were found.

Discussion: We identified different CSF-in gradient of damage in the thalamus, caudate nucleus and cortex, being more substantial in PMS patients and possibly reflecting heterogeneous pathological substrates, such as demyelination, iron loss or accumulation, that differently affect these GM structures.

Conclusions: The analysis of MTR and R2* at different layers may contribute to disentangle the heterogeneous pathological processes occurring in the deep GM and cortex of MS patients.

## SURFACE-BASED BUT NOT VOXEL-BASED MORPHOMETRY REVEALS STRUCTURAL ABNORMALITIES IN INDIVIDUALS WITH SUBJECTIVE COGNITIVE DECLINE

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Objective: Subjective cognitive decline (SCD) is a condition that defines individuals who perceive a decrease in their cognitive functioning in the absence of any detectable deficit on neuropsychological testing [1]. SCD may be regarded as the earliest clinical stage of Alzheimer's Disease (AD) [2]. Brain structural changes have been reported inconsistently across previous studies [3]. The aim of the present study was to assess both grey matter (GM) volumes and patterns of cortical folding across the AD spectrum.

Methods: 107 individuals (31 patients with AD and 23 with Mild Cognitive Impairment (MCI, 25 individuals with SCD, and 28 Healthy Subjects [HS]) underwent neuropsychological assessment and a 3T-MRI scan to collect T1-weighted volumes (MEMPRAGE sequence). MEMPRAGE images were pre-processed using CAT-12 to obtain structural maps to perform both voxel-based (VBM) and surfaced-based morphometry (SBM). The former analysis allows the investigation of regional GM volumetrics, while the latter allows the extraction of cortical thickness, gyrification, fractal dimension, and the so-called sulcus depth. A full factorial design was used in SPM-12 to assess between-group differences in each metric separately.

Results: VBM showed the expected pattern of regional GM atrophy in AD and MCI patients compared to HS, but also to individuals with SCD. Conversely, no volumetric differences were detected in SCD individuals compared to HS. Patients with AD, compared to all other groups, showed cortical surface abnormalities in all SBM measures. MCI patients showed reduced thickness compared to both SCD subjects and HS with a bilateral distribution, alongside reduced gyrification in the left hemisphere. Moreover, MCI patients compared to HS showed reduced gyrification also in the right hemisphere. When considering fractal dimension, MCI showed reduced complexity compared to both SCD and HS in the left hemisphere. In addition, they showed reduced sulcal depth compared to SCD in the left hemisphere and to HS in the right hemisphere. Finally, SCD individuals compared to HS showed reduced gyrification bilaterally and reduced sulcal depth in the right hemisphere.

Discussion: VBM confirms its high sensitivity in detecting GM changes in the clinical categories of AD and MCI only. Conversely, cortical surface abnormalities can be detected at earlier stages, thus providing an objective measure of brain damage to be used for patient stratification and monitoring in future clinical trials for disease modifying treatments.

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## DISTINCTIVE LONGITUDINAL CORTICAL ATROPHY PROGRESSION PATTERNS CHARACTERIZE CLINICAL VARIANTS OF THE FRONTOTEMPORAL DEMENTIA CONTINUUM

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Objectives: The spectrum of frontotemporal lobar degeneration (FTLD) encompasses a wide variety of clinical phenotypes, with predominant behavioural and/or language presentations. Each frontotemporal dementia (FTD) syndrome is characterized by specific patterns of atrophy underlying clinical symptoms. Recently, an emerging variant with distinctive clinical features has been described1 with the name of semantic behavioural variant FTD (sbvFTD). The main aim of the study was to provide a comprehensive overview of the structural neuroimaging correlates of each specific FTD variant at baseline and describe longitudinal patterns of disease progression for each syndrome, with a particular focus on sbvFTD, which remains relatively poorly characterized in the current literature.

Materials: Our cohort included a total of 73 patients with a clinical diagnosis of behavioral variant of FTD (bvFTD, n=38), sbvFTD (n=8), semantic (svPPA, n=13) or non-fluent/agrammatic variants of primary progressive aphasia (n=14), who underwent serial neurological evaluations, neuropsychological assessments and at least two MRI scans on a 3T scanner. Fifty-two healthy controls underwent the same protocol. Methods: For each group, vertex-based and regional cortical thickness analyses were performed at baseline and longitudinally to identify patterns of atrophy at baseline and regions of cortical atrophy progression compared to healthy controls. Longitudinal mixed effect models were corrected for multiple comparisons, and adjusted for sex, age and education levels.

Results: At baseline, both vertex-wise and regional cortical thickness analyses identified specific patterns of atrophy for each FTD variant, with bvFTD showing extensive bilateral frontotemporal involvement, svPPA presenting selective left temporal lobe atrophy with initial spread to contralateral temporal pole, and nfvPPA displaying frontoparietal atrophy, mostly lateralized to left hemisphere. Patients with sbvFTD had an intermediate atrophy pattern between bvFTD and svPPA, with right-predominant temporal pole involvement associated to significant right frontal atrophy. Longitudinally, bvFTD patients were found to progress widely bilaterally, while svPPA continued steady progression restricted to the temporal lobes, nfvPPA showed limited foci of disease progression and sbvFTD showed progression only in the left temporal lobe with limited further volume loss in the right hemisphere.

Discussion: Our study has characterized structural neuroimaging hallmarks of each FTD variant and recognized variant-specific patterns of disease progression.

Conclusions: These findings could aid in the identification of imaging biomarkers able to improve FTD diagnosis and prognostic stratification. Moreover, our results singled out sbvFTD as a relatively distinct entity, despite its partial overlap with both bvFTD and svPPA.

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## STUDY OF CEREBRAL PERFUSION IN NEWBORNS WITH MRI AND PCASL SEQUENCE

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Objectives: The term "perfusion" refers to the supply of oxygen and nutrients to the tissues via the bloodstream. Cerebral perfusion is quantified in terms of cerebral blood flow (CBF). Previous studies estimated neonatal cerebral perfusion by means of techniques with limitations, such as invasiveness, reduced sensitivity or the inability to obtain regional but only global flow measurements. Arterial Spin Labelling (ASL) is a non-invasive magnetic risonance imaging (MRI) sequence without contrast medium, able to provide CBF colorimetric maps. Our study aims at measuring the regional CBF in neonates by means of ASL and at identifying possible correlations between regional CBF values and the gestational age at birth (EG).

Materials: One hundred three subjects were initially recruited. From those we excluded subjects with ASL movement artifacts and encephalic pathologies relevant enough to compromise cerebral perfusion. The remaining 63 subjects were studied at term equivalent age (the MRI was performed at the fortieth week of corrected gestational age). Subjects were then divided into gestational age groups.

Methods: Ten regions of interest were identified via a morphological sequence (with care to include as little white matter and large vessels as possible and to maintain for all regions the same size, with a 5% variability). Regional CBF values were then estimated. T-tests were performed to compare the values between the two hemispheres, and an ANOVA model was applied to compare the CBF values in the various brain regions. Finally, Pearson correlation was used to evidence a CBF-EG relationship.

Results: No significant differences between CBF values in the two hemispheres were found. The highest perfusion values were found at the level of the thalamus and the frontal cortex, the lowest at the level of the parietal cortex. The most interesting data of our study is the demonstration that higher gestational ages correspond to higher perfusion values.

Discussion: Our study shows that, as already reported in the literature, CBF is higher in regions that can be associated with the greater motor rather than sensory activity of the fetus, in an environment relatively protected from external sensory stimuli.

Conclusions: Moreover, we showed the positive correlation between CBF and EG, not yet demonstrated in subjects in vivo. This finding can be explained by the importance of maturation of vascular and brain structures during fetal development.

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## MOTOR BAND SIGN AS AN ULTRA-EARLY NEURORADIOLOGICAL FINDING IN PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)


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Introduction: Progressive multifocal leukoencephalopathy (PML) is a demyelinating central nervous system infectious disorder caused by the reactivation of the JC virus (JCV), that usually present in immunocompromised patients. Together with HIV-related PML, iatrogenic PML accounts for an increasing proportion of cases due to the rising number of patients who received immunosuppressive treatments [1]. The diagnosis relies on the American Academy of Neurology (AAN) criteria, yet the JCV-related disease spectrum of presentations has evolved and may challenge the current diagnostic criteria [2]. An early diagnosis is of utmost importance for rapid workup and management, especially in the iatrogenic form of PML.

Case report: We describe a patient presenting with a progressive right-hand sensorimotor deficit and gait imbalance. His medical history was relevant for multiple myeloma treated with different chemotherapies lines and myelodysplastic syndrome treated with allogeneic bone marrow transplantation ten months before presentation. A brain MRI performed two weeks after the onset of symptoms showed two bilateral edematous lesions localized in the primary motor cortex characterized by FLAIR hyperintensity and low signal on susceptibility-weighted sequence (SWI) without contrast enhancement. The MRI also revealed three areas of FLAIR hyperintensities in the left centrum semiovale. A follow-up brain MRI performed one week later revealed a slight spatial progression of the lesions mentioned above. Even though an initial cerebrospinal fluid (CSF) analysis was unremarkable, with no JCV DNA copies detected, a subsequent lumbar puncture a few days later was positive; thus, the patient fulfilled the AAN criteria for definite PML.

Conclusions: Unilateral or bilateral hypointense SWI rims associated with FLAIR hyperintensity within the primary motor cortex ("motor bands") are not classically reported as a neuroradiological finding of PML. The underpinning biologics is still unrevealed, yet recent studies suggest that the motor bend sign can appear even in the presymptomatic stage of the disease as a consequence of initial iron accumulation in infected oligodendrocytes at the cortical-subcortical junction [3]. The "motor band sign" may herald an early PML onset, therefore, CSF analysis to confirm the diagnosis should be performed, and in some case repeated, even in the atypical clinical context.

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## NEUROIMMUNOLOGY AND NEUROINFECTIVOLOGY

## OCRELIZUMAB MODULATES CD8+ T CELL PROFILE AND FUNCTION IN RELAPSING MULTIPLE SCLEROSIS


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Background and Objectives: Ocrelizumab is an anti-CD20 agent with beneficial effects in Relapsing Multiple Sclerosis (RMS), prevalently due to a specific B-cell depletion [1]. Other immune cells could be modulated by this treatment, thus contributing to its therapeutic efficacy [2]. Experimental evidence suggests B cell infection by Epstein-Barr virus (EBV) as one of the promoters of a dysregulated cytotoxic CD8+ T cell response and consequent central nervous system (CNS)

tissue damage [3]. To evaluate the effect of ocrelizumab on phenotype and function of CD8+ T lymphocytes in patients affected by RMS, with a focus on EBV-specific response.

Methods: RMS subjects undergoing ocrelizumab treatment were consecutively enrolled and prospectively followed-up. Blood samples were collected just before ocrelizumab initiation and after 6 and 12 months of treatment. Immune profile and cytotoxic function of CD8+ T lymphocytes were assessed; further, CD8+ T cell anti-viral proliferative response was evaluated.

Results: Forty RMS subjects (mean age 41,95 ± 5,26 years; female sex 45,45%) were enrolled. We noticed an increase of naive (p=0.004) and a decrease of effector memory (p=0,0202) CD8+ T cells, upon ocrelizumab treatment. CD8+ T cells showed a reduced expression of the activation marker CD69 (p=0,0429), the exhaustion marker PD-1 (p=0,0019) and the effector molecule granzyme K (p<0.0001) after ocrelizumab treatment; we also noticed a significant reduction of different migration molecules on CD8+ T lymphocytes, such as CCR5 (p=0,0035), CXCR6 (p=0,0408) and CD49d (p=0,0055). Functional assays revealed an impaired CD8+ T cell cytotoxic function in RMS individuals six months after ocrelizumab administration. Indeed TCR-activated CD8+ T cell presented a reduced expression of CD107a (p=0.0313), IFN-gamma (p=0.469) and granzyme B (p=0.0156) after the treatment. Concerning virus-specific CD8+ T cell expansion, we found that ocrelizumab administration determined a selective reduction of CD8+ T cell proliferation upon EBV peptides stimulation (p=0.0464), whereas no differences were observed upon cytomegalovirus peptides and Sars-CoV-2 spike antigen stimulation.

Conclusion: Our results provide novel insights on the capability of ocrelizumab to modulate CD8+ T cell activation/migration profile and cytotoxic activity. Further, the selective impact of this agent on EBV-specific CD8+ T cell proliferation suggests a possible impact of ocrelizumab in the trialogue among CD8+ T cells, EBV and B cells, central in the pathogenesis of MS.

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## LONG-TERM NEUROLOGICAL SEQUELAE IN PATIENTS PRESENTING WITH ENCEPHALITIS


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Background and Aims: Advances in encephalitis research in the last decade have led to a better definition and assessment to define autoimmune or infectious etiologies. A few works investigated the use of antiepileptic drugs [1,2] and cognitive outcome [3] of different subtypes of encephalitis but no large studies evaluated the difference between subtypes of encephalitis in term of long-term neurological sequalae.

Objectives: To analyze long-term clinical outcome in patients with autoimmune encephalitis (AEs), to underline whether they present a different risk of relapse and clinical sequelae/ burden when compared to other subtypes of encephalitis, and to evaluate whether CSF marker on admission could predict long-term outcomes.

Methods: The retrospective study included all patients discharged from the Neurology Unit of "Spedali Civili di Brescia" with a diagnosis of encephalitis of any kind from 01.01.2011 to 16.11.2022. Patients were evaluated by phone interview using "Neurocheck list", a 16-item questionnaire evaluating the severity and frequency of neurological symptoms after hospitalization. Encephalitis cases were classified according to standard guidelines into autoimmune (AI), infectious (IE) and of unknown origin (UE)

Results: A total of 117 patients with encephalitis were consecutively evaluated and 70 of them included in follow-up (Mean age 51,29 years; mean follow-up duration 3,28 years; AE n=32, IE n=12, UE n=26). Nine patients presented a clinical relapse resulting in hospitalization (AE n=8, (16.0%);, UE n=1 (2,13%) , p=0.001). The most common symptoms reported were memory loss (n=35; 50,00%) and depressive symptoms (n=29; 41,42%). Although mRS at dismission was significantly worse in AE compared with UE (p=0,017), no significant differences were observed neither in cognitive-behavioural domains nor in non-motor symptoms. However, AI exhibited the best long-term prognosis in terms of vertigo/dizziness and headache (9,4% AE 31,6% IE+UE; 9,4% AE 31,6% IE+UE p=0,038; p=0,038). Eventually, nor higher CSF cell count neither higher CSF proteins appeared to predict long-term clinical outcome.

Discussions: In this long-term study AE have been associated with higher risk of recurrent poussèes but possibly lower burden compared to other encephalitis. Further studies are needed in order to understand the predictors of long-term sequelae in order to identify those patients who might benefit from cognitive and behavioral training after discharge.

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## THE INSIDIOUS CLINICO-RADIOLOGICAL FEATURES OF NEUROINFECTIOUS DISEASES IN EMERGENCY: TWO CLINICAL CASES


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Introduction: Below we present two clinical cases that highlight the great clinical and laboratory variability of neuroinfectious diseases.

Discussion: A 18-year-old girl comes to E.R. because of frontal intense headache. It had started 2 months earlier and had worsened. The primary physician concluded for sinusitis and started antibiotic therapy a week earlier. She hasn't flue. Neutrophilia is present (11.000 WBC/mm3). At neurological examination she is akathisiac, confused and

hypostenic to left limbs. Brain-CT shows two large areas of bifrontal hypointensity, surrounded by edema. The 2-months story of headache together with images may indicate tumor or infectious disease. Gd-MRI illustrates two T2-FLAIR hyperintense bifrontal expansive formations, abundant edema, with marked signal restriction in DWI/ADC. The walls show marked contrastographic impregnation with intense meningeal enhancement. Both lesions appear contiguous with frontal hemisenus, with focal erosion of the bony cortical. The frontal sinus present abundant inflammatory material. Clinical-radiological data are suspicious for brain abscess [1]. The girl is taken to the neurosurgical room for abscess drainage and begins intravenous antibiotic therapy for S. Pneumoniae. A 32 year-old man comes to the E.R. for subentrant seizures and confusional state. A month earlier, after car accident, the patient had a subdural hematoma, without cranial bone fractures and neurological symptoms. He denies epilepsy previously. He has no fever. CRP is 40 mg/dl at blood exams (cut-off < 5 mg/dl). He is uninhibited, disoriented, with incongruous speech. Presents mild hyposthenia in the left arm. Brain CT shows partially regressed right hemispheric subdural hematoma, and the appearance of a small hypodense area in the right temporal lobe of likely ischemic-compressive nature. The following day, another CT shows enlargement of the hypodense area. This rapid change let us hypotize a possible infectous disease. Lumbar puncture is normal in protein and cellular count, with negative bacteriological and virological exams. Brain MRI shows signal restriction in DWI/ADC and T1 hyperintense signal in subdural space, surrounded by vasogenic edema in right temporo-frontal white matter. Findings depose for evolution into empyema of the subdural hematoma [2]. The man underwent urgent neurosurgical surgery and broad-spectrum antibiotic therapy.

Conclusions: Both patients recovered without sequelae. These clinical cases underline the importance to consider, especially in young people, infectious etiology, even in the absence of fever, or changes on hematochemical or CSF examinations. Accurate and rapid differential diagnosis is important so that the correct antibiotic and possibly surgical treatment can be carried out to ensure an optimal prognosis.

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## EXPLORING THE ROLE OF EBV IN MS PATHOGENESIS STARTING FROM EBV INTERACTOME

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Epstein-Barr virus (EBV) infection has been described as one of the main risk factors for developing multiple sclerosis (MS), and recently, new epidemiological evidence has reinforced this premise. The molecular mechanisms of this association are complex and may involve different immunological routes, however the ultimate role of EBV in the pathogenesis of MS is not fully understood. To identify MS associated genes overlapping with EBV interactome and their expression in immune cell subtypes. We obtained EBV interactome from p-HIPSTER, a structure-informed atlas of human-virus interactions, the MS associated genes from NHGRI-EBI Catalog of human genome-wide association studies and the single cell gene expression from B and T-cells, astrocytes, macrophages, granulocytes, monocytes, microglia, dendritic and natural killer cells from the Human Protein Atlas. We overlapped the lists thus obtained by using the geneOverlap R package. We observed significant overlap between EBV interactome and MS associated genes in 45 genes [odds ratio (OR): 2.1, $p<0.001$]. Among the different immune cell populations, we identified a "core" group of 15 genes resulting from the overlap between EBV interactome and MS associated genes and expressed in all immune cell type selected ($p<0.001$). This "core" included ARHGAP27, ASAP1, CD226, COPB1, JAK1, JAK2, MAPK1, MAPK3, MEF2C, MINK1, NFKB1, RPS6KB1, STAT3, TYK2, YWHAG, genes expressed not only by B and T cells, but also by glial cells and cells belonging to innate immune system. The present findings suggest a broad range immune system involvement in mediating EBV effect on MS pathogenesis. In details, our results raise the hypothesis that EBV could contribute to MS pathogenesis even through its interaction with innate immunity.

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## A CASE OF SERONEGATIVE AUTOIMMUNE ENCEPHALITIS WITH A FAVOURABLE COURSE – THE IMPORTANCE OF EARLY THERAPY

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Background: Autoimmune encephalitis (AE) comprise a variety of inflammatory diseases of the central nervous system (CNS) with heterogeneous clinical manifestations and etiology [1]. Differential diagnosis of AE is often challenging thus entailing a possible delay of an early and adequate therapy.

Case report: A 29 y.o. girl, with no previous relevant clinical history, presented with the sub-acute onset of fever (39°C) following a week of mild upper respiratory tract symptoms, together with confusion and speech disturbances rapidly evolving to severe non-fluent aphasia. During neurological examination emotional distress increased, oscillating between intense crying/fast breathing periods and generic unease and restlessness. No neck rigidity or ulterior symptoms were observed. Blood tests showed increased neutrophils count (15.000 cells/uL) and high CRP levels. CT and MRI scans were normal. The clinical picture evolved in a temporal status epilepticus with respiratory distress and the patient was intubated and transferred to the ICU. Cerebrospinal fluid (CSF) revealed increased cell count (1250 cells/μL, all lymphocytes) [2], and CSF-proteins (176 mg/dL), while lactic acid and glucose were in range. Microbiological work-up in serum and CSF was negative. Waiting for the results of blood and CSF tests for AE, treatment with broad-spectrum antibiotic, antiviral and antiepileptic drugs, together with high-dose steroids (Methylprednisolone 1 g per day) was immediately started. A cycle of 5 PEX (one every three days) was also performed. EEG showed fronto-temporal epileptic figures with left prevalence. CE-MRI revealed a subtle increase in intensity through the peri-optical nerve CSF, fronto-parieto-temporal sulci, as well as diffuse cortical contrast-enhancement. Full-body 18F-FDG PET-MRI showed irregular cortical glucose absorption, with a slight front-to-back gradient and hypercaptation

in the basal ganglia and amygdala, confirming encephalitic involvement. No sign of systemic pathology was found. Following treatment, improvements in clinical, EEG and CSF examination (lymphocytes: 222 cells/uL) were observed. Immunological tests and neoplastic markers in blood were negative. The patient completly recovered after three weeks. Neuropsychological evaluation as well as serial EEG were normal. The possible infectious trigger, the clinical picture, the disease course and the response to treatments allowed the diagnosis of "Probable Seronegative Autoimmune Encephalitis" [3].

Discussion: Auto-antibody-negative AE constitute a challenging diagnosis. In the presence of no better explanation for symptoms and signs, the prompt initiation of high-dose steroid and PEX is strongly recommended.

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## COVID-19-ASSOCIATED SERUM AND CEREBROSPINAL FLUID CYTOKINES IN POST- VERSUS PARA-INFECTIOUS SARS-COV-2-RELATED GUILLAIN-BARRÉ SYNDROME

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Introduction: Guillain–Barré syndrome associated with coronavirus-2-related severe acute respiratory syndrome (COV-GBS) occurs as para-, or post-infectious forms, depending on timing of disease onset. In these two forms, we aimed to compare the cerebrospinal fluid (CSF) and serum proinflammatory cytokine profiles, to evaluate differences that could possibly have co-pathogenic relevance.

Materials and Methods: We studied a retrospective cohort of 26 patients with either post-COV-GBS (n=15), with disease onset occurring >7 days after SARS-CoV-2 infection, or para-COV-GBS (n=11), with disease onset 7 days or less. TNF-α, IL-6, and IL-8 were measured in the serum with SimplePlexTM EllaTM immunoassay. In addition to the para-/post-COV-GBS patients, serum levels of these cytokines were determined in those with non-COVID-associated-GBS (NC-GBS; n=43), paucisymptomatic SARS-CoV-2 infection without GBS (COVID, n=20), and in healthy volunteers (HV; n=12). CSF cytokine levels were measured in patients with para-/post-COV-GBS, and in those with NC-GBS (n=29), or with Alzheimer's disease (AD; n=24).

Results: Serum/CSF cytokine levels did not differ in para- vs. post-COV-GBS. We found that SARS-CoV-2 infection raises the serum levels of TNF-α, IL-6 and IL-8, as well as an increase of IL-6 (in serum and CSF) and IL-8 (in CSF) in either NC-GBS or COV-GBS than controls. CSF and serum cytokine levels resulted independent one with another.

Discussion: This study shows that the para- and post-infectious forms of COVID-19-related GBS are not associated with a different CSF or serum profile of some cytokines previously described as specifically associated with SARS-CoV-2 infection.

Conclusions: The change of cytokines linked to SARS-CoV-2 in COV-GBS appears to be driven by viral infection, although it has unique characteristics in GBS as such and does not account for cases with para- or post-infectious onset.

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## CLINICAL OUTCOMES OF COVID-19 INFECTION AMONG PATIENTS WITH NMOSD RECEIVING INEBILIZUMAB TREATMENT IN THE N-MOMENTUM TRIAL AND SAFETY DATABASE IN THE UNITED STATES

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Objective: To describe the risk and outcomes of COVID-19 infections, in patients receiving inebilizumab, an anti-CD19, B cell depleting monoclonal antibody approved for the treatment of aquaporin-4 seropositive neuromyelitis optica spectrum disorder.

Materials: Adverse reaction reports of COVID-19 infections were analyzed for participants receiving inebilizumab in the N-MOmentum clinical trial during the COVID-19 pandemic (March-November 2020), and in a post- approval safety database (data cutoff July 31, 2022) in the United States.

Methods: Demographics, comorbidities, date of COVID-19 infection, duration of treatment with inebilizumab, seriousness, hospitalization, outcomes, and action taken with the drug were summarized.

Results: In all, there were 17 reports of confirmed COVID-19 infections among inebilizumab treated NMOSD patients (women,

n=15, unknown, n=2) from March 2020-July 2022. Median (range) age was 57 (32-68) years (n=15). Among 182 patients in N-MOmentum, 2 COVID-19 infections were reported between March-November 2020, prior to vaccine availability. The incidence rate was 0.024 (E/PY). In the safety database, 15 events were reported as of July 31, 2022. Median inebilizumab exposure in the overall group was 207.5 days (range 10-2379 days, n=12) from first infusion to COVID-19 diagnosis. Of the total 17 events, 10 events were reported as serious. COVID-19 vaccination status was not known. Five patients were had pneumonia. Of 10 patients with known outcomes 6 were reported as "recovered/resolved", 2 as not recovered/resolved at the time of reporting, and 2 died: 1 patient, 62 years, in Peru, died May 2020 before vaccine availability, possible COVID pneumonia, possible renal failure, received antibiotics, hydroxychloroquine and ivermectin; and 1 patient, 32 years, in US, died Feb 2021, possibly partially vaccinated, history of obesity, deep vein thromboembolism (DVT), sickle cell trait, treated for possible COVID pneumoniae complicated by pulmonary embolism (PE) with acute cor pulmonale. Inebilizumab treatment was reported as "not changed" in 3 patients, "withdrawn" in 1 patient, and action was unknown for the rest.

Discussion: In a 28-month period, a low incidence of COVID-19 infections was reported in patients with NMOSD receiving inebilizumab in the trial and in clinical settings in the US. Due to the nature of reporting, milder COVID cases could possibly be under-reported.

Conclusion: Inebilizumab treatment was not related to a high incidence of COVID 19 infections.

Reference:

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## EFFECT OF INEBILIZUMAB ON VACCINE-GENERATED ANTIBODY TITERS IN NMOSD PARTICIPANTS: RESULTS FROM N-MOMENTUM STUDY

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Objective: To determine the impact of long-term depletion of CD19+ B-cells on childhood vaccine-generated humoral responses in participants from N-MOmentum.

Methods: Participants received INEB (300mg, intravenous) or placebo (PBO, 3:1 randomization) on Days 1 and 15 of the 28-week randomized controlled period (RCP) then every six months during the optional open label period (OLP). The median percent change from baseline (CFB) at week 156 was evaluated for measles, mumps, rubella, and varicella; all IgG mg/dL and tetanus toxoid IgG IU/mL.

Materials: Measles, mumps, rubella, and varicella IgG levels were measured in a central laboratory via sandwich enzyme-linked immunosorbent assay (ELISA). Anti-tetanus toxoid IgG levels were measured in a central laboratory via enzyme Immunoassay.

Results: The median (min, max) % CFB to week 156 for measles was 3.4 (-97.1, 204.7, n = 47) for INEB and -5.4% (-92.7, 69.2; n=10) for PBO. Mumps median (min, max) % CFB was 5.9% (-59.3, 158.2; n=47) for INEB and 11.3% (-26.1, 94.8; n=12) for PBO. Rubella median (min, max) % CFB was 3.9% (-69.2, 204.1; n=55) for INEB and -19.7% (-86.1, 111.1; n=15) for PBO. Varicella median (min, max) % CFB was 9.6% (-86.3, 280.6; n=40) for INEB and 11.5% (-25.9, 133.6; n=13) for PBO. Tetanus toxoid median (min, max) was -1.5% (-92.9, 160.7; n = 64) for INEB and -13.5 (-61.3, 45.2), n=19 for PBO. The IgG levels decreased over the study duration with a median (min, max) decrease of -13.1% (-73.2%, 192.6%) at week 52, p = 0.005 and -20.5 (-81.1, 21.8) at week 156, p = 0.0004 for INEB participants.

Discussion: Inebilizumab (INEB), a selective anti-CD19 B-cell depleting monoclonal antibody, is approved for treatment of adults with aquaporin-4 seropositive neuromyelitis optica spectrum disorder (NMOSD). A robust depletion of circulating B-cells impacting NMOSD was observed within 4 weeks of INEB treatment in the phase 2/3 N-MOmentum trial (NCT02200770) and maintained over ≥4 years with continued dosing every 6 months. This posthoc analysis assessed whether selective B-cell depletion over the long term affects antibody titers from prior measles, mumps, rubella, varicella-zoster, and tetanus toxoid vaccinations.

Conclusions: Vaccine titers did not show a meaningful reduction after 3.5 years of INEB treatment even with nearly complete peripheral B cell depletion throughout this period.

Reference:

– Cree et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. Lancet (2019);394:1352-63

## WEST NILE NEUROINVASIVE DISEASE: A CASE SERIES FROM THE 2022 ITALIAN OUTBREAK

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Introduction and Aims: A markedly steep increase in West Nile virus (WNV) infections was reported in Italy in summer and fall 2022; overall, 588 cases were confirmed, 295 of them presented in the neuroinvasive form and 37 deaths were notified to the Italian National Institute of Health. The province of Padova, in the Veneto region, was the most severely affected [1]. While WNV is already considered endemic in many European countries, such a significant increase in neuroinvasive infections had never been experienced in Northern Italy. Here, we would like to present 15 cases of West Nile neuroinvasive disease (WNND) managed at our institution between July and September 2022 and to report their neurological status at follow-up.

Materials and Methods: Data on 15 consecutive patients who were diagnosed with WNND were collected. All patients were > 18 years

old and they were admitted to the Neurology, Medicine and Intensive Care Units of the "Immacolata Concezione" Hospital of Piove di Sacco (Padova). All diagnoses were confirmed according to the National Surveillance Plan guidelines, released by the Italian Ministry of Health in 2019. Follow-up information was obtained through telephone interviews to patients and/or their family members by staff physicians.

Results: 11 out of 15 patients (73.3%) were diagnosed with encephalitis or meningoencephalitis, 2 (13.3%) with isolated meningitis, 1 (6.7%) with encephalitis associated with acute flaccid paralysis and 1 (6.7%) with encephalitis associated with facial diplegia; 7 patients (46.7%) required Intensive Care Unit (ICU). Most patients (12/80%) experienced one or more severe complications and 3 patients died (20%). While median pre-hospital mRS was 0, 8 patients out of 15 (53.3%) were completely dependent, bedridden or dead (mRS 4 or worse) at early follow-up; at late follow-up, this proportion reduced to 6 cases (40%). Most patients (88.9%) reported persistent symptoms at the 7-9 months follow-up, the most frequent being fatigue, persistent bilateral upper extremity tremor and unstable gait. One patient developed immuno-mediated ocular flutter.

Discussion and Conclusions: In the 2022 Italian outbreak, WNV has shown an increasing propensity to cause neuroinvasive disease with subsequent severe or fatal outcomes. Anthropogenic changes, with their effect on climate change, may play a role in this emerging public health problem. It is relevant to gain understanding of how WNV enters the central nervous system; moreover, efforts should be undertaken to prompt public health measures to reduce WNV circulation and to provide effective treatments.

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## ANTI-MA2 ENCEPHALITIS TRIGGERED BY GASTRIC CANCER: CHALLENGING CURRENT DIAGNOSTIC CRITERIA FOR PARANEOPLASTIC NEUROLOGICAL SYNDROMES

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Objectives: To present a rare case of anti-Ma2 encephalitis in a patient with compatible clinical features but highly atypical cancer association, highlighting possible pitfalls in the updated diagnostic criteria for paraneoplastic neurological syndromes (PNS).

Case presentation: A 71-year-old man with no significant medical history presented with an abrupt onset of oscillopsia, vertical nystagmus, and gait instability. His blood examinations were unremarkable, and a brain CT was negative. An ischemic stroke was excluded with brain magnetic resonance imaging (MRI). As the patient's symptoms were getting worse, an autoimmune encephalitis was suspected, therefore serum and cerebrospinal fluid (CSF) were tested for autoantibodies. High-titer anti-Ma2 antibodies were found positive on both samples, and this finding was confirmed on another CSF sample in a referral center. While starting immunotherapy (intravenous steroid bolus followed by intravenous immunoglobulins), we screened the patient for cancer and found a gastric adenocarcinoma (pT1b N0). Total gastrectomy with lymphadenectomy was performed and the patient required no chemo- or radiotherapy. The patient's symptoms persisted (severe oscillopsia and gait ataxia), and he also manifested REM sleep behavior disorder. Treatment with cyclophosphamide as a second-line immunotherapy was initiated (600 mg/m2 monthly for 6 months). At one year from symptoms onset, minor improvement was noticed, with reduction of nystagmus and opsoclonus. His oncological follow-up is normal, and no other tumors were found.

Discussion: Anti-Ma2 encephalitis is a paraneoplastic neurological syndrome that usually affects the limbic system, diencephalon, and brainstem; less frequently, patients may show cerebellar involvement. It is mostly associated with testicular or lung tumors. [1,2] An abrupt (stroke-like onset) is uncommon, and the association with gastric cancer is extremely rare and not included in the criteria for definite anti-Ma2 paraneoplastic neurological syndrome. [3]

Conclusion: An abrupt onset and an atypical cancer association in this case highlight the potential issues in relying on the updated diagnostic criteria for clinical diagnosis, considering that they were designed for research purposes to increase specificity, with the potential to miss atypical cases.

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## PROGNOSTIC RELEVANCE OF QUANTITATIVE AND LONGITUDINAL CASPR2 AND LGI1 ANTIBODY TESTING AND NEUROFILAMENT LIGHT CHAIN LEVELS IN PATIENTS WITH AUTOIMMUNE ENCEPHALITIS

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Introduction and Objective: Autoantibodies against leucine-rich glioma-inactivated 1 (LGI1) and anti-contactin-associated protein-like 2 (CASPR2) are diagnostic and pathogenic markers of autoimmune encephalitis (AE). Increased neurofilament light chain levels indicate axonal damage. We aimed to study the relevance of longitudinal anti-LGI1/CASPR2 titres and neurofilament light chain levels as biomarkers in autoimmune encephalitis.

Material and Methods: Retrospective cohort study including patients with anti-LGI1/CASPR2 definite AE, and at least one available longitudinal sample > 60 days from onset. Titers were measured with endpoint dilution using a live cell-based assay. 28/142 samples (20%) were classified as from "acute phase", 15 (10%) as "postacute" and 99 (70%) as "remission". Neurofilament light chain levels (Nfl) were measured on 82 serum samples (51 acquired during "remission"). Outcome was measured with modified Rankin Scale (mRS) and with Clinical Assessment Scale in Autoimmune Encephalitis (CASE).

Results: We enrolled 23 patients (anti-CASPR2=7; LGI1=15, double positive=1) and 10 were females. Median age at diagnosis was 63 (range 45-82). Manifestations at onset included seizures (22/23), psychiatric symptoms (15/23) and cognitive dysfunction (14/23). Median follow-up was 37 months (range 3-64). 8/23 patients had relapses. Acute phase samples had higher median titres (1:8000, range 20-102400) compared to post-acute (1:4000, range 500-51200) and remission (1:800, range 0-51200) samples (p<0.001), even analyzing separately anti-LGI1 (p<0.001) and CASPR2 (p=0.007) sera. Titres did not correlate with disease severity at onset/follow-up. Relapses always occurred with a positive sample (n=8), and in 3/5 patients with pre-relapse samples available titres increased at relapse. Seven patients became seronegative (2 with anti-CASPR2, 4 after rituximab) after a median time from diagnosis of 12 months (range 5-58), and none experienced post-seroconversion relapses. Median AE Nfl levels (31,5, range 5,4-164) were higher than healthy controls (15,4, range 5,4-29,3) (p<0.001) and Nfl levels at onset (45,95, range 5,4-109) were significantly higher (p=0,01) than Nfl levels measured at 10 months follow-up (25,8, range 5,4-60,6).

Conclusion: Anti-CASPR2/LGI1 titres correlate with disease phase and decrease over time. Seroconversion-to-negative might associate with reduced relapse risk. Nfl levels were significantly higher than controls and correlate with disease phase. Our preliminary data warrant further study evaluating antibody titres and Nfl as biomarkers in LGI1 and CASPR2 encephalitis.

## PREDICTORS AND CLINICAL CHARACTERISTICS OF RELAPSES IN LGI1-ANTIBODY ENCEPHALITIS

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Objectives: Relapses occur in 15-25% of patients with leucine-rich glioma-inactivated 1 antibody autoimmune encephalitis (LGI1-Ab encephalitis) and may cause additional disability. Herein, we aim to clinically characterize the relapses and identify factors predicting their appearance.

Materials: Retrospective chart review of patients with LGI1-Ab encephalitis diagnosed at our center between 2005 and 2022. Relapse was defined as worsening of previous or appearance of new symptoms after at least 3 months of clinical stabilization. Additionally, patients with LGI1-Ab encephalitis without relapses were identified and included as a control group.

Methods: Univariate analysis was performed to compare the relapsing patients with the control group and the initial encephalitis episode with the relapse. A Cox proportional hazards regression model was built to identify potential predictors of relapse.

Results: Among 216 patients, 30 (14%) experienced a total of 33 relapses. Median time to first relapse was 23.9 months (range 4.9-110.1). During relapses, clinical manifestations included memory impairment (70%), seizures (45%), psychiatric/behavioral symptoms (30%), and faciobrachial dystonic seizures (30%). Brain MRI was abnormal in 16/26 (62%), CSF was inflammatory in 11/25 (44%), LGI1-Abs positive in 16/23 sera (70%) and in 11/23 CSF (48%). Compared to the initial episode, relapses manifested with fewer symptoms (p<0.001) and lower maximal modified Rankin Scale (mRS) score (p=0.001). However, median mRS at last follow-up after relapse was significantly higher than after the initial episode (2 versus 1, p=0.005). Patients with relapses did not differ in their initial clinical and paraclinical features from 85 patients without relapses. Nevertheless, residual cognitive dysfunction after the initial episode was significantly associated with an increased risk of relapse (hazard ratio = 9.5, 95% CI 1.7-182.0, p=0.038).

Discussion: Relapses in LGI1-Ab patients present with fewer and milder symptoms compared to the initial encephalitis episode, and thus may be subtle and difficult to recognize. We observed herein that persisting cognitive dysfunction after the initial episode was a risk factor for relapse, and consequently patients with cognitive sequelae should be closely monitored. Additionally, mRS scores were significantly higher after the relapse than after the initial episode, implying that some patients develop additional disability after the relapse. Thus, preventing relapse occurrence would be of the utmost importance to improve patient outcomes.

Conclusions: Relapses may occur years after the initial encephalitis episode, are usually milder but cause additional disability. Residual cognitive dysfunction after the initial episode increases the risk of future relapses.

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## SERUM BIOMARKER PROFILES DISCRIMINATE AQP4 SEROPOSITIVE AND DOUBLE SERONEGATIVE NEUROMYELITIS OPTICA SPECTRUM DISORDER

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Background and Objectives: Glial fibrillary acid protein (GFAP) and neurofilament light chain (NfL) serum levels are increased in patients with aquaporin-4 antibodies positive NMOSD (AQP4+NMOSD) during clinical attacks suggesting a concomitant axonal and glial damage. [1] However, there are contradictory results in double seronegative NMOSD (DS-NMOSD). [1,2] The aim of this study is to characterise the neuronal, axonal, and glial damage of DS-NMOSD, in comparison with AQP4+NMOSD.

Methods: Patients with DS-NMOSD and age-matched AQP4+NMOSD with available serum samples obtained within 3 months from onset/relapse were retrospectively enrolled. Clinical and radiological data were collected. Serum NfL, GFAP, Tau and UCH-L1 levels were determined using an ultrasensitive paramagnetic bead-based enzyme-linked immunosorbent assay (SIMOA). Statistical analysis was performed using non-parametric tests and Receiver Operating Characteristic (ROC) curve analysis.

Results: We included 25 AQP4+NMOSD patients and 26 DS-NMOSD. Median age at disease onset was 35.1 years [IQR 27.4-48] in AQP4+NMOSD and 39 years [24.1-50.5] in DS-NMOSD(p=0.611). Female sex was more common in both groups (84% vs. 61.5%, p=0.072). The most common syndromes at sampling in both AQP4+NMOSD and DS-NMOSD were myelitis (56% vs. 38.5%) and optic neuritis (34.6% vs 32%, p=0.716). Median EDSS at sampling of the whole group was 3.5 [IQR 2.5-7.0] and was similar in the two groups(p=0.974). Serum GFAP, Tau and UCH-L1 levels were higher in AQP4+NMOSD patients compared to DS-NMOSD (median 308.3 vs. 103.4 pg/mL p=0.001; median 1.2 vs. 0.5 pg/mL, p=0.001; median 61.4 vs 35 pg/mL, p=0.006, respectively). The ROC curve analysis showed that GFAP, Tau and UCH-L1, but not NfL values were able to discriminate between AQP4+ and DS-NSMOSD (area under the curve -AUC- tau:0.782, p=0.001, AUC GFAP:0.762, p=0.001, AUC UCH-L1:0.723, p=0.006).

Conclusions: Serum GFAP, Tau, and UCH-L1 levels discriminate between AQP4+NMOSD and DS-NMOSD. The different biomarkers profile of AQP4+NMOSD vs. DS-NMOSD provides useful data to improve our understanding of this disease.

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## VALIDATION OF THE 2023 MOGAD DIAGNOSTIC CRITERIA IN AN ITALIAN COHORT

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Background and Aim of the study: The recently published MOG antibody-associated disease (MOGAD) diagnostic criteria are based on the combination of peculiar clinical/radiological features and MOG-Abs positivity. The international experts panel designed the criteria to help clinicians in the correct interpretation of MOG-Abs results to guide the diagnostic process. We provide the first validation of the MOGAD diagnostic criteria in an Italian cohort of patients with MOG-Abs positivity.

Methods: Patients with serum and/or CSF MOG-Abs positivity were retrospectively identified from 29 Italian centers. Clinical data were collected by referring physicians in a dedicated database and the 2023 MOGAD diagnostic criteria were applied. Four groups were identified: true positive (TP: MOGAD criteria fulfilled, final diagnosis of MOGAD provided by the enrolling centre), true negative (TN: MOGAD criteria not fulfilled, final diagnosis different from MOGAD), false positive (FP: MOGAD criteria fulfilled, final diagnosis different from MOGAD) and false negative (FN: MOGAD criteria not fulfilled, final diagnosis of MOGAD confirmed). Sensitivity (ratio TP/TP+FN) and specificity (ratio TN/TN+FP) were calculated. False negative and

false positive cases were revised by two neuroimmunologists blinded to the provided final diagnosis.

Results: 155 patients were included, mean age at onset was 40.5 years (SD 16.7), and 89 (57.4%) were females. Live-CBA was the most common assay used for MOG-Abs detection (n=135, 86.8% of cases). CSF was tested in 63 (40.6%) of cases. Overall, 66 (42.8% of cases) had serum low positive titers, 66 (42.8%) serum high positive titers, 13 (8.6%) had an unknown serum positive titer, while 10 (5.8%) were CSF only positive for MOG-Abs. Final diagnoses were: MOGAD in 139 patients (85.2%), MS in 9 (5.8%), other monophasic inflammatory diseases in 5 (5.8%), and other recurrent inflammatory diseases in 2 (1.3%). After the application of 2023 MOGAD diagnostic criteria, the patients were grouped as: TP, 126 (81.3%); FP, 6 (3.9%); FN, 13 (8.4%); and TN, 10 (6.5%). MOGAD criteria had a sensitivity of 90.6% [CI 0.86-0.95] and a specificity of 62.5% [CI 0.39-0.86].

Conclusion: The 2023 MOGAD diagnostic criteria have an overall good sensitivity but only moderate specificity for MOGAD. This first validation of MOGAD diagnostic criteria supports their utility in the clinical practice to identify MOGAD cases, but also underlines the relevant role of clinicians in selecting suggestive cases, to increase pre-test probability and reduce the risk of misdiagnosis.

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## HEARING HOOFBEATS, THINKING ZEBRAS: UNEXPECTED IGG4-RELATED PACHYMENINGITIS IN AN ELDERLY MAN

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Introduction/Objectives: IgG4-related disease (IgG4-RD) is a fibro-inflammatory disorder with a synchronous or metachronous multi-organ involvement and three histopathological hallmarks: lymphoplasmacytic IgG4 plasma-cells infiltration, storiform fibrosis and obliterative phlebitis. The involvement of the central nervous system by the disease is rare but increasingly recognized, and it consists of focal/diffuse hypertrophic pachymeningitis (HP) of the vault/base of the brain or of the spinal cord, or hypophysitis.

Materials/Methods/Results: We present a case of 82-year-old caucasian man, with a history of high blood pressure, diabetes mellitus, ischemic heart disease, autoimmune pancreatitis, left parietal meningioma and acute left hemispheric post-traumatic subdural hematoma. The patient referred to our Clinic in December 2022 for an acute onset of focal to bilateral tonic-clonic seizures and sub-acute onset of cognitive decline. The clinical examination, after seizures control, consisted of an altered mental status and hemiparesis of the right limbs. A CT scan was negative for acute ischemic/hemorrhagic lesions an electroencephalogram (EEG) showed a slowing of background activity, theta and sharp waves in the centro-temporal regions. The hemiparesis resolved within 1 day (Todd's paralysis). The brain-MRI showed an extra-axial mass at the left parietal convexity with signs of active inflammation of the left parieto-temporal dura mater, compatible with pachymeningitis with leptomeningeal and cortical involvement. Lumbar puncture, blood tests for infectious/immunological diseases and meningeal biopsy of the lesion were therefore performed. A comprehensive immunologic and infective assessment (including tuberculosis and treponema screening) performed on serum and CSF was unremarkable; IgG4 plasma levels were normal (63,8 mg/dL), IgE were elevated (231 kU/I). A meningeal biopsy was performed showing storiform fibrosis and perivascular inflammatory infiltrate, rich in IgG4+ plasma-cells. Immunostaining showed more than 10 IgG4+ plasma cells per HPF with a IgG4/IgG ratio > than 40%. Staining for pathogens was negative (Gram, Gomori-Grocott, Ziehl stains). Treatment with oral steroids was started with clinical and radiological improvement.

Discussion/Conclusions: Although the known left parietal meningioma, the atypical course and the finding of inflamed pachymeninges at brain MRI led to the suspicion of an IgG4-related pachymeningitis, then confirmed by histopathology. This treatable condition has been rarely described as a tumor-like mass, mimicking a meningioma. Despite the confounding factors such as a known lesion and history of subdural hematoma, the meningeal biopsy was clarifying, and a diagnosis of IgG4-related disease was made. Histologic confirmation by meningeal biopsy is required for correct diagnosis and appropriate therapy setting, especially in the presence of possible mimics, confounding comorbidities, and non-diriment laboratory investigations.

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## A CASE OF CAVERNOUS SINUS SYNDROME DUE TO SPHENOIDAL SINUS MUCORMYCOSIS

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Introduction: Mucormycosis ("the black fungus") is a rare, opportunistic fungal infection, reported usually in immunocompromised patients with underlying diseases such as diabetes mellitus, organ transplant or with extensive use of corticosteroids. Extension of fungal infection to cavernous sinus leads to cavernous sinus syndrome (CSS), defined as the involvement of two or more among Third, Fourth, Fifth or Sixth cranial nerves or one with radiological involvement of cavernous sinus. Patients affected may present headache, ptosis, proptosis, ophtalmoplegia, orbital pain, diplopia, visual loss, nasal discharge, and fever. Multidisciplinary competences are necessary to recognize it and perform optimal medical e surgical treatment.

Case report: We present a case of a 59-year-old man with persistent headache, non-responsive to FANS since several days, without any neurological signs at the first clinical examination at Emergency Department. In past medical history he was affected by hypertension, dyslipidemia and ischemic cardiopathy. After two days, he developed acute and progressive ptosis, proptosis, ophthalmoplegia, fever, photophobia and visual loss in the right eye with radiologically documented bilateral purulent collection in sphenoid sinus and thrombosis of right cavernous sinus. He was treated in emergency with sphenoidal sinus endoscopic debridement; based on histological results from a surgical resection, we started intravenous amphotericin B, later switched to oral isavuconazonium for elapsing acute kidney injury. Excavated pulmonary thickenings as septic likelihood type were detected in chest CT, while cerebral angiography and echocardiography did not show

respectively mycotic aneurism and endocardial vegetation. For the cavernous sinus thrombosis, he started anticoagulation therapy. After 3 months he had complete clinical and radiological recovery, so he stopped antifungal drug and continued only with anticoagulant therapy.

Discussion: According to clinical symptoms and radiological signs, we made a diagnosis of CSS due to sphenoidal sinus mucormycosis in a patient without risk factors. He showed a complete resolution, probably for his immunocompetence and prompt combination therapy. In literature most patients have a poor prognosis with complete visual loss, eye resection or death by septic state. Recently, a growing number of cases was detected probably due to the extensive use of corticosteroids in patients with Sars-Cov2 infection, especially in developing countries.
Conclusions: Acute and progressive onset of unilateral ocular symptoms needs to exclude CSS and underlying fungal infection, in particular if patients may have risk factor for immunocompromise state, because prompt treatment allows preserving life and vision and sparing mutilating surgeries.
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## SINGLE FIBER EMG IN THE DIAGNOSTIC WORKUP OF DIPLOPIA AND PTOSIS


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Diplopia and ptosis are common neuro-ophthalmologic signs. Yet identifying the specific aetiology can be challenging due to the different potential causes. In this prospective study, we evaluated the reliability of the stimulated single fiber electromyography (SFEMG) in supporting the diagnosis of myasthenia gravis (MG) presenting with diplopia and ptosis. We included 66 patients who presented with diplopia (n=27), ptosis (n=13), or both (n=26), and underwent SFEMG. Patients received a comprehensive diagnostic workup involving detailed history investigation, physical examination, orbital and brain imaging, thyroid function and antibody screening, orthoptic evaluation, ice pack test (when applicable) and repetitive nerve stimulation test (RNS). SFEMG yielded positive results in 23 of 66 (34.8%) patients of the cohort. Among the patients diagnosed with MG (n=29), SFEMG showed a sensitivity of 72.4% (95% CI: 0.55 – 0.86) and specificity of 94.6% (95% CI: 0.84 – 0.99) with a positive predictive value of 91.3% (95% CI: 0.76 – 0.99) and a negative predictive value of 81.4% (95% CI: 0.68 – 0.91). Notably, SFEMG was positive in 7 seronegative MG cases and in 11 cases with negative RNS. In the non-MG group (37/66 patients), SFEMG was negative in the majority (35 patients, 94.6%) of cases, further supporting its value in ruling out MG. A relevant proportion (17/37) of these cases remained undiagnosed. Our findings suggest that SFEMG is a valuable tool in the diagnostic workup of diplopia and ptosis and in the differential diagnosis of MG, especially in seronegative MG cases and in those with negative RNS results.
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## EXTENSIVE SPINAL HYPERTROPHIC PACHYMENINGITIS IN IGG4-RELATED DISEASE


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Objectives: We describe a 66-year-old woman previously healthy with a two-month history of neck stiffness, limbs dysesthesias and progressive weakness to inability to walk, diagnosed as an isolated extensive spinal hypertrophic pachymeningitis (HP) due to IgG4-related disease (IgG4-RD).

Materials and Method: Hypertrophic pachymeningitis (HP) is a rare disease-causing thickening of the dura mater and it is often a neurological manifestation of rheumatologic, infectious, and neoplastic diseases. Immunoglobulin G-4-related disease (IgG4-RD) is a systemic inflammatory disorder that results in fibrous inflammation of virtually any organ. In some cases, HP has emerged as a rare presentation of IgG4-RD.

Results: Upon admission, neurological examination showed: neck stiffness, upper limbs muscle weakness (medical research council, MRC 4) hands paresthesia, severe lower limbs muscle weakness (MRC 2) with diffuse sensory impairment starting from a mid-abdominal level; bilateral Babinski sign and lower limbs hyperreflexia was also noted. Cervicothoracic-MRI disclosed almost complete obliteration of cerebrospinal fluid signal in the entire spinal tract, with marked contrast enhancement of the meningeal envelopes, signal alteration in the cervical-thoracic spinal cord due to compressive myelopathy. A complete workup disclosed high serum concentration of IgG4, total body CT scan and FDG-PET showed signs of subclinical aortitis. Meningeal biopsy revealed lymphoplasmacytic infiltrate, with high-level-per-field plasma-cells and an IgG4+/IgG+ ratio >40%, confirming HP due to IgG4-RD. Our patient was treated with high-doses steroids, followed by rituximab (two-1g infusions 15 days apart), with clinical and radiological improvement. At the 1-year follow up the patient walked with minimal assistance, spinal cord MRI showed dramatic improvement and FDG-PET showed no meningeal nor aortic hypermetabolism.

Discussion: Only few cases of HP with isolated spinal involvement due to IgG4-RD have been described, however, such an extensive spinal involvement is quite unique. Spinal cord compression due to IgG4-RD is a very rare cause of myelopathy and may progress rapidly, leading to severe and irreversible neurological deficits, therefore early recognition is of utmost importance. HP diagnosis due to IgG4-RD could be challenging because clinical features are non-specific. Medical assessment should include comprehensive evaluation to exclude differential diagnosis and histopathological exam represents the diagnostic gold standard.

Conclusion: In patients with "high-risk" manifestation of IgG4-RD, such as neural involvement, aggressive immunosuppression must be used as first-line treatment: in particular, rituximab, a B-cells depleting

monoclonal antibody, has shown to induce long-lasting disease remission. In our case, rituximab has stopped disease progression, in addition to dramatically changing the patient clinical condition.

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## CLINIC AND LABORATORY PREDICTIVE FACTORS IN DIFFERENT TYPES OF ENCEPHALITIS: THE ENCOVID MULTICENTRE STUDY

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Objectives: Encephalitis is defined by the presence of an inflammatory process of the brain in association with clinical evidence of neurologic dysfunction. The diagnosis and treatment are still challenging and prognostic studies are currently lacking. We aimed to investigate the predictive factors associated with poor outcomes in a large spectrum of subjects with different subtypes of encephalitis.

Methods: In this observational multicenter study, 216 patients diagnosed with 4 different types of encephalitis were recruited. The four groups were compared through ANOVA and k2 test, were appropriate. Linear and logistic regression models explored predictors of mortality and worse progression of the disease.

Results: The different types of encephalitis showed several clinical and laboratory differences. Linear regression analysis confirmed lymphocytes at admission (p=0.025) and CSF cells count (p=0.035) as the strongest predictive factors of poor outcomes, independently from demographic, clinical and laboratory characteristics. Logistic regression analysis identified apathy (p=0.018) as the most significant predictor of mortality, adjusting for demographic features and neurologic/systemic symptoms.

Discussion and Conclusion: In patients with encephalitis, CSF cells count and blood lymphocytes value appear to indicate worse disability at discharge. Apathy, on the other hand, is the strongest predictor of mortality, independently from the diagnosis. Further prospective studies are needed to confirm our findings, to identify patients at high risk of mortality and poor outcomes, and to develop specific strategies for prognostic improvement.

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## CASPR2 ANTIBODY–ASSOCIATED DISEASE: THE IMPORTANCE OF KNOWING TYPICAL CLINICAL PATTERNS OF A RARE DISEASE

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Background and Aims: A 41-years-old man was admitted to our Neurology Unit for the onset of pain in the lower limb two years before, stocking and gloves burning paresthesia, hyperidrosis and insomnia. After few months the patients experienced onset of cramps, subcutaneous vermicular movements, tremor, hypertension, tachycardia, syncopal episodes, akathisia, anxiety, behavioral changes, hyporexia and weight loss. The patient has consulted many specialists over time without a precise diagnostic framework and underwent various treatment (including SSRI, opioids, antiepileptic drugs) without clinical response.

Methods: We performed brain and spinal cord MRI with contrast, routine blood tests, extended autoimmune, infectious and hormonal screening (including urinary metanephrines), autoantibodies vs intracellular and surface neuronal antigens, electroencephalography, electroneuromyography, and total body PET-CT.

Results: Blood and urinary exams performed showed: hyponatremia, increase of renin and urinary metanephrines; electroneuromyography showed signs of neuromyotonia in all examined muscles. Surface neuronal antigens antibodies screening were positive for anti-Contactin-associated protein-like 2 (Caspr2) and anti- leucine-rich glioma-inactivated1 (LGI1) Abs. Total body PET-CT sowed normal findings.

Discussion: The association between neuromyotonia, autonomic dysfunction and central nervous system involvement in association with the relief of anti-Caspr2 and anti-LGI1 Abs supported the final diagnosis of Morvan Syndrome. Nine plasmapheresis cycles were administrated with partial clinical improvement. Afterwards, intravenous high dose steroid therapy was administrated, with improvement of hyporexia, and hyperidrosis, but persisted cramps, fasciculations, and myokymia. At one month-follow up we retest the patient for anti-CASPR and anti-LGI1 Abs, still positive. For this reason, the patient underwent second line treatment (rituximab).

Conclusion: The presence of antibodies to VGKC is reported in patients with acquired neuromyotonia (Isaac Syndrome), Morvan syndrome, and limbic encephalitis. Precisely, antibodies are not directed against the VGKC subunits but to associated proteins. Two of these proteins are LGI1 and Caspr2. In less 30% of cases, this Abs are associated with neoplasms, that in 50% of cases of Caspr2 positivity is thymoma, and in 10% of LGI1 positivity is neuroendocrine neoplasm. For the heterogeneity of their symptoms, these syndromes are often undiagnosed or diagnosed later. The knowledge of the core symptoms of these syndromes will improve their early recognition, that is important because immunotherapy and tumor treatment (if needed) are often effective.
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## ORBITAL INFLAMMATORY DISEASE IN A PATIENT WITH PSORIATIC ARTHRITIS TREATED WITH ADALIMUMAB: A PARADOXICAL ADVERSE EVENT?

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Background and Aims: A 71-year-old woman with a diagnosis of psoriatic arthritis since 2019 under treatment with Methotrexate and Adalimumab was admitted to our Neurology Unit for an acute/sub-acute onset of ocular pain, swelling, conjunctival injection and progressive visual loss in right eye. The patient reported also a concomitant onset of right-sided pulsating headache of moderate intensity (NRS 6/10) responsive to common NSAIDs. The neurological examination showed, in right eye: amaurosis, proptosis, exotropia and partial ophthalmoplegia, miosis.

Materials and Methods: Diagnostic protocol included brain and orbital MRI with Gadolinium, routine blood tests and an extended autoimmune (including IgG4), infectious, hormonal, paraneoplastic screening.

Results: MRI showed enlargement and increased T2 -signal with contrast enhancement within the right inferior rectus muscle, mildly in the right lateral and medial rectus muscles without tendon involvement; inhomogeneous signal of the right orbital adipose tissue at the orbital apex with congestion of perivenous and vascular structures of the optic nerve. Other tests were negative.

Discussion: The abovementioned findings supported the diagnosis of Orbital Inflammatory Disease (OID). Steroid therapy with methylprednisolone 1gr for 10 days was administered with slowly taper in 3 months; after two weeks, she has a clinically important improvement in extraocular motility and a minor improvement in visual acuity. The etiology and pathogenesis of IOIS are currently unknown, but the pathogenesis can be idiopathic, post-infectious/immunization and associated with autoimmune disease or systemic disease (i.e. sarcoidosis, systemic lupus erythematosus, hyper-IgG4 related disease). Nonetheless, anti-TNF-α agents (such as adalimumab), despite being effective management options in various inflammatory and autoimmune diseases, have been associated with new onset or exacerbation of autoimmune diseases (uveitis, optic neuritis/neuropathy, scleritis, demyelinating diseases and others).

Conclusions: In the present case report, the onset of Orbital Inflammatory Disease in a patient with psoriatic arthritis under treatment with Adalimumab suggest the possibility of a link between the administration of anti-TNF-α agents and the onset of this autoimmune condition. Physicians using these medications should be aware of this serious vision-threatening paradoxical adverse events, in order to recognize them early and establish an appropriate treatment.
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## FACIAL DIPLEGIA: A RARE VARIANT OF GUILLAN BARRE' SYNDROME FOLLOWING ADENOVIRUS VECTOR COVID 19 VACCINES

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Introduction: Guillain-Barrè syndrome (GBS) is an acute immune-mediated neuropathy, possibly triggered by a recent infection or vaccination, and driven by an immune attack targeting the peripheral nervous system. Although an increasing number of case reports of Guillan Barrè Syndrome (GBS) in patients receiving COVID-19 vaccination have been reported both during the pre-clinical phase and after large-scale authorities' approval [1)] it's noteworthy the emerged potential association between adenovirus-based COVID-19 vaccines and a GBS specific phenotype with facial diplegia [2].

Objective: We herein report 4 cases of GBS with facial diplegia occurring 7 to 21 days after administration of ChAdOx1-nCoV-19 vaccination.
Methods: Patients underwent a multidimensional assessment including neurological, neurophysiological and laboratoristic evaluation, with a longitudinal follow up.

Results: Four patients developed facial diplegia within the 6-week period after ChAdOx1-nCoV-19 vaccination (range 7-21 days). In all cases, electrophysiological study revealed multifocal demyelinating sensorimotor polyradiculoneuropathy consistent with the diagnosis of GBS, AIDP variant; lumbar puncture revealed albumin-cytological dissociation; screening for other infectious, autoimmune, metabolic, or systemic diseases was unremarkable except for serum positivity to GM3(IgM) antibody in one patient. Autoantibody characterization is on going.

Discussion: The link between GBS atypical variant with facial diplegia and ChAdOx1-nCoV-19 vaccination is suggested by the temporal association between vaccine administration and clinical manifestations and by the lack of other known factors able to trigger GBS. Besides, the specific phenotype of this rare neurological condition supports a causal relationship between such exposure and this syndrome. An antibody-mediated autoimmune mechanisms may be relevant in the pathogenesis of GBS with facial diplegia after adenovector vaccines.

Conclusions: Future research should aim to determine the predisposing host factors and biological mechanisms underlying this association and the high frequency of facial nerve involvement.
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## CHARACTERISTICS OF PATIENTS WITH AN ELEVATED KAPPA INDEX AND ABSENT CEREBROSPINAL FLUID IGG OLIGOCLONAL BANDS

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Objective: The kappa index (cerebrospinal fluid -CSF/serum kappa free light chains -KFLC- divided by the CSF/serum albumin ratio) is a marker of intrathecal immunoglobulin synthesis (IS). Contrarily to CSF IgG oligoclonal bands (OCB), the current gold standard for IS detection, KFLC are not specific for the IgG isotype, as they also include contributions by IgM, IgA, IgD and IgE. Aim of the study was to assess the intrathecal IgM/IgA production in consecutive patients with an elevated kappa index (≥5.8, hereafter named kappa+) and absent CSF IgG OCB (OCB-), and to ascertain their diagnoses.

Methods: IgM/IgA IS was determined using quantitative methods (Optilite turbidimetric analyser) and by calculating the IgM/A index (CSF/serum IgM/A divided by the CSF/serum albumin ratio). Intrathecal IgM OCB were sought using isoelectric focusing. Control groups were randomly chosen OCB+/kappa+ and OCB-/kappa- patients. Diagnoses were classified as Multiple Sclerosis (MS), other inflammatory central nervous system (CNS) diseases (INFL), infectious CNS diseases (INFECT) and miscellaneous non-inflammatory disorders (OTHER).

Results: Of 119 patients (58M, 61F), 69 were OCB-/kappa+, 24 OCB-/kappa- and 26 OCB+/kappa+. Mean kappa index was 16.37, 1.33 and 116.67, respectively. OCB-/kappa+ were mostly patients with MS (nr=30), followed by INFECT (nr=16); OCB+/kappa+ were mostly MS/INFL (20/26) and OCB-/kappa- OTHER (15/24). Median IgM index and the frequency of CSF IgM OCB did not differ between the three groups, while IgA index was higher in the OCB-/kappa+ group (0.32) compared to the OCB-/kappa- group (0.25) (p=0.008). The vast majority of INFECT (16/18) belonged to the OCB-/kappa+ group. Median IgM/A indexes were higher (0.34/0.36) in INFECT (nr=18) compared to MS (0.06/0.27) (nr=49), INFL (0.08/0.3) (nr=19) and OTHER (0.09/0.27) (nr=33) (p<0.001/p=0.004). IgM/A indexes were greater than the cut-off (of 0.1 and 0.4, respectively) in a greater proportion of INFECT (17/18 for IgM and 6/18 for IgA) compared to the remaining patients (41/101 for IgM and 15/101 for IgA)(p<0.001). CSF IgM OCB were more frequent in INFECT (10/18) compared to the remaining patients (19/101) (p=0.001).

Conclusion: OCB-/kappa+ patients mostly had a diagnosis of MS or of an infectious CNS disease and showed an intrathecal IgM or IgA synthesis in 54% of cases. Increased IgM/IgA indexes and CSF IgM OCB were more frequent in patients with infectious CNS diseases compared to the remaining patients.

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## A RETROSPECTIVE MULTICENTER STUDY ON CLINICAL AND SEROLOGICAL PARAMETERS IN MUSK MYASTHENIA GRAVIS PATIENTS WITH AND WITHOUT GENERAL IMMUNOSUPPRESSION

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Aim: To investigate the effects of immunosuppressive treatment on IgG4 and MuSK IgG4 levels in Muscle-specific kinase (MuSK) Myasthenia Gravis (MG).

Materials and Methods: We analysed the clinical data and sera from 52 MuSK-MG patients (45 female, 7 male, mean age 48 years ) from Italy, the Netherlands, Greece and Belgium, and 43 AChR-MG patients (22 female, 21 male, mean age 58.44 years) from Italy, that were receiving Prednisone, Azathioprine, Cyclosporine, Intravenous immunoglobulin (IVIG), combinations thereof or no immunosuppression, and sera from 45 age- and sex-matched non-disease controls (with no diagnosed diseases, 38 female, 8 male, mean age 47.8 (range 20-68) years) from the Netherlands. We analysed the disease severity (assessed as MGFA or QMG score), and measured concentrations of MuSK IgG4, MuSK IgG, total IgG4 and total IgG in the sera by ELISA, RIA and nephelometry.

Results: We observed that MuSK-MG patients showed a robust clinical improvement and reduction of MuSK IgG after therapy, and that MuSK IgG4 concentrations, but not total IgG4 concentrations, correlated with clinical severity. MuSK IgG levels and MuSK IgG4 concentrations were reduced after immunosuppression in 4/5 individuals with before-after data, but data from non-linked patients showed no significant difference. Total serum IgG4 levels were within the normal range in most MG patients, and we observed a mild relative enrichment of IgG4 in both AChR-MG and MuSK-MG patients. MuSK-MG patients improved within the first four years after disease onset, but longer disease duration (>4 years) did not lead to further clinical improvement or MuSK IgG4 reduction, and only 14/52 (26.92%) patients in total, of which 13 (93.3%) received general immunosuppression, reached clinical remission.

Discussion and Conclusions: Based on our observations, we conclude that MuSK-MG patients improve clinically with general immunosuppression, especially during the first four years of treatment, but may require further treatment to reach remission. Inter-assay variability may hide individual changes of MuSK IgG4 levels, therefore longitudinal testing of individual patients may be clinically more useful than single measurements. Since no significant differences in the serum IgG4 concentrations and IgG4/IgG between AChR- and MuSK-MG patients were observed, previous observations of a MuSK-MG specific enrichment of IgG4 could not be reproduced. This suggests that further study with larger patient and control cohorts are necessary.

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## AUTOIMMUNE MOVEMENT DISORDERS IN THE ERA OF IMMUNE CHECKPOINT INHIBITORS

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Objectives: The aim of this study is to characterize autoimmune movement disorders (MDs) occurring as an immune-related adverse event (irAE) of immune checkpoint inhibitors (ICIs).

Materials: Systematic literature review.

Methods: A systematic review of the literature was performed including patients who developed autoimmune MDs (excluding the distinct entity of isolated cerebellar ataxia) after exposure to ICIs. Clinical, paraclinical, and oncological accompaniments were analysed and collected by two independent investigators.

Results: From 1654 eligible papers, 24 articles with 26 patients were included. 18 patients were male and median age at onset was 66 years-old (range 18-77). Non-small cell lung cancer (n=7) and melanoma (n=6) were the most frequent oncological accompaniments. These iRAEs were frequently associated with anti PD-1 treatments (n=14, 54%) and occurred after a median of 5 doses. Features of movement disorders were myoclonus (n=9), tremor (n=7), hyperkinetic MDs (n=5), opsoclonus (n=5), stiff person syndrome (n=3), parkinsonism (n=2), dystonia (n=1), and unspecified movement disorder (n=1). 5 patients presented >1 core feature and onset was either acute (n=10) or subacute (n=8). MDs occurred in isolation in 6 patients, while in the remaining cases were frequently associated with encephalitis-iRAE. Brain imaging was unfrequently abnormal (9/24), with more common basal ganglia involvement, whereas an inflammatory CSF profile was frequently encountered (increased cell count 12/21, increased protein concentration 11/17, and CSF-restricted oligoclonal bands 5/11). Autoantibodies were detected in 12/19 patients being Hu, PDEA10A, and Ri the most frequently identified. Patients were treated either with steroids (n=22), immunoglobulins (n=6), plasma exchange (n=4) or other treatments (n=6). Median number of treatments per patient was 1 (0-3) with 12 patients receiving >1 treatment. ICIs were discontinued in 21/22 cases and 3/10 patients were rechallenged. At last follow-up (median 5 months, range 1-27) 11/24 patients improved, 7/24 deceased, 3/24 obtained neurological remission, 2/24 were stable, and 1/24 worsened. Relapses were reported in 4 patients in association with rapid steroid tapering/ICI rechallenge.

Discussion: ICI-related MDs usually occur in association with anti PD-1 treatment and lung cancer or melanoma. Clinical features are heterogeneous and frequently overlaps with those of other iRAEs. Treatment and ICI discontinuation led to improvement in most cases. Acute/subacute onset, coexistence of other iRAEs, MRI imaging involving basal ganglia, and an inflammatory CSF profile support the diagnosis.

Conclusion: Autoimmune MDs are a rare complication of cancer immunotherapy, but neurologist should be aware and recognize this condition to offer patients a prompt diagnosis and treatment.

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## INVESTIGATING THE SPECTRUM OF DIFFERENTIAL DIAGNOSES AND MISDIAGNOSES OF AUTOIMMUNE ENCEPHALITIS

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Aims: The diagnosis of autoimmune encephalitis (AE), beside the fulfillment of clinical, paraclinical and radiological criteria, requires the reasonable exclusion of other conditions. Indeed, an erroneous diagnosis of AE may delay a correct treatment and expose patients to inappropriate immunotherapies. Thus, the proper identification of potential confounding factors is of utmost importance. The aim of this study is to characterize mimickers and misdiagnoses of AE.

Materials: Systematic review of the literature.

Methods: A systematic review including 1) patients with other neurological disorders but mimicking AE, or 2) patients with alternative neurological disorders misdiagnosed as AE was performed according to PRISMA guidelines by two independent investigators. Relevant clinical, therapeutic, and paraclinical data were extracted and diagnostic criteria for AE were applied. A comparison across the different diseases and age groups was performed (Fisher's exact test or Chi-square test).

Results: After screening 3669 records, 58 studies incorporating data from 66 patients (52 adults and 14 children) were included in the analysis. Median age at onset was 43.5 years (range 4-48) and 44 patients were male. Neoplastic (n=17), infectious (n=15), genetic (n=13), neurodegenerative (n=8), and other neurological (n=8) or systemic autoimmune (n=5) disorders were the main misdiagnoses. Thirty-eight patients fulfilled the diagnostic criteria for "possible AE", 11 for "definite limbic AE", and 4 for "antibody negative but probable AE". MRI showed lesions in 61 cases. Isolated temporal EEG abnormalities were found in 7 cases. Increased CSF white blood cells, protein concentration, and the presence of oligoclonal bands were reported in 27, 26, and 5 cases, respectively. Non-specific autoantibodies were detected in 12 patients. Forty-two patients received immunotherapy, with improvement reported in 21. Neoplastic disorders were more frequent in adults, whereas genetic conditions were more common in children.

Discussion: The spectrum of AE mimics is broad, and the recognition of these disorders is crucial as they can present paraclinical findings and treatment response similar to that observed in AE, leading to misdiagnosis and inappropriate treatment. The lack of fulfillment of the diagnostic criteria for AE, the presence of atypical neuroimaging lesions, non-inflammatory CSF findings, non-relevant autoantibodies,

and a partial response to immunotherapy are major red flags suggesting a possible misdiagnosis.

Conclusions: The present study provides a characterization of mimics and misdiagnoses of AE and clues to aid their identification. The recognition of these conditions is crucial for a correct treatment and to prevent unnecessary exposure to side effects of immunotherapies.

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## KELCH-LIKE PROTEIN-11 (KLHL11) PARANEOPLASTIC SYNDROME: A REPORT OF THE FIRST ITALIAN CASES

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Introduction: Antibodies directed against Kelch-like protein-11 (KLHL11) are markers of a recently described paraneoplastic neurological syndrome (PNS). An ongoing multicenter Italian study (Network Italiano Neurologia Autoimmune-NINA-) is currently aiming to characterize this syndrome in the Italian population. As preliminary data, we herein describe the first two Italian cases with anti-KLHL11-associated PNS.

Materials: Serum and/or CSF of patients with suspected PNS or compatible phenotype according to the most recent diagnostic criteria were tested.

Methods: Patients' serum and CSF samples were tested at the Neuropathology Laboratory, University of Verona, using an in-house cell-based assay employing HEK293T cells transfected with a plasmid encoding KLHL11 protein. Samples were also tested locally or centrally with in-house immunofluorescent tissue-based assays to confirm the peculiar "sparkling" pattern. Clinical, video-EEG/polygraphic, demographic, and oncological data were collected.

Results: Two patients resulted positive for anti-KLHL11 antibodies (one in serum which was the only specimen available, the other one in both serum and CSF) on both cell- and tissue-based assays.

Discussion: Patient#1 is a 72-years-old man who developed subacute cerebellar ataxia two years after surgical treatment of testicular seminoma. Brain MRI demonstrated microangiopathic changes and CSF analysis showed increased protein and cell concentrations. He was treated with steroids with partial improvement. A total body CT scan showed enlarged pelvic and abdominal lymph nodes that were hypermetabolic on 18FDG-PET scan. The lymph nodes were treated with local radiotherapy. He was then re-evaluated and repeated a CSF analysis (increased protein concentration) and audiometric testing demonstrating moderate-to-severe sensorineural hearing loss. KLHL11 antibodies were positive in serum. He was treated with intravenous steroids and immunoglobulins. Patient#2 is a man with a previous history of azoospermia who underwent testicular resection in the suspect of malignancy, then not confirmed. At the age of 42, he developed subacute cerebellar ataxia and was diagnosed as seronegative autoimmune cerebellitis. Five months later, memory loss and focal (left temporal) nonconvulsive status epilepticus occurred. CSF analysis revealed increased protein concentration, a total body 18FDG-PET scan was normal, whereas brain PET scans showed a left temporal inflammatory hypercaptation, which was confirmed on MRI scans. KLHL11 antibodies tested positive in serum and CSF. Treatment with intravenous steroids and immunoglobulins led to partial improvement.

Conclusion: We herein describe the first two Italian cases of anti-KLHL11 asssociated paraneoplastic syndrome. Anti-KLHL11 PNS typically presents as a rhombencephalitis that occurs in men with testicular neoplasms, even though the spectrum of clinical phenotypes and oncological accompaniments is progressively expanding.

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## CONCORDANCE BETWEEN RADIOIMMUNOASSAY AND CELL-BASED ASSAY IN RIA-ACHR POSITIVE ASYMPTOMATIC SUBJECTS

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Objective: Detection of acetylcholine receptor antibodies (AChR Abs) is crucial in myasthenia gravis (MG) diagnosis and currently radioimmunoassay (RIA) is the gold standard. It is well known that RIA can be positive in non-MG thymoma and in patients in complete stable remission (CSR). Aim of this study was to evaluate the concordance between RIA and fixed cell-based assay (CBA) in asymptomatic RIA-AChR positive subjects.

Materials and Methods: 604 AChR-positive subjects were consecutively seen at the Neurology Unit of IRCCS Fondazione Policlinico Gemelli in Rome between January 2000 and May 2023; clinical follow-up was $\geq$ 1 years. MG diagnosis was based on clinical examination, electrophysiological studies and Abs detection. AChR Abs were tested by RIA in the whole cohort. Serum samples from RIA-positive asymptomatic subjects were re-tested by fixed-CBA. The two assays were performed at the same time in each sample.

Results: Serum samples of 6 RIA-positive subjects were tested. Four subjects were RIA-positive for AChR Abs although they had never suffered from MG symptoms (repetitive nerve stimulation studies were negative). Two of these 4 subjects had undergone thymectomy for B2 thymoma (with a follow-up of 12 and 10 years, respectively), 1/4 had thymic hyperplasia and 1/4 had never undergone chest imaging. Two additional samples were collected in 2023 from MG patients: one who has been in CSR since 2016 and a 26-year-old woman who presented transient ptosis in 2019. AChR-Abs were not detected by fixed CBA in four samples (vs 4.80, 5.07, 5.90 and 1.47 nM/L by RIA). The two non-MG thymoma cases resulted positive for both fetal and adult AChR Abs (vs 8.70 and 5.50 nM/L by RIA).

Discussion: RIA has almost 100% specificity and false positivity for AChR Abs is extremely rare (< 1%) [1]. CBA is thought to be more sensitive than RIA in confirming MG diagnosis, especially in ocular cases, as it can detect low-affinity Abs [2]. On the other hand, RIA can detect Abs against intracellular epitopes and thus not pathogenic. Our

preliminary results show that CBA can be more specific than RIA in detecting pathogenic Abs. However, CBA resulted positive in non-MG thymoma patients, suggesting that these subjects can present Abs binding AChR without symptoms.

Conclusion: From our data, AChR detection by CBA may have a better correlation with clinical status than RIA. Future studies should assess if there is binding to intracellular epitopes of the AChR by these likely non-pathogenic Abs.

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## NEUROLOGICAL OUTCOMES IN IMMUNE CHECKPOINT INHIBITOR-RELATED NEUROTOXICITY

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While the spectrum of neurological immune checkpoint inhibitor-related adverse events is expanding, patients outcomes are not well documented. This study aimed to assess outcomes of neurological immune-related adverse events and to identify prognostic factors. All patients experiencing grade ≥2 neurological immune-related adverse events identified at two clinical networks (French Reference Center for Paraneoplastic Neurological Syndromes, Lyon; and OncoNeuroTox, Paris) over five years were included. Modified Rankin scores were assessed at onset, 6, 12, 18 months, and last visit. A multi-state Markov model was used to estimate the transition rates between minor disability (mRS <3), severe disability (mRS 3-5), and death (mRS 6), over the study period. The state-to-state transition rates were estimated using maximum likelihood and variables were introduced into the different transitions to study their effects. A total of 147 patients were included out of 205 patients with a suspicion of neurological immune-related adverse events. Median age was 65 years (range 20-87), and 87/147 patients (59.2%) were male. Neurological immune-related adverse events involved the peripheral nervous system in 87/147 patients (59.2%), the central nervous system in 51/147 (34.7%), and both systems in 9/147 (6.1%). Paraneoplastic-like syndromes were observed in 30/147 patients (20.4%). Cancers included lung cancers (36.1%), melanoma (30.6%), urological cancers (15.6%), and others (17.8%). Patients were treated with PD(L)1 inhibitors (70.1%), CTLA4 inhibitors (3.4%), or both (25.9%). Severe disability was reported in 108/144 patients (75.0%) at onset, and in 33/146 patients (22.6%) at last visit (median follow-up duration: 12 months, range 0.5-50); 48/147 (32.7%) patients died, from cancer progression (17/48, 35.4%), neurological toxicity (15/48, 31.2%), other causes (10/48, 20.8%), or unknown causes (6/48, 12.5%). The rate of transition from severe to minor disability independently increased with melanoma (compared to lung cancer, HR=3.26, 95%CI [1.27; 8.41]) and myositis/neuromuscular junction disorders (HR=8.26, 95%CI [2.90; 23.58]), and decreased with older age (HR=0.68, 95%CI [0.47; 0.99]) and paraneoplastic-like syndromes (HR=0.29, 95%CI [0.09; 0.98]). In patients with neurological immune-related adverse events, myositis/ neuromuscular junction disorders and melanoma increase the transition rate from severe to minor disability, while older age and paraneoplastic-like syndromes result in poorer neurological outcomes; future studies are needed to optimize the management of such patients.

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## EFFECTIVENESS AND SAFETY OF INTRAVENOUS IMMUNOGLOBULIN FOR PERIPHERAL NEUROPATHY IN EGPA PATIENTS: A RETROSPECTIVE STUDY

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Introduction: Eosinophilic granulomatosis with polyangiitis (EGPA), is a small-vessel vasculitis belonging to the spectrum of small-vessel vasculitis associated with antineutrophil cytoplasmic antibodies (ANCAs), also characterized by eosinophilic infiltration of target organs. Peripheral neuropathy (PN) represents a vasculitic involvement, affecting about 2/3 of the patients as a presenting symptom, mainly in the form of mononeuritis multiplex. Few studies have addressed the role of intravenous immunoglobulin (IVIg) for the treatment of PN. This monocentric retrospective study aims at assessing the effectiveness and safety of IVIg in patients with PN as the main acute manifestation at EGPA onset.

Materials and Methods: Out of 93 EGPA patients followed at the Vasculitis Centre of the Careggi University Hospital, we collected data from 39 patients with disease onset characterized by PN. Minimum follow up was of 6 months and last follow up of 18 months. All patients were treated with high dose corticosteroid (CS) alone or associated with other immunosuppressive or immunomodulatory drugs at disease onset. 18 (46%) patients were treated with IVIg at disease onset and throughout the maintenance of remission (IVIg group), while the other 21 (54%) with other therapies (no IVIg group). The two groups were compared by risk of relapse and long-term disability, measured by the modified Ranking Scale (mRS).

Results and Discussion: During the 18 months follow-up, 33% (7/21) of the patients in the no IVIg group developed a relapse, versus only 5% (1/18) in the IVIg group. IVIg treatment significantly reduced the frequency of neurological and systemic relapses and it also reduced the long term neurological disability, due to a stable improvement of peripheral neuropathy. Although no significant difference was observed between the two groups in mRS at disease onset (3-3), there is a statistical difference after 18 months follow-up (2-1; p-value= 0,019). None of the patients treated with IVIg experienced serious adverse reactions.

Conclusion: These exploratory data support the effectiveness of the IVIg treatment as an add-on therapy at onset in EGPA patients developing PN as presenting symptom. The treatment with IVIg appears to be effective in reducing the risk of relapse and long-term disability.

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## NIVOLUMAB-RELATED SERONEGATIVE ENCEPHALITIS IN A PATIENT WITH SQUAMOUS CELL ESOPHAGEAL CANCER. A CASE REPORT

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Immune checkpoint inhibitors (ICIs) like nivolumab have become important in cancer treatment due to their effectiveness and apparent safety. However, the use of ICIs has led to several complications, particularly in the autoimmune spectrum. This report presents a case of nivolumab-related encephalitis, with abrupt onset and spontaneous recovery after discontinuing treatment. A 63-year-old man with a history of stage IIA squamous cell esophageal cancer and previous diffuse large B-cell lymphoma, started nivolumab as adjuvant immunotherapy six weeks after esophagectomy. Six weeks later, the day after the second dose, he experienced fever, dizziness, gait instability, cognitive impairment and expressive aphasia. In the following days due to progressive worsening and onset of right hemiparesis he underwent an urgent brain MRI at his local hospital in the suspicion of a cerebrovascular event, but the results were negative. He was discharged on antiplatelet therapy. A subsequent evaluation at our center one week later showed gradual motor recovery, but persistent cognitive impairment, temporal disorientation and anomic aphasia. EEG results indicated diffuse encephalopathic patterns, leading to admission one week later. Neurological assessment showed mild cognitive impairment while laboratory tests, including tumor markers and immunological assessments, were normal. A control EEG showed partial improvement, despite diffuse slow tracing still persisted. Cerebral MRI with Gadolinium and CSF analysis were within limits, except for mild pleocytosis and hyperproteinorrhaquia and a mirror pattern. CSF immunophenotyping revealed abnormal T-cell levels with a reduced CD4+CD3+ count (173.1 cells/uL, normal range 510-1270/uL). Antineuronal and neuronal surface antibodies were negative both in serum and CSF and neither viruses or bacteria were detected. Over four days his neurological status gradually improved, with only slight psychomotor retardation at discharge. Nivolumab was discontinued and one month later his follow-up neurological examination was normal. Neurological disorders, accounting for 7.2% of ICI-related complications, can range from myasthenia gravis to encephalitis. They usually manifest within weeks of starting treatment and often recover after discontinuing the drug and administering steroids. In this case, the patient's symptoms were initially misdiagnosed as a stroke. The pathogenesis is thought to be T-cell mediated, which may explain the infrequency of antineuronal antibody detection. Except for preexisting autoimmune conditions, which relapse in 20-40% of patients undergoing treatment, no clear demographic or clinical features are associated with increased risk of ICI-related neurological complications. Clinicians should be aware of these potential complications to ensure timely diagnosis and improve multidisciplinary approach to cancer patients.

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## AUTOIMMUNE LIMBIC ENCEPHALITIS: BEYOND THE KNOWN – CASE REPORT

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Introduction: Paraneoplastic limbic encephalitis (PLE) associated with Ma2 antibodies is a rare neurocognitive disorder, usually presenting with a subacute onset of the symptoms. The presentation of these syndromes regularly precedes the diagnosis of cancer, complicating their recognition as a PLE [1]. They are usually associated with small cell lung carcinoma and testicular carcinoma [2].

Case Report: Here, we report the case of a 82-year-old woman with a history of arterial hypertension, dyslipidemia and Hashimoto's thyroiditis who presented with an acute onset of subjective vertigo and disequilibrium since awakening. Neurological examination showed left cerebellar signs, left VI cranial nerve palsy, inexhaustible up-beating nystagmus and a severe retropulsion causing gait instability. CT angiography and perfusion CT showed no large vessel occlusion and/or areas with hypoperfusion and brain MRI was unremarkable. After 20 days of rehabilitation, a worsening of symptoms was detected. A repeated brain MRI showed left hippocampus and uncus T2-hyperintensity with no diffusion restriction and no gadolinium enhancement. Testing onconeural antibodies, both CSF and serum anti-Ma2 autoantibodies were positive. Total body PET-CT displayed a left-hypochondrium hypermetabolic solid lesion resulting in epitheliod-type peritoneal mesothelioma. No other primary and/or secondary lesions were found. Despite a 5-day intravenous high dose corticosteroid therapy (methylprednisolone 1g/die) the patient showed no clinical improvement. While waiting for surgical evaluation, she suddenly died from oncological disease-related complications.

Discussion and Conclusions: This case shows a PLE with acute onset of symptoms associated with pleural mesothelioma. The diagnosis was confirmed by the typical neuroradiological images and the findings of onconeural antibodies. The acute onset is atypical, but previous similar cases have been described in literature [3]. On the other hand, to our knowledge, our case is the first in the literature describing the association between peritoneal mesothelioma and anti-Ma2 PLE.

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## HERPES SIMPLEX ENCEPHALITIS MIMICKING ISCHEMIC STROKE IN A PATIENT WITH ANATOMICAL VARIANT OF WILLIS CIRCLE

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Aim: To report an atypical case of Human Herpesvirus 6 (HHV6) encephalitis mimicking ischemic stroke in a patient with an anatomical variant of Willis Circle.

Materials and Methods: We describe herein a 62-year-old man who arrived at the emergency department with altered mental status and behavioral changes since a few hours. After having excluded toxic and metabolic diseases we apply the diagnostic work-up for cerebrovascular accidents and infective diseases. Neurological examinations, blood tests, neuroimaging (brain CT and MRI), Electroencephalogram (EEG), neuropsychological tests, and Cerebrospinal Fluid analysis (CSF) were performed.

Results: Neurological examination revealed disorientation, motor aphasia, and uncertain gait. Blood tests including Reactive C Protein (RCP) and Procalcitonin (PCT) were negative. Brain MRI showed symmetric bilateral frontal and on-vertex hyperintensity with mild meningeal contrast graphic impeachment. These lesions revealed a high signal in T2, FLAIR, and DWI sequences and a low signal in Gradient Echo as laminar necrosis. EEG presented sporadic spikes on the left central derivation. CT angiography showed a fusion of the Anterior Cerebral Arteries (ACAs) over a short distance. Neuropsychological tests showed deficits in autobiographic, recent, and past memory, in verbal and praxis function. The patient underwent lumbar puncture with evaluation of standard analysis and a FilmArray Meningitis/Encephalitis panel, revealing the presence of HHV6. Treatment with acyclovir was started at a standard dose (10mg/Kg Intravenous, every 8 hours), combined with corticosteroid therapy for 14 days. Neuropsychological evaluation was repeated, detecting an improvement in patient's verbal and executive functions. Furthermore brain MRI, performed twelve days after therapy starting, showed a global reduction of cerebral lesions and swelling.

Discussion & Conclusions: HHV6 can cause different neurological manifestations, depending on the patient's immunological status. [1] Most commonly HHV6 cerebral lesions are localized at temporal lobes[2]. In contrast, our case presented an atypical involvement of frontal lobes which represented a confounding element together with the presence of the ACAs variant. However, the appearance of the laminar necrosis since the first day and the neuroradiological lesions evolution led to a correct diagnosis. We encourage to consider HHV encephalitis in case of patients with clinical and instrumental findings suggesting an infective disease, even if radiological lesions localization is uncommon. Moreover, a good response to antiviral and corticosteroid therapy could support the diagnosis as an ex-adiuvantibus criterion.

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## IMMUNE CHECKPOINT INHIBITOR-RELATED NEUROMUSCULAR TOXICITY: AN OBSERVATIONAL MONOCENTRIC STUDY

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Objectives: To characterize severe (grade III-IV CTCAE) neuromuscular toxicity following Immune Checkpoint Inhibitor (ICI) administration including clinical and paraclinical features, response to immunosuppressive therapy, neurological and oncological outcome.

Materials and Methods: We included 6 adult patients developing new-onset neuromuscular symptoms within 12 months from the last ICI infusion that were treated at a tertiary referral center (2019-2022).

Results: Most patients were male (5/6; 83.3%) and the median age was 77 (range 55-85). Associated tumors were melanoma (n=2), non-small cell lung cancer (NSCLC, n=2), renal clear cell carcinoma (n=1) and concomitant NSCLC and thymic squamous carcinoma (n=1). Two patients had a pre-existing autoimmune disease (chronic gastritis and thyroiditis). Pembrolizumab was the ICI adopted in most cases (4/6, 66.7%). Neuromuscular symptoms developed a median of 6 weeks (range: 4-30.6) after ICI onset. Neurological involvement was peripheral in 5/6 patients (83.3%), central and peripheral in 1/6 (16.7%). Myositis-myocarditis overlap syndrome was diagnosed in 2/6 (33.3%) patients, myasthenia-myositis overlap syndrome in 1/6, myasthenia-myocarditis overlap syndrome in 1/6, myasthenia in 1/6 and myositis in 1/6. Concomitant unilateral optic neuritis was diagnosed in one patient. Four patients developed other non-neurologic immune-related Adverse Events (irAEs) (1) (66.7%). Laboratory tests within two weeks after symptoms onset showed increased levels of creatine kinase (CK) in 5/6 patients (83.3%), AST and ALT in 6/6 (100%), and positive Troponin I in 3/6 (50%). Myositis-specific and -associated autoantibodies were found in 2/6 (33.3%) patients. Anti-acetylcholine receptor antibodies were not detected. ICI was withdrawn in all patients and all cases received immune-modulating therapy: 4/6 (66.7%) corticosteroids and IVIg (two of which also received a second-line immunotherapy including one patient treated with anti-IL6R tocilizumab) and 2/6 (33.3%) corticosteroids only. Concerning neurological outcome, 4/6 (66.7%) patients improved with residual disability, 1/6 (16.7%) did not improve and 1/6 worsened. A complete tumor response was observed in 1/6 (16.7%) patients, while in 5/6 (83.3%) disease stability or progression was recorded.

Discussion: The time lag between ICI initiation and symptoms onset appears to be short and the disease course severe. Interestingly, the only patient who is currently disease free at 14-months follow up also developed CNS toxicity. It would be worth investigating the relationship between neurological and oncological outcome in patients experiencing neuromuscular toxicities.

Conclusions: In our case series, ICI-related neuromuscular toxicity more commonly associated to male sex and pembrolizumab therapy, developing early after ICI onset. Most patients developed concomitant iRAEs.

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## TEMPORAL LOBE GLIOMA: AN UNCOMMON MIMIC OF AUTOIMMUNE LIMBIC ENCEPHALITIS

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Background and Objective: The aetiologic spectrum of autoimmune encephalitis (AIE) mimics is broad. Primary brain tumors can present with clinical and MRI features that can resemble AIE, making the differential diagnosis challenging. Herein we describe a case of temporal lobe glioma mimicking AIE.

Materials and Methods: The clinical presentation and diagnostic approach leading to the diagnosis of glioma are presented.

Results: A 41-year-old man presented to the emergency department for rapidly progressive vertigo, confusion and language disturbances, followed by focal, refractory status epilepticus (oculogyric crisis) within 24 hours, and was admitted to the ICU. Brain MRI revealed a T2/FLAIR cortical-subcortical hyperintensity involving the right temporal pole (mostly in its ventral and lateral surface), extending to the insular cortex and frontal lobe, not accompanied by gadolinium enhancement or restricted diffusion. CSF analysis was unremarkable. Treatment with acyclovir and ceftriaxone was empirically started, but later discontinued due to negative HSV-PCR and bacterial infectious screening. Repeat lumbar puncture 5 days later revealed 12 white blood cells, normal proteins and absence of oligoclonal bands. Search for common antineuronal antibodies in serum and CSF was negative. Whole body CT failed to reveal occult malignancies. A diagnosis of possible seronegative AIE was considered based on the Graus 2016 diagnostic criteria. During the first two weeks, he was treated with intravenous methylprednisolone (1 g daily for 5 days) and intravenous immunoglobulin (IVIG) in addition to levetiracetam (3000mg/die), lacosamide (400mg/die) and sodium valproate (1200mg/die), with resolution of the status epilepticus. Repeat MRI and brain MRI spectroscopy showed stability of the lesion and increased Cho/NAA ratio suggestive for neoplasm. A brain biopsy confirmed a low-grade astrocytoma.

Discussion and Conclusions: Temporal lobe gliomas are rare but well recognized mimics of AIE. Our patient met the diagnostic criteria for possible seronegative AIE (rapid progression of altered mental status and unexplained seizures, absence of well characterised autoantibodies in serum and CSF, MRI abnormalities compatible with autoimmune encephalitis and inflammatory CSF). However, the limited involvement of the mesial part of the temporal pole, and lack of improvement of MRI abnormalities after treatment represented major red flags.

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## PROGNOSTIC PERFORMANCE OF BLOOD NEUROFILAMENT LIGHT CHAIN PROTEIN IN HOSPITALIZED PATIENTS WITH COVID-19: AN INDIVIDUAL PARTICIPANT DATA META-ANALYSIS

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Background and Aims: Neurofilament light chain protein (NfL) is a blood biomarker of neuroaxonal injury, the levels of which are increased in hospitalized COVID-19 patients, even without major COVID-19- associated CNS manifestations and seem to be associated

with poor clinical outcomes. [1,2,3] Our study aimed to investigate the prognostic value of blood NfL levels in the acute phase of COVID-19.

Methods: We conducted an individual participant data (IPD) meta-analysis after screening on MEDLINE and Scopus to 23 May 2022. We included studies with hospitalized adult COVID-19 patients without major COVID-19-associated CNS manifestations and with a measurement of blood NfL in the acute phase and data regarding at least one clinical outcome including ICU admission, need of mechanical ventilation (MV) and death. We derived the age-adjusted measures NfL Z scores and conducted mixed-effects modelling to test associations between NfL Z scores and other variables, encompassing clinical outcomes. Summary receiver operating characteristic curves (SROCs) were used to calculate the area under the curve (AUC) for blood NfL.

Results: We identified 382 records, of which 7 studies were included with a total of 669 hospitalized COVID-19 cases (mean age 66.2±15.0 years, 68.1% males). Median NfL Z score at admission was elevated compared to the age-corrected reference population (2.37, IQR: 1.13–3.06, referring to 99th percentile in healthy controls). NfL Z scores were significantly associated with disease duration and severity. Higher NfL Z scores were associated with higher likelihood of ICU admission, MV, and death. SROCs revealed AUCs of 0.74, 0.80 and 0.71 for mortality, MV and ICU admission, respectively.

Conclusions: Blood NfL levels were elevated in the acute phase of COVID-19 and associated with clinical severity and poor outcome. The marker might ameliorate the performance of prognostic multivariable algorithms in COVID-19.

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## HIV-ASSOCIATED VACUOLAR MYELOPATHY: A CASE OF SENSITIVE ATAXIA AND SPASTIC PARAPARESIS MIMICKING SUBACUTE COMBINED DEGENERATION

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Background: HIV-associated vacuolar myelopathy is an increasingly rare manifestation of HIV, especially following the introduction and diffusion of the Highly Active AntiRetroviral Therapy (HART). In this clinical case, we reported MRI findings of a 52-year-old man, with subacute spastic paraparesis and sensitive ataxia due to Human Immunodeficiency Virus (HIV)-associated vacuolar encephalomyelopathy in newly diagnosed Acquired Immune Deficiency Syndrome (AIDS).

Case report: A 52-year-old male presented with a 2-month-long history of progressively worsening spastic paraparesis, lower limbs dysesthesias and sensitive ataxia leading to gait instability. Urinary hesitation and loss of sexual function were present. He could not walk on his toes or heels, fell in Romberg, and exhibited hypo-pallesthesia at the hips, ultimately resulting in a loss of vibration and statokinesic sensation in his feet. Cranial nerves and upper limbs were normal, except for a slight telekinetic tremor in the left hand. Deep tendon reflexes were hyperexcitable. The patient denied any use of drugs, contact with toxins, or exposure to any professional risks. Somatosensory and motor evoked potentials were altered, indicating a prolonged central conduction time. Brain-MRI showed T2/Fluid Attenuated Inversion Recovery (FLAIR)-hyperintensities in the optic chiasm and optic tracts without gadolinium-enhancement or diffusion restriction. Similar FLAIR-lesions were found in the pyramids within the brainstem and in the lateral and posterior funiculi of the cervical and dorsal spinal cord. A metabolic or toxic etiology was excluded, and no vitamin deficiencies were found. In particular, the patient had normal levels of B12 vitamin and methylmalonic acid. We hypothesized an infective origin due to lymphopenia at blood sample, and indeed HIV-testing resulted positive, with CD4+-count of 129 cells/μL. There were no other viral or bacterial infections and even HTLV I/II antibodies were negative. Therefore, we diagnosed an HIV-associated vacuolar myelopathy in a newly diagnosed of AIDS. HART was started with no significant clinical improvement at 3-month-follow-up.

Discussion and Conclusions: HIV-associated vacuolar myelopathy is clinically resemblant to subacute combined degeneration of spinal cord, due to impaired B12 vitamin utilization and neurotoxic effects of HIV. Therefore, it is important to consider it in the differential diagnosis of subacute myelopathy. [1] Interestingly, our case report presented also subclinical involvement of the brainstem and optic tract/chiasm, as previously described. [2]

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## PLASMA AND CSF LEIOMODIN-1 ANTIBODIES IN PATIENTS WITH LONG STANDING NODDING SYNDROME

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Objectives: Nodding syndrome (NS) is a complex neurological disorder of unknown aetiology. A previous study suggested a role for Onchocerca volvulus induced antibodies cross reacting with human proteins such as leiomodin-1 in the pathogenesis of the disease [1].

Here we investigated the role of autoimmunity to neuronal antigens in NS patients.

Material: We screened for the presence of leiomodin-1 as well as neuronal antibodies in plasma and CSF of 240 NS patients enrolled in a phase II trial of doxycycline for the treatment of nodding syndrome.

Methods: Plasma obtained on enrolment were tested for circulating antibodies to both Onchocerca volvulus (Ov16 and Ov3261) and to leioimodin-1. The mean duration of symptoms was 8.3 (SD 2.8) years. Infection by this filarial worm was defined as a positive antibody test to any of the two Onchocerca volvulus antigens. Antibodies to leioimodin-1 were tested using a standard luciferase immunoprecipitation system (LIPS) assay. For CSF, we initially screened 50 sera and 50 CSF samples for IgG binding to rodent brain tissue by immunohistology and to specific antigens including leiomodin-1; the sera bound widely but non-specifically. For specific testing, the presence of neuronal antibodies was investigated by immunohistochemistry (IHC) on mouse brain sections and by antigen specific cell-based assays for neuronal proteins and leiomodin-1. Antibody levels in the 240 NS CSF samples were compared to 40 CSFs from European controls.

Results: A total of 232/240 (96.7%) plasma samples tested positive for Onchocerca volvulus (228/240 to Ov16 and 25/240 to Ov3261) and leiomodin-1 antibodies were detected in 77/240 (32.1%) plasma samples and in 26/240 (10.8%) of CSF samples. Circulating leioimodin-1 antibodies (76/232 [32.8%] Ov16/Ov3261 positive vs 1/8 [12.5%] Ov16/Ov3261 negative, p=0.044) but not CSF leioimodin-1 antibodies (25/232 [10.8%] Ov16/Ov3261 positive vs 1/8 [12.5%] Ov16/Ov3261 negative, p=1.0) was associated with infection by Onchocerca volvulus. However, CSF leiomodin-1 antibodies were more likely to be present in patients with myoclonic seizures or drop attacks. Neuropilar staining by IHC was found in 28/240 (11.7%) NS CSFs. Among them, 2 had GABAbR antibodies and one had CASPR2 antibodies. Only 8/28 (28.6%) patients had both leiomodin-1 and neuropilar antibodies.

Conclusion: NS is associated with infection by Onchocerca volvulus and circulating antibodies to leioimodin-1. In addition, patients with CSF leioimodin-1 antibodies present with myoclonic seizures and drop attacks. Further studies are needed to understand the pathogenesis of disease.

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## ATYPICAL PRESENTATION OF ANTI-LGI1 ENCEPHALITIS: A CASE REPORT

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Objectives: Anti-LGI1 encephalitis is characterized by subacute and progressive disturbance with cognitive and behavior symptoms, seizures and sleep disorders [1]. Faciobrachial dystonic seizures are very specific for this disease, although not always present [2].

Materials and Methods: An 63-year-old man developed axial rigidity and autonomic dysfunction within the last 4 months. In that period, he presented one tonic-clonic seizure. He was diagnosed with atypical parkinsonism (multiple system atrophy) and the episode of loss of consciousness was interpreted as convulsive syncope. He was admitted to the emergency department following the acute onset of confusion, agitation and cognitive impairment. Neurological examination showed mild axial rigidity, myoclonus in the 4 limbs (with lower limbs predominance) and pyramidal signs. A complete blood count were unremarkable; his cerebrospinal fluid (CSF) analysis revealed high values for protein (115 mg/dl) without pleocytosis. Polymerase chain reactions for neurotropic viruses, bacteria and mycetes on CSF were normal. An EEG revealed diffuse slow waves, without any specific epileptogenic activity; Brain magnetic resonance imaging showed mild hyperintensities in the bilateral mesial temporal lobes and cortical atrophy. Antibodies for autoimmune and paraneoplastic encephalitis were sent and while awaiting the results, the patient started on steroid. After about three weeks his serum autoimmune encephalitis panel returned positive for anti-LGI-1 antibodies. He also started on intravenous Immunoglobulin. The CT chest-abdomen and pelvis were performed and were negative for malignancy. During the course of his hospital stay, he presented an improvement of motor disorders with complete regression of pyramidal deficit and myoclonus; cognitive and autonomic dysfunction (low blood pressure, tachycardia) persisted, and these symptoms had a fluctuating course. He was discharged from the hospital in quite good conditions but unfortunately after few weeks he presented a sudden death, presumably due to his severe haemodynamic instability.

Discussion and Conclusions: Diagnosis of encephalitis can be challenging. Our patient developed LGI-1 encephalytis with an atypical presentation with diffuse myoclonus and pyramidal signs, which are hardly described in this form, in the absence of faciobrachial dystonic seizures which are usually more frequent; moreover, it is possible that the previous diagnosis of multisystem atrophy was a misdiagnosis, and that the onset of LGI-1 encephalitis itself was characterized by atypical parkinsonism that would have preceded the more classic symdrome. To date, only one case of autoimmune encephalitis presenting with atypical parkinsonism has been described [3], but in the case of that patient LGI-1 antibodies were negative.

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## CHOROID PLEXUS AND PERIVASCULAR SPACES ENLARGEMENT IN NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

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Objectives: Choroid plexus (CP) enlargement has been suggested as a marker of neuroinflammation, for instance in multiple sclerosis [1]. CP involvement has also been hypothesized in the immunopathology of systemic lupus erythematosus (SLE) [2]. However, the associations between CP volume, neuropsychiatric involvement, auto-antibody status and brain structural damage have not been fully explored yet. We investigated whether CP enlargement occurs in SLE patients compared to healthy controls (HC) and whether it is associated with neuropsychiatric involvement. Additionally, we explored the abnormalities along the glymphatic network in SLE patients through enlarged perivascular spaces (PVS) quantification in basal ganglia (BG) and centrum semiovale (CS).

Materials: Brain dual-echo and 3D T1-weighted MRI sequences of 32 SLE patients and 32 sex- and age-matched HC were acquired using a 3 Tesla scanner, together with a clinical evaluation.

Methods: CPs were manually segmented on 3D T1 sequence and enlarged PVS were assessed on paired T2 and T1 sequences through Potter's score [3].

Results: Compared to HC, SLE patients showed higher normalized CP volume (nCPV) ($p=0.023$), with neuropsychiatric SLE patients (NPSLE) showing significantly higher CP enlargement than non-NPSLE patients ($p=0.027$). SLE patients with antiphospholipid antibodies (APA) positivity had higher nCPV compared to HC ($p=0.012$), while APA negative ones did not. SLE patients had also higher Potter's score than HC both in BG and CS regions ($p<0.001$), with NPSLE patients showing a tendency to higher Potter's score in BG, compared to non-NPSLE, without reaching statistical significance ($p=0.09$). Among the demographic, clinical and MRI variables tested by means of a random forest analysis, nCPV emerged as a significant predictor of NPSLE, together with brain T2-hyperintense white matter (WM) lesion volume (LV) and APA positivity (out-of-bag AUC 0.81).

Discussion: CP enlargement occurs in SLE, especially in patients with neuropsychiatric involvement. CP volume also proved to be a predictor of NPSLE together with brain T2-hyperintense WM LV and APA positivity. Enlarged PVS are more prevalent in SLE patients, with a potential greater alteration in NPSLE, which needs to be further investigated.

Conclusions: CP and PVS abnormalities, which could reflect the impairment of blood-cerebrospinal fluid barrier and glymphatic system, point out the possible role of these structures in the pathophysiology of NPSLE.

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## HUMAN HERPESVIRUS 6 RELATED FOCAL PACHYMENINGITIS IN AN IMMUNOCOMPETENT ADULT

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Introduction: Human herpesvirus 6 is the etiological agent of Roseola Infantum and, rarely, meningoencephalitis in infants. Reactivation of the infection with central nervous system involvement may occur in immunocompromised adults whereas it is rare in immunocompetent patients [1]. In this report we describe a case of a HHV-6 related focal pachymeningitis occurred in an immunocompetent adult.

Case presentation: A 76-year-old woman presented in the Emergency Department with new-onset left body focal motor seizures. She reported a history of fever and weakness of the left limbs in the week prior to hospitalization. Head CT-scan was unremarkable, while EEG showed bilateral frontotemporal theta activity. Admitted in our unit, the patient presented another left-sided focal motor seizure and anticonvulsant therapy (Levetiracetam 500 mg twice day PO) was started with the resolution of seizures. Neurological examination was unremarkable. A brain MRI was indicative of frontoparietal pachymeningitis. CSF analysis revealed lymphocytic pleocytosis with normal glucose levels and hyperproteinorrachia. Polymerase chain reaction (PCR) was negative for several viral agents except for HHV-6. Inflammatory, autoimmune, infectious, and neoplastic causes of focal pachymeningitis were excluded. To confirm HHV6 acute infection, a hair follicle genomic integration test was carried out, which resulted negative. Intravenous Ganciclovir and Ampicillin was started, and 5 days after a new brain MRI showed a slight reduction in the thickening of the pachymeninges. A new lumbar puncture documented 1/mm3 cells and normal protein level, while the HHV-6 PCR was still positive. After 21 days, Ganciclovir was interrupted due to the significant improvement of brain MRI findings. At three months from the discharge, the patient remained seizure-free.

Conclusions: In our case some peculiar feature emerged: 1. HHV-6 meningeal involvement occurred in a immunocompetent patient. 2. Focal pachymeningeal involvement has never been reported as related to HHV-6 reactivation. 3. The clinical course of our patient was benign with complete remission, in contrast with more severe clinical pictures reported in literature. HHV6 has the unique ability to incorporate itself into host DNA. According to literature reports, PCR is unable to distinguish between active viral DNA replication and DNA already integrated into the host chromosome, leading to an increase in false positive results in screening tests. Thus, more infectious and non-infectious etiologies need to be excluded before diagnosing HHV-6 meningitis [2]. Due to the lack of standard treatment guidelines for the management of HHV-6 meningitis in immunocompetent adults [3], we relied on the data provided by case reports, showing good clinical, radiological and CSF response to Ganciclovir therapy.

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## ROZANOLIXIZUMAB RESPONDER AND MINIMAL SYMPTOM EXPRESSION RATES IN GENERALISED MYASTHENIA GRAVIS: POOLED PHASE 3 AND EXTENSION STUDIES

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Objectives: The Phase 3 MycarinG (MG0003/NCT03971422) trial demonstrated efficacy of one 6-week cycle of rozanolixizumab in generalised myasthenia gravis (gMG). [1] We aimed to assess the long-term efficacy and safety of repeated cycles of rozanolixizumab using data pooled across MycarinG, MG0004 and MG0007.

Materials and Methods: After 6 weeks of weekly rozanolixizumab/placebo in MycarinG, patients entered MG0004 (NCT04124965: ≤52 weeks of weekly rozanolixizumab) or MG0007 (NCT04650854: initial 6-week cycle; subsequent cycles administered on symptom worsening as determined by investigator's discretion, e.g., Myasthenia Gravis Activities of Daily Living [MG-ADL] increase ≥2/Quantitative Myasthenia Gravis [QMG] increase ≥3; "symptom-driven cycles"). The efficacy pool included data for patients with ≥2 symptom-driven cycles pooled across MycarinG, MG0004 (first 6 weeks) and MG0007 (interim analysis). The safety pool included data for patients with ≥1 cycle across MycarinG (symptom-driven) and MG0007 (fixed/symptom-driven).

Results: In total, 127 patients received ≥2 symptom-driven cycles of rozanolixizumab 7 mg/kg (initial dose, n=69) or 10 mg/kg (initial dose, n=58). MG-ADL change from baseline to Day 43, responder rates at Day 43 for MG-ADL, Myasthenia Gravis Composite and QMG and minimal symptom expression at any visit were consistent across cycles. Treatment-free intervals (time from previous dose to first dose in symptom-driven Cycle 1) were <4 weeks for 9.0%, 4–<8 weeks for 35.9%, 8–<12 weeks for 22.8%, 12–<24 weeks for 13.8% and ≥24 weeks for 4.8% of patients, with similar proportions at the next cycle. Treatment-emergent adverse events (most mild to moderate) occurred in 169 (89.9%) patients receiving ≥1 cycle of rozanolixizumab: 103 (77.4%) and 120 (91.6%) patients receiving rozanolixizumab 7 mg/kg and 10 mg/kg, respectively.

Discussion and Conclusions: Rozanolixizumab efficacy was maintained over symptom-driven cyclical treatment and multiple endpoints.

Funding: UCB Pharma.

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## ANTI-GABABR ENCEPHALITIS PRESENTING AS ISOLATED DYSAUTONOMIA: LACK OF CANCER AND ANTI-KCTD16 PREDICT RECOVERY

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Objectives: (i) To describe a case of anti-GABABR encephalitis mimicking vasodepressor syncope at onset and (ii) the possible role of cancer and ancillary antibody (anti-KCTD16) status to determine prognosis.

Materials: The patient underwent a comprehensive screening for antibodies against extracellular/synaptic neuronal antigens and intracellular antigens in serum and CSF using commercial kits (Euroimmun, Lübeck, Germany), which revealed an anti-GABABR positivity confirmed by indirect immunofluorescence assay (IIFA). In addition, the samples were also tested at the French Reference Center using inhouse cell-based assays for anti-GABABR confirmation and for anti-KCTD16 testing, a novel antibody that was found to associate to paraneoplastic anti-GABABR cases.

Methods: Case report.

Results: A previously healthy 43-year-old man presented with isolated syncope of undetermined origin, occurring without prodromes. No associated cognitive, epileptic, or psychiatric symptoms were noted. Brain computed tomography (CT) and routine laboratory tests were negative/normal. During the overnight stay in the Emergency Department, he developed severe bradycardia (30 bpm) followed by tachycardia (133 bpm) and was found unconscious. Echocardiogram and brain magnetic resonance imaging (MRI) with gadolinium were normal. Tilt-test resulted positive for vasodepressor syncope and the patient was discharged. Two weeks later, he was re-admitted for recurring episodes of loss of consciousness. He became aggressive and confused and a single generalized tonic-clonic seizure was observed. Electroencephalogram (EEG) showed sharp theta-delta activity and sharp waves in the left temporal region. Antiseizure medications were started. Cerebrospinal fluid examination showed pleocytosis (14/μL). Microbiological screening was negative. GABABR antibodies were positive in both CSF and serum, while KCTD16 antibodies were negative. Immunotherapy with intravenous immunoglobulin (IVIG) and steroid bolus was started, with gradual improvement. Total body CT and PET-CT scans performed every 4 months for 1 year were negative. After an additional IVIG cycle, he fully recovered. Complete neurological and neuropsychological evaluation at last follow-up were normal.

Discussion: Anti-GABABR encephalitis typically presents with prominent epileptic symptoms, including status epilepticus. Some patients develop cognitive and behavioural symptoms. [1] Conversely, dysautonomia as an early symptom is rare. [2,3] Only another case of anti-GABA-B-R encephalitis mimicking syncope has been described. [2]

Conclusions: Non-paraneoplastic anti-GABA-B-R encephalitis may have a better response to immunotherapy and an atypical clinical onset (e.g. dysautonomia). The diagnosis can be challenging as the neuroimaging studies can be negative. Testing KTCD16 antibodies may help to exclude a paraneoplastic association and to support a favourable prognosis.

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## GASTRO-INTESTINAL DYSFUNCTION AS FIRST SYMPTOM OF FATAL DOUBLE POSITIVE (SOX1, HU) ENCEPHALITIS

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Objectives: Here we report a man with subacute gastro-intestinal symptoms (diarrhea and vomiting) followed by chronic intestinal pseudo-obstruction (as typically described in DPPX encephalitis), who had encephalitis correlated to a double positivity of anti-Sox1 and anti-Hu antibodies, without evidence of cancer with fatal course.

Methods: A 73 years-old male, with no other relevant past medical history, complained for a month of epigastralgia, loss of appetite, hiccups and vomiting and diarrhea. He presented to our hospital for acute intestinal obstruction. The night before presentation he had an episode of absence with fluctuating state of consciousness, and subsequently developed a non-convulsive status epilepticus (NCSE).

Results: Neurological examination showed: altered vigilance, with no other neurological signs. Only a moderate hyponatremia (127) was found. Extensive infectious, paraneoplastic, biochemical panel was normal. EEG showed sub-continue left temporal discharges, and brain MRI confirmed an unilateral left limbic involvement. Lumbar puncture was negative for infectious causes. He was started immediately on high dose methyl-prednisolone plus IV-immunoglobulin therapy. No evidence of intestinal obstruction on total-body-CT, gastroscopy and colonoscopy was found. Three days after initial recovery he died. Positivity of Anti-Hu and anti-Sox1 antibodies were found, on serum and CSF.

Conclusion: Gastro-intestinal manifestations are notoriously associated with anti-DPPX encephalitis [1]. Recently, also anti-Hu encephalitis has been reported to cause gastro-intestinal motility impairment [2]. Clinicians should keep in mind that isolated gastroparesis could be the initial sign of an encephalitis, moreover multiple antibody positivity is increasingly recognized as predictive of a worse outcome [3].

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## STEROID-RESPONSIVE ENCEPHALOPATHY ASSOCIATED WITH AUTOIMMUNE THYROIDITIS (SREAT): A DIAGNOSIS OF EXCLUSION

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Introduction: Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) is an uncommon neurological syndrome associated with autoimmune thyroid disease. The pathogenesis of SREAT is uncertain even if the last evidence point towards a probable autoimmune etiology due to vasculitis or other inflammatory processes. Clinical manifestations of SREAT are various and unspecific. Due to the lack of any specific diagnostic investigations, SREAT is mainly a diagnosis of exclusion to be considered in the setting of subacute onset encephalopathy with high titers of anti-thyroid peroxidase (anti-TPO) and/or anti-thyroglobulin (anti-Tg) antibodies and responsiveness to glucocorticoid therapy in the absence of other neural autoantibodies [1].

Case report: A 56-year old woman arrived to our hospital complaining a ten days history of speech arrest, impairment in executive and attentional functions, dizziness and postural tremor of the limbs. The EEG showed diffuse slow sharp waves. The brain MRI and the body CT did not show significant finds. Her cerebrospinal fluid (CSF) analysis was normal. We found in the clinical history an hypothyroidism treated by specific therapy. During hospitalization, thyroid hormones title was normal but thyroid peroxidase antibody (anti-TPO-Ab) resulted higher than normal. All other blood investigations, including antinuclear antibodies titers and serological and virologic tests, were negative [2]. The patient was treated by intravenous methylprednisolone with a dramatic symptoms improvement within 72 hours.

Discussion: The majority of SREAT cases presents a fluctuating course with variable features such as cognitive impairment, seizures, tremor, ataxia, sleep disturbance, headache, focal neurological deficits, depression or psychosis. Disease manifestations of SREAT occur independently to the thyroid status. High titers of anti-TPO-Ab are found in nearly all reported cases till to be considered a hallmark of the disease even if its role in pathogenesis of SREAT is still uncertain. Our patient had elevated anti-TPO-Ab titers and also showed a dramatic improvement following intravenous steroid therapy which are both described as typical clinical characteristics of SREAT.

Conclusions: The diagnosis of SREAT is primarily based on the exclusion of other infective, inflammatory, autoimmune and neoplastic etiologies of encephalopathy. A subacute onset of symptoms compatible with an encephalopathy, an high anti-thyroid antibodies level and a dramatic clinical response to steroid therapy should suggest a possible diagnosis of SREAT. This case also emphasizes that patients with subacute encephalopathy should be screened for antithyroid antibodies despite their euthyroid status.

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## ISOLATED RETROGRADE AMNESIA IN ANTI-CASPR2 ENCEPHALITIS: A CASE SERIES AND SYSTEMATIC LITERATURE REVIEW

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Introduction and Aims: Anti-leucine-rich glioma inactivated 1 (LGI1) and anti-contactin-associated protein-like 2 (CASPR2) antibodies can associate with limbic autoimmune encephalitis (LAE) typically manifesting as anterograde amnesia, behavioral disorders and seizures. Retrograde amnesia has also been rarely described. We report a case series of CASPR2-positive pure episodic-autobiographical retrograde amnesia and we systematically review the literature data on memory impairment in CASPR2/LGI1 encephalitis.

Materials: Clinical data have been collected from medical records.

Methods: A systematic literature search of all published CASPR2 and LGI1 encephalitis with memory impairment was performed.

Results: A 72-year-old male patient presented with seizures and behavioral changes. Brain Magnetic Resonance Imaging (MRI) revealed bilateral temporomesial abnormalities. Anti-CASPR2 antibodies were found in both cerebrospinal-fluid (CSF) and serum. He additionally complained of retrograde amnesia involving the 6 months preceding the onset of LAE, during which his behavior was completely unaffected according to his wife. A 52-year-old male patient presented with seizures, behavioral changes, and retrograde amnesia dating back more than 12 months to the onset of LAE. Brain MRI showed blurred hyperintensity of limbic structures. Anti-CASPR2 antibodies were found only in serum. Among 21 studies describing 452 patients with LGI/CASPR2 LAE, retrograde amnesia was reported in only 7/415 anti-LGI1 (1,69%), 5/452 (0,92%) with anti-VGKC and in none with anti-CASPR2, and always in association with anterograde amnesia.

Discussion: Retrograde amnesia is a rare entity mostly attributed to post-traumatic-stress-disorder and has been associated with high Ca2+ levels due to neuroplastin loss interfering with signal transmission in Cornu Ammonis 3 (CA3) hippocampal region. We report the first two cases of pure retrograde amnesia in CASPR2 LAE. This manifestation is extremely rare in LGI1/CASPR2 LAE, where it commonly associates with anterograde amnesia. We suggest an integrated model of the pathogenesis characterized by alteration of plasma membrane Ca2+ ATPase proteins, abnormal signal transmission in GABA-A and AMPAR synapses, and higher voltage-gated potassium channel (Kv1) expression in the CA3 hippocampal region.

Conclusions: Exploring the effects of CASPR2 antibodies on CA3 might provide insight into the pathophysiology of retrograde amnesia.

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## NEUROINFLAMMATION AND BASAL GANGLIA CIRCUIT DYNAMICS: A STUDY ON THE EFFECTS OF ACUTE PERIPHERAL INFLAMMATION ON DOPAMINERGIC NEURONS

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Background: The basal ganglia (BG) circuit is a neuronal network mediating locomotor activity and movement execution, emotional states, social behavior, reward, and motivation. The activity of the nucleus striatum, the input station of the circuit, is strongly regulated by dopamine (DA)-releasing midbrain neurons [1]. An abnormal activation of the immune system (IS) characterizes the pathogenesis of both psychiatric and neurological disorders and is known to influence neuronal network functioning in the cerebral cortex [2,3]. To date, the influence of IS activation on DA-releasing cells and BG circuit dynamics is poorly understood.

Materials and Methods: Electrophysiological analyses of midbrain DA neurons activity and striatal synaptic plasticity were performed in lipopolysaccharide- (LPS) treated animals, 24 hours after treatment, and in control animals. Local inflammation patterns and dopamine neuron markers were assessed through immunohistochemistry.

Results: Acute peripheral inflammation increased midbrain DA neurons' firing rate and excitability state and was associated with impaired striatal synaptic plasticity. Immunohistochemical analysis showed an unaltered number of midbrains DA cells, while it showed increased activation of microglial, but not astroglial markers at the level of the substantia nigra and no changes in inflammatory markers at the level of the nucleus striatum.

Discussion: The obtained data suggest that acute systemic inflammation results in functional alterations of the BG circuit at multiple levels.

Conclusions: The involvement of DA neurons after IS activation could underlie cognitive and psychiatric symptoms in neuroinflammatory brain disorders.

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## A RETROSPECTIVE COMPARATIVE STUDY OF AUTOIMMUNE COMORBIDITIES IN AUTOIMMUNE ENCEPHALITIS AND MULTIPLE SCLEROSIS

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Background: Autoimmune comorbidities and anti-nuclear antibodies (ANA) may provide a diagnostic clue in the diagnosis of autoimmune encephalitis (AE). The aim of this study is to evaluate the prevalence of ANA in patients with AE.

Materials and Methods: In this retrospectively study we included consecutive patients with "definite AE" (defined as seropositive AE) and "possible AE" or "antibody negative, but probable AE" or "definite limbic encephalitis" (defined as seronegative AE) diagnosed according to 2016 Graus' criteria. A group of patients with multiple sclerosis (MS) was included as controls. ANA were tested with indirect immunofluorescence (IIF) using human epithelial type 2 cells, neuronal antibodies were tested with immunohistochemistry, cell-based assays and immunoblots, as appropriate. Autoimmune comorbidities, clinical, paraclinical and demographic data were retrospectively collected. A comparison between groups was performed using Mann-Whitney U and chi-square tests, as appropriate.

Results: 48 patients with AE (34 seronegative, 14 seropositive) and 50 patients with MS were included. Mean age at sampling was 54.3 ±17.1 and 40.4 ±12.4 years-old respectively ($p<0.0001$), with no differences in terms of gender (25 and 32 females, respectively, $p=0.85$). ANA positivity was reported in 35 (72.9%) patients with AE and in 24 (48%) cases with MS ($p=0.01$), whereas autoimmune comorbidities were reported in 20 (41.7%) and 10 (20%) patients, respectively ($p=0.01$). Either one between ANA positivity or autoimmune comorbidities were reported in 40 (83.3%) patients with AE versus 31 (62%) patients with MS ($p=0.01$). Paired ANA positivity and autoimmune comorbidities were more frequent in AE group (n=15, 31.3% vs n=3, 6% $p=0.001$). Lastly, seronegative AE showed increased ANA/autoimmune comorbidities compared to seropositive cases (n=9, 64.3% vs n=31, 91.2%, $p=0.02$).

Conclusion: Our study shows that patients with AE have more frequent positive ANA/autoimmune comorbidities when compared to patients with MS. This finding may be related to the loss of B cell tolerance that leads to the production of autoantibodies. The presence of autoimmune comorbidities or positive ANA may be useful in the diagnostic process of seronegative AE.

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## COGNITIVE PROFILE IN ADULT PATIENTS WITH MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY-ASSOCIATED DISEASE (MOGAD): A COMPARATIVE STUDY WITH MULTIPLE SCLEROSIS

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Background: Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a recently defined antibody-mediated disorder of the central nervous system (CNS). In the last decade, several studies defined the clinical and radiological phenotypes of the disease, but data on neurocognitive outcomes are limited. We herein compared the cognitive performance of patients with MOGAD to those with MS.

Methods: The Brief Repeatable Battery of Neuropsychological Test (BRB-N) and the Stroop Color Word Test (SCWT) were administered to 15 patients with MOGAD (age: 38.7±16.4; females: 60%; disease duration: 22.8±11.7 months) and 13 with MS (age: 33.4±8.2; females: 77%; disease duration: 39.9± 32.6 months). Descriptive statistic was generated for demographic variables. The Mann-Whitney U test was used to compare the BRB-N and SCWT outcomes between groups ($p < 0.05$, two-sided).

Results: MOGAD patients performed slightly worse than MS patients in the Long Term Storage (MOGAD: 39.6, MS: 45.1, $p=0.19$), Consistent Long-Term Retrieval (MOGAD: 31.2, MS: 36.4, $p=0.10$) and Symbol Digit Modalities (MOGAD: 44.4, MS: 49.5, $p=0.26$), and slightly better in the Paced Auditory Serial Addition Test (MOGAD: 39.6, MS: 37.5, $p=0.44$), but the difference did not reach statistical significance.

Discussion: MOGAD patients showed a trend towards more difficulties in verbal immediate learning and concentration skills that did not reach statistical significance. The small sample size and the imbalance in baseline conditions might have contributed to the present results.

Conclusions: MOGAD patients seem to have a specific cognitive profile, further demonstrating the peculiarity of this condition.

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## EPSTEIN-BARR VIRUS-SPECIFIC ANTIBODIES IN MOGAD COMPARED TO MULTIPLE SCLEROSIS

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Background: Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is an antibody-mediated disorder of the central nervous system (CNS) with distinct pathomecnanisms, clinical

phenotypes, and treatment response. Recent evidence demonstrated an association between multiple sclerosis (MS) and an antecedent Epstein Barr virus (EBV) exposure. The possible association between EBV and MOGAD has not been studied, yet. We performed a retrospective study comparing the EBV serological status of MOGAD versus MS patients at diagnosis. Additional cases are now on recruitment.

Materials and Methods: We enrolled 18 patients with MS and 9 patients with MOGAD referred to our Neuroimmunology Center. Epstein-Barr nuclear antigen (EBNA)-1 and viral capsid antigen (VCA) antibodies were measured in diluted sera by chemiluminescence immunoassays (CLIAs) at "A. Cardarelli" Hospital Laboratory. Antibodies to MOG were detected with an in house live cell-based assays at the Neuroimmunology and Neuropathology Laboratory, University of Verona.

Results: No differences in gender (6 females in the MOGAD cohort, 12 in the MS group, 66.7%, p=1.0) nor in age distribution (mean 38.1 ± 15.4 vs 38.9 ±10.4) were observed in the two groups. All included patients were positive at the VCA IgG test (limit value >20 U/ml). In addition, 88.9% of MOGAD patients and 94.4% MS cases were also positive for EBNA IgG, with no differences between the two groups (p=1.0). Mean VCA IgG values was higher in the MOGAD group, with no differences compared to the MS group (424 U/ml vs 324 U/ml, p=0.418). EBNA IgG mean value (±sd) was 464 U/ml (±256) for MOGAD patients and 475 U/ml (±199) for MS cases, with no differences (p=0.611).

Conclusion: Our data suggest that EBV might play a pathogenetic role in MOGAD, similarly to MS. Further prospective studies are needed to clarify the causal link between EBV and MOGAD.

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## A CASE OF ACUTE HYPERTENSIVE HYDROCEPHALUS IN A QUANTIFERON-POSITIVE PATIENT WITH AN INFLAMMATORY MENINGOENCEPHALITIS


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The diagnosis of neuroinflammatory diseases is still challenging in some cases. In addition, exclusion of mimics (especially infections) remains an important aspect of management to avoid inappropriate treatment. Hydrocephalus can be one of the acute manifestations of neuroinfectious and neuroinflammatory diseases and has been reported in almost 5-10% of neurosarcodosis cases. We present a particularly challenging case. An Indian patient was admitted to our hospital after 1 week of fever and headache only partially responsive to symptomatic drugs. He had a silent medical history. The neurological examination revealed an alert patient, oriented to person and space, with a marked neck stiffness. The lumbar puncture revealed a limpid cerebrospinal fluid with elevation of mononucleated-cell count (320 cells), no red cells, slightly reduced level of glucose (34 mg/dl) and elevated total proteins (138 mg/dl). A broad-spectrum antibiotic and antiviral therapy was started and then stopped after the negative results of bacterial and viral PCR on CSF. After a few days the patient developed acute mental confusion, drowsiness and the palsy of the right 6th cranial nerve was noted. An urgent CT showed acute hypertensive hydrocephalus and an external ventricular shunt was immediately positioned. Meanwhile, interferon-y release assay for tuberculosis resulted positive and BK culture on CSF was required. An antitubercular therapy was initiated. A thorax CT showed a solid non- calcified nodule in the superior right pulmonary lobe with a few enlarged lymph nodes. The MRI revealed abnormalities in the mesencephalic tegmen, quadrigeminal tubercles, left hypothalamic region and bilateral hippocampal alterations. After 3 weeks the results of the BK culture excluded tubercular infection. Clinically, the patient progressively worsened becoming comatose. Unfortunately, it was not possible to carry out either a meningeal biopsy or a lung biopsy. Therefore, according to the criteria of 2018 (Stern et al.) a diagnosis of possible neurosarcoidosis was formulated after having excluded a tubercular and brucellar meningitis, neurobehcet, neuromyelitis optica spectrum disorder (NMOD) and CNS lymphoma. A therapy with high dose corticosteroids was finally started with success. At the three-month follow-up, the patient had recovered almost completely except for bilateral hearing loss and mild memory impairment. Radiological improvement was also noted. This case highlights the importance of a differential diagnosis among the possible causes of acute hypertensive hydrocephalus in order to start the most appropriate therapy as early as possible.

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## LONG-TERM SAFETY, TOLERABILITY, AND EFFICACY OF EFGARTIGIMOD IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS: CONCLUDING ANALYSES FROM THE ADAPT+ STUDY


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Goal: Efgartigimod is a human IgG1 antibody Fc-fragment that reduces total IgG and pathogenic IgG autoantibody levels through neonatal Fc receptor blockade. ADAPT was a 26-week, global, multicentre, randomized, controlled, phase 3 trial evaluating efgartigimod in patients with generalized myasthenia gravis (gMG). Patients who completed ADAPT were eligible to enroll in the ADAPT+ open-label extension study to evaluate the long-term safety and efficacy of efgartigimod.

Methods: Efgartigimod (10 mg/kg IV) was administered in cycles of once-weekly infusions for 4 weeks, with subsequent cycles initiated based on clinical evaluation. The primary objective in ADAPT+ was to evaluate long-term safety and tolerability of efgartigimod in patients with gMG. Long-term efficacy was also assessed utilizing Myasthenia Gravis Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) scales.

Results: 90% of patients (151/167) from ADAPT entered ADAPT+ and 145 (111 anti-AChR-Ab+/34 anti-AChR-Ab-) received ≥1 cycle as of 30 June 2022. With 229 patient-years of follow-up (mean duration per patient: 610 days), the most common adverse events were headache (25%), concomitant COVID-19 infection (16%), nasopharyngitis (14%), diarrhea (10%), and urinary tract infections (9%) which were mostly mild-moderate and did not increase in frequency with subsequent cycles. AChR-Ab+ patients with ≥1 year of follow-up across ADAPT/ADAPT+ (n=95) received a median (range) 5.2 (0.5–7.5) cycles per year. In anti-AChR-Ab+ patients (n=111), consistent improvements in MG-ADL (mean[SE] change week 3 of cycle 1: -5.0[0.33]; up to 16 cycles) and QMG (-4.7[0.41]; up to 7 cycles) scores were observed during each cycle, mirroring repeatable reductions in total IgG (mean[SE] reduction: -55.9%[1.15]; up to 7 cycles) and anti-AChR autoantibody levels (-56.1%[1.43]; up to 7 cycles).

Conclusions: These analyses of ADAPT+ suggest long-term efgartigimod treatment is well-tolerated and results in consistent and repeatable reductions in IgG antibody levels and clinical outcomes (MG-ADL and QMG) in patients with gMG.

## LONG-TERM SAFETY, EFFICACY & SELF-INJECTION SATISFACTION WITH ZILUCOPLAN IN MYASTHENIA GRAVIS: RAISE-XT INTERIM ANALYSIS

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Objectives: Long-term data from RAISE-XT (NCT04225871), a Phase 3, multicentre, open-label extension study, will enhance our understanding of the safety, efficacy and self-injection satisfaction of zilucoplan, a C5 complement inhibitor with dual mechanism of action,[1] in patients with generalised myasthenia gravis (gMG).

Materials and Methods: Adults (aged 18–75 years) with gMG who completed a qualifying zilucoplan study (Phase 2 NCT03315130/Phase 3 NCT04115293 [RAISE] [1]) self-administered daily subcutaneous injections of zilucoplan 0.3 mg/kg. Primary outcome was incidence of treatment-emergent adverse events (TEAEs). Secondary efficacy outcomes included change from qualifying double-blind study baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) score. The Self-Injection Assessment Questionnaire (SIAQ; domain scores 0–10; higher scores indicate more positive experience) was completed by US patients directly after self-injection and measured patient satisfaction with self-injection.

Results: At data cut off (8 September 2022), 200 patients had enrolled in RAISE-XT. Median (range) exposure was 1.2 (0.11–4.45) years. TEAEs occurred in 188 (94.0%) patients; 64 (32.0%) patients experienced a serious TEAE. Mean (standard deviation) changes from double-blind study baseline in MG-ADL score continued to decrease through Extension Week 12 and were maintained through to Extension Week 48 (Week E48) for the zilucoplan and placebo-switch groups: −5.95 (4.14) and −6.85 (5.13) at Week E48, respectively. In the SIAQ domain of satisfaction with self-injection, median score was 8.20 (range: 3.9–10.0; n=63).

Discussion and Conclusions: In this interim analysis of RAISE-XT, zilucoplan demonstrated a favourable long-term safety profile and sustained efficacy through to Week E48. High satisfaction rates with self-injection were reported. Funding: UCB Pharma.

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## LONG-TERM SAFETY, TOLERABILITY, AND EFFICACY OF SUBCUTANEOUS EFGARTIGIMOD PH20 IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS: INTERIM RESULTS OF THE ADAPT-SC+ STUDY

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Goals: Evaluate long-term safety, tolerability, and efficacy of subcutaneous (SC) efgartigimod PH20 (coformulated with recombinant human hyaluronidase PH20) in patients with generalized myasthenia gravis (gMG) enrolled in the ADAPT-SC+ open-label extension study. In ADAPT-SC, efgartigimod PH20 SC 1000 mg was shown to have non-inferior total IgG reduction to efgartigimod IV 10 mg/kg (approved in US, Japan, and EU) resulting in similar clinical improvement in patients with gMG. Patients completing ADAPT-SC, or enrolled in ADAPT+, were eligible to participate in the ongoing open-label extension, ADAPT-SC+.

Methods: Efgartigimod PH20 SC 1000 mg was administered in cycles of 4 weekly injections. Subsequent cycles were initiated at least 28 days from the last dose based on clinical evaluation. Clinical efficacy was assessed utilizing the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale.

Results: As of March 2022, 164 participants received ≥1 dose of efgartigimod PH20 SC. Patients received ~3 cycles over a mean (SD) study duration of 170 (59) days, resulting in 72 patient-years of observation. Adverse events (AEs) were predominantly mild to moderate. The most frequent AEs were injection site erythema (25.6%), headache (15.2%), and COVID-19 (11.6%). All injection site reactions (ISRs) were mild/moderate and did not lead to treatment discontinuation. ISRs typically occurred within 24 hours of administration, resolved spontaneously, and incidence decreased with subsequent cycles. Two deaths were reported (metastatic renal cancer and COVID-19); neither were deemed efgartigimod-related per investigator. Improvement from cycle baseline in MG-ADL total score (mean [SE] improvement at week 4: –4.0 [0.25]) was observed in cycle 1, with consistent and repeatable improvements seen in subsequent cycles. Long-term treatment with efgartigimod PH20 SC 1000 mg can reduce disease severity, as assessed by the MG-ADL scale, and improve the quality of life of patients with gMG. Speed of onset, magnitude, and repeatability of improvements in MG-ADL were similar to those with efgartigimod IV during ADAPT/ADAPT+.

Conclusions: Results demonstrate that efgartigimod PH20 SC treatment was well tolerated, with no safety concern identified. Treatment with efgartigimod PH20 SC led to consistent and repeatable reductions in MG-ADL total score, and the observed safety and efficacy profile was consistent with ADAPT/ADAPT+.

## INVESTIGATING THE EFFECT OF ANTI-MENINGOCOCCAL VACCINE IN PATIENTS ON ECULIZUMAB THERAPY

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Objectives: To evaluate the response to meningococcal vaccination in patients receiving Eculizumab therapy.
Materials: Serum samples were collected from five patients candidate for Eculizumab therapy. Four patients (pt 1-4) with a diagnosis of refractory generalized myasthenia gravis (gMG) associated with acetylcholine receptor (AChR) antibodies (Ab) and one patient (pt 5) with both neuromyelitis optica spectrum disorder associated with aquaporin 4 (AQP4) Ab and AChR-Ab+ gMG were recuited. All patients received meningococcus B and ACWY conjugate vaccination at least two weeks before sample collection, without receiving a booster dose.

Methods: Immunogenicity was assessed using the Serum Bactericidal Assay (SBA) for serogroups A, C, W, and Y with an exogenous source of rabbit complement. A titer of 1/8 was considered protective for neutralizing antibodies (NAb). Immunogenicity for serogroup B was not assessed since the assay employs the endogenous human C5 fraction that is inhibited by Eculizumab.

Results: In all patients, the response to meningococcal vaccine for serogroups A, C, W, and Y was incomplete. Patient 1 showed high antibody titers to serogroups A and C (NAb titer for serogroup A: 1/1024; for serogroup C: 1/128) and a poor response to vaccination for serogroups W and Y (NAb titers <1/4 in both cases). Patient 2 showed a good response to serogroups A, W, and Y (NAb titers A: 1/512; W: 1/256; Y: 1/256) and no response to serogroup C vaccination (NAb titer <1/4). The meningococcal serology of patient 3 showed a protective response to all tested serogroups (NAb titers A: 1/512; C: 1/128; W: 1/128; Y: 1/1024). Patient 4 and Patient 5 showed a poor response to all four serogroups (NAb titers less than 1/4 for all serogroups).

Discussion and Conclusions: Patients receiving Eculizumab infusions are at increased risk of systemic infections caused by encapsulated bacteria. Fatal meningococcal infections have been reported in patients receiving complement inhibitors. Therefore, meningococcal vaccination for serogroups A, C, W, Y, and serogroup B is required at least two weeks before starting therapy. Alternatively, antibiotic coverage must be prescribed. Booster doses are mandatory only for serogroup B, while booster doses of tetravalent vaccine are not usually administered. Four out of five patients on Eculizumab therapy did not develop a protective antibody response against ACWY meningococcal serogroups. Monitoring antibody levels may be useful in-patient management to assess the need for booster doses of the ACWY vaccine.
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## SATRALIZUMAB, A NEW THERAPEUTIC CHANCE IN NEUROMYELITIS OPTICA SPECTRUM DISORDER

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Background: Satralizumab is the first monoclonal antibody that acts blocking interleukin-6 (IL-6) receptor, approved for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in patients seropositive for aquaporin-4 immunoglobulin G (AQP4-IgG). Interleukin-6 (IL-6), a multifunctional cytokine, is thought to play a key role in NMOSD pathophysiology. IL-6 signaling stimulates B-cell differentiation into plasmablasts that produce pathogenic AQP4-IgG.

Case report: In April 2022, a 50 years-old woman came to our Emergency Department for a subacute walking impairment and feet burning dysesthesia. She was hospitalized and she attended an electromyography that resulted negative and a brain and spine MRI that underlined a multimetameric central dorsal (D2-D6) T2-STIR lesion with contrast enhancement. No brain lesions. The visual evoked potentials showed bilateral prolonged P100 latency. She completed the diagnostic plan with rheumatic screening test not significative, a lumbar puncture that showed negative cerebrospinal fluid analysis and

isoelectrofocusing. We also tested serum antibodies to AQP4 and MOG (myelin oligodendrocyte glycoprotein), finding a high-titer AQP4 positivity. She started high dose of steroids for 7 days without results, so we decided for PLEX (plasmapheris). After a long hospitalization she moved into a rehabilitation.

Discussion: In June 2022, after a complete screening for viral infections, she started Rituximab, a chimeric antibody that targets CD20+ B cells. Few days later, she did routine blood tests that showed very high elevations of transaminases suggesting acute hepatitis. She was hospitalized again and underwent screening for autoimmune hepatitis, resulting a doubtful positivity for antibodies against PML (promyelocytic leukaemia protein) and gp210 (nuclear pore membrane glycoprotein 210). Gastroenterology Consultants concluded for Rituximab-Related Reversible Hepatocellular damage. She discontinued Rituximab and after a period of observation we registered a decrease of liver enzymes. We were afraid about clinical and radiological relapses so we thought about an alternative. Even though in previous studies mild and moderate elevations of liver enzymes in patients treated with IL6-inhibitors have been observed, we had high hope that this drug might be the right opportunity. In November 2022, she started Satralizumab with a strict supervision. She repeated routine blood examinations twice a month and everything was in range. No clinical attacks were noticed. In April 2023 she did a new brain and spine MRI that was stable.

Conclusion: Satralizumab has been shown to be a well tolerated and safe drug. The most common adverse events are infection, headache, arthralgia, decreased white blood cell count, hyperlipidaemia and injection-related reactions.

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## RECURRENT "CLOCC" LESION RELATED TO URINARY INFECTION: A CASE REPORT


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Background: Reversible lesions in the splenium of the corpus callosum (SCC) are a clinical and radiological phenomenon characterized by a hyperintense signal on T2- weighted, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted images (DWI) and diffusion coefficient (ADC) decreased on ADC maps. Because of these radiological features, these lesions have been recently redefined as "cytotoxic lesions of the corpus callosum" or "CLOCC" lesions. Their clinical presentation is usually a mild encephalitis/encephalopathy with reversible splenial lesion (MERS). Causative factors include epilepsy, infections, metabolic disorders, malignancies, vascular or traumatic brain diseases.

Case report: A 49 years-old man, affected by severe tetraparesis due to C3-C4 cervical fracture occurred four years before, presented to our emergency department for involuntary arms movements and a gradual worsening of upper limbs strength in the last month. Three days after admission to our neurological department he developed a sudden severe sensory deterioration (GCS 3). Blood examinations (D-dimer, troponin, blood gas analysis) and instrumental findings (electrocardiogram and electroencephalogram) were normal. After two hours there was a spontaneous recovery of the state of consciousness, immediately followed by an acute onset of a psychotic state characterized by visual hallucinations and delusional ideas with a religious content. CSF examination (including physical chemistry, film array and DNA of the main pathogens) was normal. Brain MRI showed a T2, FLAIR and DWI hyperintensity of the body, genu and splenium of the corpus callosum and of the corona radiata bilaterally, characterized by severe restriction in ADC. On the same day he developed fever up to 40° and Cytrobacter freundii was isolated in urine cultures. During the hospitalization, he was transferred to the intensive care unit for respiratory failure and generalized seizures. After antibiotic therapy, he underwent a gradual clinical and cognitive improvement. Brain MRI performed after 12 days showed disappearance of the previous signal alterations, except for a more tenuous but still present hyperintensity in the splenium of corpus callosum. Two other hospitalizations were made for psychomotor slowdown related to urinary infection. Brain MRI performed during the second hospitalization showed a recurrence of signal alteration in the splenium of the corpus callosum, which then disappeared again.

Conclusion: Our clinical case highlights how reversible lesions of the corpus callosum have a heterogeneous clinical spectrum with even severe life-threatening encephalopathies. Recurrence, correlation with urinary infection and normal CSF examination support the hypothesis of a reversible cytotoxic edema caused by systemic cytokine release.

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## ONE YEAR FOLLOW-UP OF HUMORAL AND CELLULAR RESPONSE AFTER THE THIRD DOSE OF BNT162B2 MRNA COVID-19 VACCINE IN MULTIPLE SCLEROSIS PATIENTS TREATED WITH B-CELL DEPLETING THERAPY


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Introduction and Objectives: Vaccination against SARS-CoV-2 virus has been the most effective way of containing the COVID-19 pandemic. However, its efficacy and durability in patients undergoing immunosuppression with B-cell depleting therapy is less known. This study aimed to assess the immunization to SARS-CoV-2 and to analyze humoral and cellular response in a cohort of multiple sclerosis (MS) patients treated with Ocrelizumab (OCR).

Materials and Methods: In this prospective observational study, we measured humoral and cellular immunity using neutralization assay and specific interferon-gamma (IFN-g) release assay (IGRA) respectively, before and after the third or fourth dose of BNT162b2 and/or after COVID-19. Data were then compared with healthy controls (HC) using independent-samples t-test.

Results: The study included 8 MS patients treated with OCR and 13 HC. As for the patient's group, all of them received at least 3 doses of BNT162b2, only two 4 doses and none received the fifth. Two patients developed COVID-19, both with mild symptoms. The median of total exposures in included subjects group (vaccine shots and/or infections) was 3 and vaccination was the last event for 75% of patients. None of

the patients and the HC were found negative for neutralizing assay or IGRA test after the third dose and in early 2023 Independent-samples T test showed a statistically significant difference (p=0.047) between the mean delta of neutralizing antibodies (after 3rd dose and in early 2023) of the two groups. The same comparison for IGRA test did not show significant differences between the two groups (p=0.49).

Discussion: The results show how humoral response significantly decreased during the follow up period in the Anti-CD20 group compared to HC, while similar evolution resulted for cellular immunity in both groups. None of the patients nor the HC presented negative results in both tests, confirming the immunogenicity of three doses of BNT162b2 vaccine with both cellular and humoral response.

Conclusions: Patients undergoing OCR therapy showed comparable responses in terms of cellular immunity, while, as expected for a CD20-depleting therapy, humoral response appeared reduced, even though not entirely absent, during the follow up period.

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## ANTI-RECOVERIN ANTIBODIES IN A CEREBELLAR SYNDROME WITHOUT RETINAL INVOLVEMENT


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Objective: This case report aims to describe a rare case of anti-recoverin positive cerebellar syndrome in a patient without any evidence of malignancy or retinopathy. The objective is to discuss the underlying pathophysiology and clinical management of this condition.

Materials: The materials used for this case report include the medical records, neuroimaging data, and laboratory results of a 57-year-old male patient. The patient had a history of drug addiction, uncontrolled hypertension, and obesity. He presented to our hospital with subacute dizziness, ataxia, and a feeling of light-headedness. Despite prior treatment for labyrinthitis, his symptoms persisted and he also developed dysarthria and dysphagia. Neurological evaluation revealed a left VII cranial nerve deficit, dysarthria, left lower limb hyposthenia, bilateral dysmetria and dyssynergy at limbs, severe ataxia with multidirectional oscillations and widened base in orthostatic position, requiring bilateral support.

Methods: The patient underwent a neurological evaluation to assess the extent and nature of his symptoms. Radiological examinations were performed, such as brain MRI to investigate the brain structure, a chest-abdomen CT with ultrasound completion of the thyroid and testicles to investigate a possible paraneoplastic syndrome. Diagnostic lumbar puncture was carried out to analyze cerebrospinal fluid for protein levels, leukocyte counts and oligoclonal bands. Laboratory tests, electroneurography and blink reflex test results were considered. The patient was treated with intravenous immunoglobulins and, subsequently, received high-dose steroid therapy. Follow-up assessments were conducted after the initial treatment, including re-evaluation of symptoms and monitoring of clinical improvements.

Results: Radiological examinations did not show any abnormalities. Lumbar puncture revealed mild protein elevation and lymphocytic pleocytosis. Serological tests were positive for anti-recoverin antibodies. Treatment with intravenous immunoglobulins and high-dose steroids led to clinical improvement, including regression of the cranial nerve deficit and improved trunk control.

Discussion: The absence of retinopathy or cancer posed challenges in the diagnosis and treatment of this case. Despite the patient's multiple comorbidities, other potential causes were ruled out. The presence of anti-recoverin antibodies in the patient's serum, along with the positive response to immunomodulatory therapy, suggests a possible association between anti-recoverin antibodies and cerebellitis.

Conclusion: This case report highlights an unusual case of anti-recoverin positive cerebellitis without retinopathy or neoplasia. Although the absence of these antibodies in the cerebrospinal fluid is a limitation, the clinical improvement with immunomodulatory therapy supports an autoimmune etiology. Further research is necessary to better understand the underlying mechanism and establish diagnostic and therapeutic guidelines for similar cases.

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## A REAL-LIFE EXPERIENCE WITH ECULIZUMAB AND EFGARTIGIMOD IN GENERALIZED MYASTHENIA GRAVIS PATIENTS


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Introduction: Eculizumab, a complement active monoclonal antibody, is reimbursed in Italy for anti-acetylcholine receptor antibody positive (AChR-Ab+) patients showing persistent symptoms, despite therapy with corticosteroids (CS) and ≥2 non-steroidal immunosuppressants (NSISTs). Efgartigimod, a human IgG1 antibody Fc-fragment that blocks neonatal Fc receptor, is available in Italy through an expanded access program and treatment can be administered to both AChR-Ab+ and seronegative patients.

Methods: We included patients receiving either Eculizumab or Efgartigimod as part of our clinic practice and retrospectively collected data on their MG status using the MG activities of daily living (MG-ADL), quantitative MG scale (QMG), previous and current therapies, adverse events, and concomitant medication use.

Results: We enrolled 16 patients treated with Eculizumab and 14 with Efgartigimod. Of the Efgartigimod group, 7 were Ab-AChR positive and 7 were seronegative. Both treatments were well tolerated, with minor adverse events. Overall, MG-ADL decreased by -6.9 points (p<0.001), and qMG by -5.9 (p<0.001). Eculizumab reduced the

MG-ADL by -6.6 points (p=0.002), and the qMG by -7.4 (p<0.001). Efgartigimod reduced the MG-ADL by -7.3 points (p<0.001), and the qMG by -4.7 (p<0.001). MG-ADL responders were 15/16 (94%) of patietns treated with Eculizumab and 10/14 (71%) of those treated with Efgartigimod. For the Efgartigimod group, respoders were identical between Ab-AChR positives and negatives (5/7, 71% for each group). Mean prednisone reduction was -13.75 mg for the Eculizumab treated group ad -8.5 in the Efgartigimod group (p=NS).

Conclusion: Eculizumab and Efgartigimod proved to be both effective treatments in a real world setting. Both treatments reduced MG-ADL and qMG in difficult to treat gMG patients. For both treatments responder rate was higher than previously reported in clinical trials. Responder rate was higher in Eculizumab than Efgartigimod treated patients. This was paralleled by a non-significant higher prednisone reduction effect.

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## HBV RISK MANAGEMENT IN MULTIPLE SCLEROSIS PATIENTS

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Background: Hepatitis B virus (HBV) reactivation during immunosuppressive/immunomodulatory therapy is still a hot topic worldwide. In case of serological signs of current or past HBV infection, appropriate therapeutic or preventive strategies are suggested, according to the risk of HBV reactivation [1]. Anti-HBc antibodies, together with HBsAg, play an important role in identifying patients with a need for a more intensive follow-up or a prophylaxis against HBV reactivation, especially as anti-HBc antibodies are considered to persist lifelong, except in immunocompromised patients [2].

Objective: In a 4-years follow-up, people with MS were longitudinally evaluated each 6 months during DMTs, focusing on HBV reactivation with HBV-DNA and HBV surface antigen periodic assessment.

Methods: Serological parameters such as HBsAg, anti-HBs, and anti-HBc (IgM and IgG), were periodically measured by chemiluminescence immunoassays. HBV-DNA was investigated by real-time PCR in each subject showing previous resolved HBV exposure. A preemptive strategy was chosen to manage people with previous resolved exposure to the virus.

Results: In this four-year observational cohort study, we collected real-world data on the infectious risk before starting or switching or during DMT in people with MS patients. Two hundred and twenty-seven people with MS were enrolled (135 women, 92 men) with a median age of 49 [41-59]. Among them, 80 patients were ocrelizumab-treated. At baseline 3 patients candidates to ocrelizumab treatment, were HBsAg+ with HBV-DNA detectable and started antiviral therapy before starting DMTs; 18 patients were anti-HBc+. No patients with anti-HBc+ showed a detectable HBV-DNA and all started DMT. During DMTs, two ocrelizumab-treated patients with HBsAg- and anti-HBc+ developed HBV reactivation. After 4 years of follow-up, 2 of 18 patients with anti-HBc+ treated with ocrelizumab, lost Hbc antibodies.

Conclusion: Screening of infectious diseases in DMT candidate MS patients helps to mitigate the infectious risk and choose the most appropriate treatment in MS management. HBV screening should be performed at the beginning to know patient's serological status to decide the most appropriate therapy and/or follow-up for MS patient. Moreover, as in solid orgarn transplant recipients, MS patients treated with anti-CD20 can lose anti-HBc maybe due to an inefficient immune response. Permanent or intermittent anti-HBc loss is common in immunocompromised hosts (i.e hematologic/oncologic patients). To date, no data on people with MS and permanent or intermittent anti-HBc loss were reported. Periodic HBV screening is mandatory to highlight an active or past HBV infection in patient with high risk HBV reactivation.

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## TOSCANA VIRUS MENINGO-ENCEPHALITIS: AN INFECTIOUS DISEASE TO INCLUDE IN DIFFERENTIAL DIAGNOSIS IN ELDERLY PATIENT WITH CONFUSIONAL STATE AND ALTERED CONSCIOUSNESS

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Introduction: Acute confusional state and alertness disturbances are frequent neurological presentations of a plethora of diverse underlying diseases, including central nervous system infections. These ones are most commonly due to viral diseases and, among these, Toscana virus is the 3rd etiologic agent of aseptic meningitis after enteroviruses and herpesviruses. Despite this evidence, Toscana virus is not routinely considered in patients with altered consciousness level and disorientation.

Aim: To describe a case of meningo-encephalitis due to Toscana virus infection in an 82-year old man presented with headache, confusion and drowsiness.

Methods and Results: An 82-year old dyslipidemic and diabetic man, living in the countryside of North-East Italy, came to our attention for orbitofrontal headache and photophobia in the last three days followed by fever, confusion and drowsiness. Suspecting a central nervous system infection, the patient has been hospitalized. On admission, cerebrospinal fluid (CSF) examination documented hyperproteinorrachia (1.11 g/L) and pleocytosis (monocytes 109 u/L). Microbiological assays of common central nervous system pathogens, including Toscana virus in both CSF and blood were performed. A cerebral MRI with contrast and an electroencephalogram were unremarkable. In the meanwhile, an empiric intravenous antibiotic and antiviral therapy was started. After three days polymerase chain reaction (PCR) for Toscana virus resulted positive either in CSF and blood, in association with a high titer of specific IgM and IgG in blood, so that the diagnosis of meningo-encephalitis due to Toscana virus was made. Therefore, it was possible to withdraw the ongoing unnecessary empiric therapy. Supportive care measures were adopted and, after one week, the patient

showed a complete remission of symptoms. CSF analysis was repeated and documented the absence of Toscana virus RNA.

Conclusion: Toscana virus infections should be considered in the differential diagnosis of confusional states in the elderly, especially during summer in the Mediterranean area, when the vector's activity is higher. Nowadays, thanks to advanced diagnostic methods it is possible to make a diagnosis of Toscana virus meningoencephalitis quickly, reducing unnecessary use of antibiotics and unuseful medical resources.

Disclosures: I hereby certify that, to the best of my knowledge, no aspect of my current personal or professional circumstance places me in the position of having a conflict of interest with this presentation.

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## AFFECTIVE AND EMOTIONAL CHANGES AS ONSET SIGNS IN AUTOIMMUNE ENCEPHALITIDES

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Introduction and Aims: Over the last years great attention has been given to psychiatric manifestations in autoimmune encephalitides (AEs). There is a new consensus on the definition of the entity of autoimmune psychosis. However, there is little evidence about behavioral, affective, emotional changes and cognitive impairment in those conditions. During a revision of the patients with AE admitted to our Clinic we evidenced how these symptoms, usually underestimated, can precede the clinical manifestation by months. Here, we present a sub-group of patients with a diagnosis of AE with specific behavioral, cognitive and psychic symptoms at the onset.

Materials and Methods: We selected 14 patients with a diagnosis of AE (according to 2016 Graus et al. diagnostic criteria) and admitted to our department between 2010 and 2023. Patients with pre-morbid psychiatric conditions have been excluded. All patients underwent electroencephalography (EEG), MRI, CSF analysis and a thorough neuropsychological examination.

Results: Fourteen patients with a diagnosis of probable AE (mean age 51.7±20.1 years, 57% women) have been enrolled in the study. Fifty percent of patients (n=7) presented seizures at the onset. Nine patients (64%) presented affective and emotional changes before the onset of the disease (depression, unexplained feel of fear), with a mean of 3 months before the admission to the hospital. Five patients (36%) presented behavioral changes (apathy, irritability, fatuous behavior) at the onset of the disease. Seven patients (50%) presented cognitive symptoms (memory and attention impairment, arithmetical problems) before the admission. EEG showed some abnormalities in 86% of patients (n=12). Nine patients (64%) presented fronto-temporal abnormalities, with left prevalence in 5 cases, right prevalence in 2 cases, no prevalence in the remaining 2 cases. One patient presented diffuse slow rhythm, one temporo-occipital abnormalities and one diffuse triphasic waves. Positivity for antibodies has been found in half cases (anti PNMA2, GAD, LG1, NMDA, HU in 2 cases, and against a novel intracellular antibody in one case). MRI was suggestive of encephalitis in 11 cases (79%).

Discussion and Conclusions: Our data, in line with previous published data, show that autoimmune encephalitides, even with different autoantibodies and etiology, present common clinical, EEG and MRI features. In particular, affective and emotional changes can precede of about three months the onset of the disease, representing a red flag of an encephalopathic process. Therefore, these changes in previous healthy patients should raise the suspicion of AE and induce the begin of a diagnostic workup. Further studies are needed to confirm these findings.

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## AUTOIMMUNE ENCEPHALITIS WITH PSYCHIATRIC ONSET AND POSITIVITY FOR AN UNKNOWN ONCONEURONAL ANTIBODY: A CASE REPORT

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Introduction: Among autoimmune encephalitides (AE) a subgroup is related to a paraneoplastic mechanism. An exact diagnosis is necessary for adequate treatment. However, paraneoplastic syndromes, such as paraneoplastic encephalitides, may even appear several years before the detection of malignancy. Here we describe the case of a woman with a psychiatric presentation. An onconeuronal antibody against intracellular antigens has been found in the cerebrospinal fluid (CSF) of the patient with no evidence of tumors.

Clinical Case and Discussion: A 48-year-old woman was admitted to our clinic for the appearance of confusion, irritability and fluctuating consciousness. In the last year, the patient had presented feelings of unexplained fair, anxiety, anorexia and insomnia. The first brain magnetic resonance imaging (MRI) showed hyperintensity of temporo-parietal cortex and white matter on FLAIR sequence. EEGs showed aspecific slow-wave rhythms. A CSF analysis evidenced hyperproteinorrachia (927 g/dL) and neutrophilic pleocytosis (78 cells). A standard panel for known autoimmune antibodies on CSF and blood serum resulted negative. With a clinical suspicion of paraneoplastic encephalitis, an extensive oncologic screening has been performed and resulted unremarkable. Patient showed a good clinical response to intravenous methylprednisolone at high dose, with resolution of the behavioral and cognitive fluctuations. However, twenty days after discontinuation of steroids, she presented irritability, muteness and drowsiness. At this stage, patient had a partial recovery after high dose steroids, and immunotherapy with azathioprine was started. At that point, even if the patient presented a full recovery in terms

of movement and alertness, she continued to present irritability and occasional paranoid ideas. After two months, patient was readmitted for infective pyelonephritis, right hemiplegia and global aphasia. MRI at that time showed bilateral hippocampal and left thalamic hyperintensity on long TR sequences. Treatment with steroids at first and plasma-exchange therapy were unsuccessful. At that time, an indirect immunohistochemistry on cerebellar cells of rat revealed the positivity of CSF on Purkinje cells' cytoplasm. Finally, patient started therapy with rituximab with improvement of speech and partial recovery of strength in her right side.

Conclusions: Psychiatric manifestations in AE are common, and commonly lead to misdiagnosis. Clinical suspicion of AE should be made when a patient presents with a new-onset and atypical psychosis and necessitates an extensive diagnostic work-up. There is no consensus yet about treatment of these conditions. In our case, an onconeuronal antibody has been found after several attempts and months. Patient responded to rituximab when no other immunosuppressive treatments were successful anymore.

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## HEAD-TO-HEAD COMPARISON OF FIXED VERSUS LIVE CELL-BASED ASSAYS FOR AQP4-IGG DETECTION IN REAL-LIFE DIAGNOSTIC SETTING

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Background: Neuromyelitis Optica Spectrum Disorders (NMOSD) is an inflammatory demyelinating disease of the central nervous system in differential diagnosis with MS, from which is distinguished by prognostic features and response to specific treatments. The presence of pathogenic anti-aquaporin 4 (AQP4) IgG is highly specific for NMOSD diagnosis and, considering the relevant clinical implication, laboratory assays with the highest accuracy are of the utmost importance. To date, both commercial fixed cell-based assay (CCBA) and in-house live cell-based assay (LCBA) have been used for AQP4 detection, but there are only few data on the concordance of these two tests, especially in a real life setting.

Objective: To compare the analytic performances of CCBA and LCBA in routine diagnostic practice.

Materials and Methods: We included patients whose samples were sent to our centre for AQP4-IgG testing from 2018 to 2023. Serum samples from each patient were analyzed in parallel with CCBA and LCBA. Medical records were reviewed to assess if patients fulfilled 2015 NMOSD criteria.

Results: We included 1882 consecutive samples. A total number of 104/1882 samples (5.5%) from 71 patients were positive in at least one diagnostic test. A concordant positive result was found in 87 samples from 71 patients, all diagnosed with NMOSD. Seventeen/104 samples from 13 patients showed discrepant results, and 7 patients were diagnosed with NMOSD. CCBA+/LCBA- results were found in 5 sample from 4 patients, 2 diagnosed with NMOSD, and CCBA-/LCBA+ results were found in 12 samples from 10 patients, 5 diagnosed with NMOSD. Cohen's kappa for LCBA and CCBA was 0.91 (agreement of 99.1%). PPV for LCBA and CCBA was respectively 0.89 and 0.94.

Conclusions: Both LCBA and CCBA have high analytic performances and are reasonable alternatives for AQP4-IgG testing, with a slightly higher PPV for CCBA. As discrepant results are more frequently associated with false positives, testing selected patients with a second assay might be helpful in improving accuracy.

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## A CASE OF THYMOMA-ASSOCIATED ENCEPHALITIS AFTER THYMECTOMY

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Objectives: To describe an atypical case of thymoma-associated encephalitis.

Materials and Method: A 50-year-old woman with a past medical history of a surgically removed thymoma, thyroiditis and pemphigus vulgaris successfully treated with corticosteroids and two courses of rituximab was admitted to our department for a generalized seizure preceded by headache, sleep disturbances and recurrent right hemifacial spasm (HFS). Electroencephalography showed left frontal-temporal slow waves.

Results: The laboratory examination showed microcytic anaemia and raised serum ferritin without sign of systemic infection; cerebrospinal fluid (CSF) examination was unremarkable, and neuroinfectious aetiology was ruled out by multiplex-PCR assay. Prolonged drowsiness, expressive aphasia and persistent HFS characterized the postictal seizure phase. The initial brain MRI imaging showed multifocal cortical ill-defined T2/ FLAIR hyperintense lesions with contrast enhancement, leading to a diagnosis of possible autoimmune encephalitis. Combined immunotherapy with intravenous methylprednisolone and immunoglobulins was started. Serological rheumatologic screening test showed an abnormal title of antinuclear antibodies of 1:1280 without other indicative findings of systemic autoimmune disease. Further serum and CSF analysis for an expanded paraneoplastic/autoimmune encephalitis panel revealed the presence of autoantibodies (Abs) anti-collapsin response mediator protein 5 (CRMP5, also known as CV2), anti-titin and anti-acetylcholine receptor (ACh-R) without signs of cerebellar ataxia and myasthenic syndrome. Contrast CT and PET-CT total body scans

did not reveal occult neoplasm, including residual thymoma. Despite first-line immunomodulatory treatment, a repeat brain MRI showed new and enlarged T2/FLAIR lesions with persistent enhancement after one month. After a second cycle of high-dose steroid treatment, long-term immunosuppression with azathioprine was started with a complete resolution of the lesions in two months. After a year of clinical stability, she complained again about HSF, and a new brain MRI revealed a breakthrough in the disease. Therefore, she started rituximab with clinical and MRI improvement.

Discussion: The Abs anti-AchR, anti-titin and anti-CRMP5/CV2 suggested the loss of self-tolerance usually associated with thymoma. Therefore thymoma-associated paraneoplastic/autoimmune encephalitis diagnosis was supposed to be. Nevertheless, two following PET-CT scans conducted six months apart for cancer screening were consistently negative. For this reason, we conducted T cell receptor excision cyrcles (TRECs) quantification and CD31 expression on CD4+ T cells evaluation, which are suitable markers for thymic function evaluation.

Conclusions: This case highlights how thymoma-related paraneoplastic/autoimmune CNS disorders can develop even after thymectomy but still underlie a permanent thymic output detectable by TRECs, the evaluation of which could play a role in cases without a instrumental detectable thymoma recurrence.

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## EFFICACY OF INNOVATIVE THERAPIES IN MYASTHENIA GRAVIS: SYSTEMATIC REVIEW, META-ANALYSIS AND NETWORK META-ANALYSIS


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Introduction: Therapy of Myasthenia Gravis (MG) is undergoing a profound change with new treatments being tested. These include complement inhibitors and neonatal Fc receptor (FcRn) blockers. Objective of the study was to perform a meta-analysis and network meta-analysis of randomized and placebo-controlled trials of innovative therapies in MG with available efficacy data.

Methods: We assessed statistical heterogeneity across trials with Cochrane Q test and I2 values. We pooled mean differences with the random effect model. We derived treatment efficacy after 26 weeks of treatment with Eculizumab and Ravulizumab, 28 days with Efgartigimod, 43 days with Rozanolixizumab, 12 weeks with Zilucoplan, and after 16, 24 or 52 weeks with Rituximab.

Results: We observed an overall mean MG-ADL change of -2.17 points (95% CI -2.67, -1.67; p<0.001) as compared to placebo. No significant difference emerged between complement inhibitors and anti-FcRns (p=0.16). The QMG change was -3.46 (95%CI -4.53, -2.39; p<0.001), with a higher reduction with FcRns (-4.78 vs -2.60; p<0.001). Rituximab did not significantly improve the MG-ADL (-0.92, CI95% -2.24, 0.39; p=0.17), or QMG (-1.9, 95%CI -3.97, 0.18, p=0.07). At the network meta-analysis, Efgartigimod had the highest probability to be the best treatment, followed by Rozanolixizumab.

Interpretation: Anti-complement and FcRn treatments proved to be both effective in MG patients, whereas Rituximab did not show a significant benefit for patients. With the limitations of this meta-analysis, including efficacy time-points, FcRn treatments showed a short-term higher effect on the QMG. Real-life studies with long-term measurements are needed to confirm our results.

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## EVIDENCE-BASED EXPERT CONSENSUS GUIDANCE FOR ONGOING ASSESSMENT OF GENERALISED MYASTHENIA GRAVIS


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Goal: Regular and consistent disease assessment could provide a clearer picture of burden in generalised myasthenia gravis (gMG) and improve patient outcomes; however, there is lack of standardisation on use of assessment tools in practice. This modified Delphi consensus was conducted to review current evidence on assessment tool use in gMG and propose expert-derived guidance for good practice.

Methods: A European expert panel comprising 15 experienced gMG neurologists contributed to development of this guidance, four of whom formed a lead Sub-committee. The PICO (population, intervention, control, outcomes) framework was used to define six themes on gMG assessment tools and a systematic literature review was conducted. Consensus was reached when >=70% of the experts rated agreement with a statement as >=8 on a scale of 1–10.

Results: 18 guidance statements were developed based on evidence and expert opinion covering six themes: 1) tools for understanding gMG burden in clinical practice, clinical trials/research, and telemedicine; 2) use of depression, anxiety, and fatigue scales in patient assessment; 3) outcomes/symptoms excluded from existing gMG assessment tools; 4) thresholds for clinically important/meaningful differences; 5) assessment of treatment-related burden; 6) assessments supporting treatment decisions. Expert panel consensus was reached on 16/18 statements after one voting round.

Conclusion: This process provides evidence- and expert consensus-based guidance for use of objective and subjective assessment tools across gMG care to improve outcomes for patients.

## ISOLATED CENTRAL NERVOUS SYSTEM WHIPPLE'S DISEASE: THE ROLE OF BRAIN BIOPSY IN A DEMANDING DIAGNOSIS

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Background and Aims: Whipple's disease (WD) is considered a very rare systemic disease caused by gram-positive bacillus Tropheryma whipplei (TW). However, a recent study reported a surprisingly high prevalence (4.9%) of TW in stool samples from Italian patients attending the Sicilian Center for Tropical Diseases [1], thus suggesting that WD might be more common than previously thought. These findings stress the importance of sharing uncommon or atypical cases of WD, in order to improve diagnostic accuracy of this clinically variable condition.

Case description: We report the case of a 64-year-old woman who complained of recurrent short-lasting episodes of confusion and epigastric pain followed by numbness in her left arm. A few months later, hypersomnia and slowly progressive cognitive impairment were documented; due to an episode of generalized seizure, she was then admitted to the hospital. Brain MRI showed bilateral contrast-enhanced lesions in the medial temporal lobe. Initial suspicion of herpetic encephalitis was not confirmed by poor response to steroids and acyclovir treatment. Because of persistence of neurologic symptoms, the patient was referred to our tertiary centre for further evaluation. Brain MRI documented volume increase of lesions causing secondary hydrocephalus; EEG revealed epileptiform activity in the right temporal lobe. The suspicion of viral encephalitis and autoimmune/paraneoplastic disease were rejected respectively due to normal results at CSF investigations, lengthy clinical presentation and negative screening for autoimmune disorders and malignancies. With further progression of patient's symptoms, brain biopsy of the right hippocampus was performed. Histological examination showed the presence of numerous perivascular foamy histiocytes with cytoplasmic intensely positive Periodic acid-Schiff (PAS) stain, a feature strongly suspicious of WD. The diagnosis was subsequently confirmed by a Tropheryma whipplei-specific PCR analysis of the brain tissue that, interestingly, was negative on CSF. Importantly, the patient had no diarrhoea, abdominal cramps, arthralgia, weight loss, or cardiac/pulmonary symptoms. General physical examination showed no lymphadenopathy or skin hyperpigmentation and duodenal biopsy was normal. Intravenous ceftriaxone followed by oral trimethoprime-sulfamethoxazole were administered for 12 months with good neurological recovery.

Conclusions: This report highlights the difficulties in diagnosing brain-isolated forms of WD due to their variable clinical presentation and their shared features with more common viral and autoimmune/paraneoplastic encephalitis [2]. Brain imaging and CSF examinations might not be informative [3]. As WD is a treatable condition, a missed diagnosis may have catastrophic consequences on patient's management. Our experience supports the role of cerebral biopsy in the diagnostic process of atypical encephalitis.

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## ACUTE FLACCID PARALYSIS DUE TO WEST NILE VIRUS NEUROINVASIVE DISEASE IN THE 2022 VENETO OUTBREAK: CLINICAL AND PROGNOSTIC IMPLICATIONS

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Objectives: The West Nile Virus Neuroinvasive Disease (WNND) can present as meningitis, encephalitis, or acute flaccid paralysis (AFP). The overall mortality is 9%, while it reaches 13-14% in AFP [1]. The 2022 WNV outbreak in Veneto was particularly severe and characterised by co-circulation of the new WNV strain 1, along with the endemic strain 2 [2]. The present study aims at describing the clinical phenotypes, the main clinical and pathological findings of patients evaluated during this outbreak.

Materials and Methods: We included all patients hospitalised in the Azienda Ospedale-Università di Padova, between 12/07/22 and 21/09/22 with definite or probable WNND [3], collecting anamnestic, clinical, laboratory, imaging, and pathological data in 3 patients. Statistical analyses included descriptive statistics, Pearson's correlation and chi-square tests.

Results: Forty-seven patients were included (45 definite, 2 probable WNND; 29 males, mean age: 71±14 years), all diagnosed with WNV strain-1. At onset (mean: 4.5 days before hospitalisation), symptoms included fever (91%), flu-like symptoms (45%), headache (30%), gastrointestinal symptoms (28.3%), rash (11%). Neurological symptoms at onset included confusion (30.4%), impaired vigilance (17.5%) and motor deficits (2.2%). The clinical phenotypes included AFP (42.6%), encephalitis (34%), paucisymptomatic disease (12.8%) and meningitis/meningo-encephalitis (10.6%). Liquor analysis showed CSF pleocytosis with both mononuclear and polymorphonuclear cells (mean 158.5 elements/microliter), increased proteins and lactates (mean values: 100 mg/dl and 2.93 mmol/L, respectively). The most common MRI finding was the multi-level enhancement of the anterior ± posterior spinal nerve roots (10/19 patients), especially the cauda equina. All had AFP phenotype. The overall 3-month and 7-month mortalities were 19.1% and 25.5%, reaching, 35% and 45% in AFP cases. Mean mRS changed from 1.2 pre-event to 3.3 at hospital discharge. Post-event mRS and length of hospitalisation correlated positively ($p<0.05$) with CSF lactate levels, the severity of motor and tendon reflex deficits, and were significantly higher in AFP. Predictors of death and ICU admission ($p<0.05$) were: AFP, encephalopathy, motor and tendon reflexes deficit, spinal nerve roots' involvement, and, for ICU admission only,

the encephalitic phenotype. All AFP patients underwent intravenous immunoglobulins and/or steroid treatments, yet this was not associated with better outcomes. Autopsies revealed multifocal extensive inflammatory infiltrate with microglial nodules in the brain and spinal cord.

Discussion and Conclusions: The 2022 Veneto WNND outbreak had outstandingly high AFP frequency and mortality. This aggressive phenotype is probably conveyed by the new WNV strain-1. The mechanisms underlying the different "neuro-virulence" of distinct WNV strains require further studies.

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## AUTOIMMUNE THROMBOCYTOPENIA IN A PATIENT WITH GENERALISED MYASTHENIA GRAVIS IN TREATMENT WITH ECULIZUMAB: A CASE-REPORT

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Objective: Myasthenia Gravis is an autoimmune disorder caused by an inflammatory response directed towards the neuromuscular junction. In the last few years, the therapy of Myasthenia Gravis has experienced a profound change with the introduction of complement inhibitors and FcRn blockers. However, no study has been conducted on the management of these new therapies in patients with polyautoimmunity which are up to 15-20% of patients with Myasthenia Gravis. We report a case of a gMG patient treated with Eculizumab developing a SLE-mediated thrombocytopenia after prednisone reduction.

Case description: We describe the case of A.B.K. female, 43 y.o. diagnosed with Sjogren disease in 2009 and Myasthenia Gravis AchR+ in 2015. She underwent treatment with Eculizumab in November 2022 together with pyridostigmine and prednisone 25 mg. In January 2023 she was admitted to our Center due to thunderclap headache resulting from a subarachnoid haemorrhage confirmed after a CT exam. At the moment of admission, the patient was on prednisone 5 mg after progressive down-tapering, and her platelet count was 0. We administered daily platelet infusion, a 5-day cycle of IVIg and prednisone 75 mg for 10 days with no benefit and suspended the scheduled infusion of Eculizumab. We also performed an autoimmunity panel, that showed positivity to ds-DNA and ANA 1:512 so diagnosis of SLE was made according to EULAR criteria. We then introduced Romiplostim with slight but encouraging benefit. We discharged the patient as a SLE-induced thrombocytopenia and a home-therapy with Romiplostim and prednisone 25 mg.

Results: After the introduction of Romiplostim and Prednisone, platelet count was increased to 20.000 units. After one-month she was re-scheduled for Eculizumab infusion as her MG symptoms were deteriorating. After two infusions of Eculizumab her platelet count went back to normal (235.000 units).

Discussion: Our patient suffered from a SLE-induced thrombocytopenia which was reasonably fostered by the progressive reduction of Prednisone. Pre-Eculizumab prednisone helped keep SLE latent and undiagnosed. The precautionary suspension of Eculizumab was unnecessary as MG symptoms worsened and platelet count returned to normal after its re-administration.

Conclusion: In conclusion, although new treatments allow a reduce of corticosteroids and immunosuppressants, we should use caution in patients with polyautoimmunity. We demonstrate that Eculizumab is safe in gMG patients with immunological comorbidities.

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## AN UNCOMMON CLINICAL-RADIOLOGICAL PRESENTATION OF ANTI-NMDAR ENCEPHALITIS: A YOUNG ADULT WITH LOUDNESS INTOLERANCE AND CLOCCS

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Objective: Aim of this case report is to describe an uncommon presentation of Anti-N-methyl-D-aspartame receptor (anti-NMDAR) encephalitis with atypical radiological findings of Cytotoxic Lesions of Corpus Callosus (CLOCCs). Which, to our knowledge, has only been reported in few cases in Eastern countries [1,2].

Materials: A 17 years old male presented to our attention with a story of three months of loudness intolerance, preceded by three days flu. He made in an external structure audiometric tests and auditory brainstem response without anomalies and brain MRI that revealed a single midline rounded lesion in the splenium of the Corpus Callosum. Neurological examination was in the range of normality.

Methods: The patient made laboratory screening for systemic autoimmunity, infectious markers; oncological markers; resulted negative. A Lumbar puncture was performed, and Cerebrospinal Fluid did not show pathological findings at routine exams. In the suspicion of autoimmune encephalitis (AE), we made a panel for testing AE-autoantibodies, and he was positive for Anti-NMDAR on serum and CSF. He made also an electroencephalography that was normal. The symptomatology considerably improved after intravenous administration of steroids, with complete recovery after a month. A follow-up MRI revealed regression of the lesion. A whole-body PET-CT scan was planned to rule out malignancy.

Discussion: Anti-NMDAR encephalitis is the most common type of AE, accounting for 6% to 10% of all encephalitis3. It is characterized by the presence of an IgG1 antibody directed against the NR1 subunit of the NMDAR on the neuronal cell surface or synapses in the CSF. Cytotoxic lesions of the corpus callosum (CLOCCs) are secondary lesions associated with various entities4. In all of these conditions, cell-cytokine interactions lead to markedly increased levels of extracellular glutamate, with consequent excitotoxic damage. CLOCCs have been found in association with drug therapy, malignancy, infection, subarachnoid hemorrhage, metabolic disorders, trauma, and other entities – including AE. In our case, loudness intolerance, which we interpreted

as a cognitive/behavioral disorder, and anti-NMDAR antibody positivity allowed us to make a diagnosis of definite anti-NMDAR AE according to the latest diagnostic criteria [3].

Conclusions: In our case we made hypothesis that anti-NMDAR antibodies may have a more complex mode of operation and could even play a role in the pathogenesis of cytotoxic edema in CLOCCs, similar to the excitotoxic action of glutamate broadly reported in these lesions.

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## IMMUNE PROFILING UNVEILS THE SYSTEMIC CYTOKINE MILIEU ASSOCIATED WITH ACUTE REVERSIBLE ENCEPHALOPATHY WITH CYTOTOXIC LESION OF THE CORPUS CALLOSUM (CLOCC) SECONDARY TO EBV INFECTION

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Aim: We present the case of an 18-year-old male who experienced acute-onset reversible encephalopathy with a cytotoxic lesion of the corpus callosum (CLOCC) during the course of Epstein Barr virus (EBV) infection. The immune signature of this condition is still largely unknown [1,3].

Diagnostic work-up: The patient had no relevant medical history. He was admitted to our Section due to generalized tonic–clonic seizures and mental deterioration. In the 7 days before the admission, he experienced fever, cervical lymphadenopathy, sore throat and fatigue. On admission, his GCS was 11 (E4, V2, M5), he was confused and his body temperature was 38°C. High-field 3T brain MRI revealed hyperintense lesions within the splenium of the corpus callosum, subcortical white matter, and cortical regions. The lesions exhibited hyperintensity on DWI, FLAIR, and T2 sequences, along with hypointensity on ADC maps. Serial EEG recordings showed slow and paroxysmal abnormalities bilaterally. Serological analysis demonstrated positivity for EBV VCA-IgM and negativity for EBNA IgG, as well as a positive PCR for EBV, suggesting an acute systemic EBV infection. CSF analysis revealed mild lymphocytic pleocytosis and elevated protein levels. Microbiological tests on the CSF, including film array and PCR for neurotropic agents (including EBV), yielded negative results. These findings supported the hypothesis of a systemic inflammatory response leading to central nervous system manifestations secondary to EBV infection [2].

Follow-up data: Prompt administration of intravenous dexamethasone resulted in significant clinical improvement within 10 days. A follow-up brain MRI performed one week later demonstrated the disappearance of the callosal lesion, further confirming the diagnosis and emphasizing the reversible nature of the condition [1]. Immunological profiling: To gain further insight into the systemic immune response, plasma samples were subjected to detailed analysis using Luminex technology. Baseline profiling revealed low levels of interleukin 12-p70 (IL-12p70) and elevated levels of interferon gamma (IFN-γ), IL-6, IL-18, IL-10, IL-17A, IL-23, and IL-1α. Subsequent analyses demonstrated a dynamic pattern, with increasing levels of IL-12p70 and decreasing levels of the other cytokines over time, coupled with the clinical improvement.

Discussion: This case sheds light on the occurrence of CLOCC in the context of infectious disorders, with EBV infection serving as a compelling example [2]. It underscores the pivotal role of systemic inflammation in driving central nervous system manifestations and provide specific information on the associated cytokine milieu.

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## MULTIPLE CRANIAL NEUROPATHY DUE TO VARICELLA ZOSTER VIRUS REACTIVATION WITHOUT VESICULAR RASH: A CHALLENGING DIAGNOSIS

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Objective: Ramsay Hunt syndrome, or zoster oticus, is a rare condition caused by reactivation of varicella-zoster virus (VZV) in the geniculate ganglion of facial nerve. Accounting for less than 1% of all herpes zoster cases, it is characterized by a clinical triad of ipsilateral facial paralysis, otalgia and vesicles in the auditory canal. However, up to 30% of cases may occur without skin vesicular eruption, and other cranial nerves, may be involved further complicating the diagnosis.

Case Discussion: A 77-year-old man presented to the emergency department with left facial palsy, speech difficulties with voice hoarseness, and mild gait abnormalities. He had experienced pharyngodinia, headache, and left otalgia a few days earlier. Initial tests including MRI with and without contrast were normal, while laboratory tests showed high levels of IgG and borderline levels of IgM antibodies against VZV, not diagnostic. Serum VZV-DNA was not detected. Because of voice hoarseness and swallowing difficulties, he underwent video-laryngoscopy documenting paralysis of the left palate and vocal cord, pointing to an involvement of glossopharyngeal and vagus nerves. Cerebrospinal fluid analysis confirmed the presence of VZV DNA, leading to a diagnosis of multiple cranial neuropathy due to VZV reactivation (Ramsay Hunt syndrome). The patient was treated with antiviral therapy and steroids, and showed gradual improvement over a couple of months, with complete recovery of speech and swallowing and partial recovery of facial nerve function.

Discussion: The case report highlights the diagnostic challenge of identifying Ramsay Hunt syndrome, when it presents in non canonical ways. Clinicians need to be aware of the possibility of multiple cranial nerve involvement in this syndrome. While peripheral facial nerve palsy is often idiopathic (Bell's palsy), a thorough evaluation is necessary to rule out secondary causes such as VZV reactivation. Antiviral therapy is effective in treating VZV reactivation, and steroids are also beneficial for improving nerve function in peripheral facial nerve palsy. The involvement of other cranial nerves in Ramsay Hunt

syndrome may occur due to the spread of VZV beyond the geniculate ganglion or through vascular pathways. The exact mechanism of cranial nerve dissemination is not yet fully understood.

Conclusion: This case report emphasizes the importance of considering Ramsay Hunt syndrome as a possible diagnosis in cases of atypical peripheral facial nerve palsy. Clinicians should be familiar with the diverse clinical presentation of the syndrome and the effectiveness of antiviral therapy in promoting nerve function recovery.

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## SHOULD WE CONSIDER MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY-ASSOCIATED DISEASE (MOGAD) A PARANEOPLASTIC DISEASE?


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Objectives: To detect the incidence of neoplastic conditions in a cohort of patients with MOGAD and analyze their clinical and paraclinical features.

Materials: Retrospective cohort study and systematic literature review.

Methods: We retrospectively identified patients referred to our center from 1/1/2015 to 1/1/2023 with positive MOG antibodies tested with a live cell-based assay and associated with clinical features consistent with MOGAD. We then selected those with a diagnosis of tumor received within two years from disease onset and subsequently performed a systematic literature review to detect previous cases of co-occurrence between MOGAD and a neoplastic condition. Clinical and paraclinical data of all patients were collected and statistical analysis was performed.

Results: Among 150 patients, 2 (1%) received a diagnosis of tumor within two years. After literature review, 15 additional patients were collected. Median age was 39 years-old (range 16-73) and 12 patients were female. ADEM (n=4; 23.5%), encephalomyelitis (n=3; 17.6%), and monolateral optic neuritis (n=2; 11.8%) were the most frequent phenotypes. Median number of treatments was 1 (range 1-4) and improvement was reported in 14/17 cases (82.4%). Oncological findings were teratoma (n=4), CNS (n=3), melanoma (n=2), lung (n=2), hematological (n=2), ovary (n=1), breast (n=1), gastrointestinal (n=1), and thymic (n=1) neoplasms. Median time from tumor diagnosis to MOGAD onset was 0 months (range -60 to 20). MOG expression in neoplastic tissue was detected in 2/4 patients tested. Median Paraneoplastic Neurologic Syndrome (PNS)-Care score was 3 (range 0-7) being 11 patients classified as “non-PNS”, 5 as “possible-PNS”, and 1 as “probable-PNS”.

Discussion: Our study demonstrates that neoplastic conditions are rare in MOGAD. In addition, neurological manifestations and oncological accompaniments are extremely variable, MOG is usually not detected in neoplastic tissue, and most cases do not meet the criteria of paraneoplastic syndromes (PNS).

Conclusions: These findings suggest that MOGAD is not a paraneoplastic disease and that cancer screening should not be performed in patients with MOGAD on a routine basis.

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## DEFINING THE ETIOLOGIC SPECTRUM AND CHARACTERISTICS OF NON-DEMYELINATING NMOSD MIMICS


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Objective: Differentiating neuromyelitis optica spcectrum disorder (NMOSD) from its mimics is crucial to avoid misdiagnosis, especially in the absence of aquaporing-4-IgG. While multiple sclerosis (MS) and myelin oligodendrocyte glycoprotein-IgG associated disease (MOGAD) represent well established differential diagnoses, non-demyelinating NMOSD mimics remain poorly characterized. In this study we aimed to define the etiologic spectrum and characteristics of non-demyelinating NMOSD mimics.

Materials and Methods: A systematic search was conducted in Pubmed on January 2023 to identify reports of patients with non-demyelinating neurological disorders in whom NMOSD was suspected or misdiagnosed. Cases with uncertain or poorly defined final diagnoses, and articles predating the discovery of AQP4-IgG were excluded. Three novel cases seen at the authors' institutions were also included. Clinical-MRI characteristics of included cases were analysed and red flags for NMOSD misdiagnosis identified.

Results: After screening 2404 articles, 65 patients were included in the study in addition to 3 patients seen at the authors' institutions, for a total of 68 patients. Median age at symptoms onset was 44 years (range 1–78), 35 (52%) were females. Fifty-six (82%) patients did not meet the 2015 NMOSD diagnostic criteria at the time of misdiagnosis. The clinical syndromes misinterpreted for NMOSD were isolated myelopathy (43%), myelopathy and optic neuropathy (38%), isolated optic neuropathy (7%), or other (12%). Alternative etiologies included genetic/metabolic diseases (n=20), neoplasms (n=11), infections (n=11), vascular diseases (n=8), spondylotic myelopathy

(n=5), and other autoimmune disorders (n=13). The most common red flags for NMOSD misdiagnosis were lack of cerebrospinal fluid (CSF) pleocytosis (57%), lack of response to immunotherapy (55%), progressive disease course (54%), lack of gadolinium enhancement on MRI (31%), and presence of CSF-restricted oligoclonal bands (31%). AQP4-IgG positivity of no clinical significance (or false) was detected in 5 patients by enzyme-linked immunosorbent assay (n=2), cell-based assay (n=2: serum, 1; CSF, 1), and a non-specified assay (n=1).

Conclusions: The etiologic spectrum of NMOSD mimics is broad. Misdiagnosis frequently results from incorrect application of NMOSD diagnostic criteria, in patients with multiple identifiable red flags. False AQP4-IgG positivity, generally from nonspecific testing assays, may rarely contribute to misdiagnosis.

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## CEREBROSPINAL FLUID AND PLASMA BIOMARKERS IN PATIENTS WITH CENTRAL NERVOUS SYSTEM INFECTIONS: A RETROSPECTIVE STUDY

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Background: Analysis of CSF and plasma biomarkers could be helpful to differentiate specific CNS condition and setting an appropriate therapy. A major advance in the field of neurology has been the development of blood-based biomarkers.

Materials and Methods: Patients presenting with signs and symptoms were enrolled if, before receiving a diagnostic lumbar puncture, signed a written informed consent. We retrospective analyzed CSF and plasma levels of several biomarkers of neuronal damage (NfL), astrocyte damage (GFAP), monocyte/macrophage activation (sCD163 and sCD14) and blood-brain barrier permeability (MMP-9 and TIMP-1).

Results: Eight-four subjects were included. Patients were affected by herpesvirus encephalitis (21/84), neuro-COVID (17/84), progressive multifocal leukoencephalopathy (PML, 14/84), HIV-associated neurocognitive disorders (13/84), bacterial meningitis (7/84), infection by unknown pathogens (6/84) and subjects without CNS involvement (control group, 6/84). Overall, positive correlation between CSF and plasma levels of NfL was found ($\rho$=0.8290, p<0.0001) as well as between CSF and plasma levels of GFAP ($\rho$=0.5752, p<0.0001). Both CSF NfL and GFAP levels were positive correlated with CSF levels of sCD163 ($\rho$=0.5730, p<0.0001 and $\rho$=0.4177, p=0.0007) as well as with CSF TIMP-1 levels ($\rho$=0.6286, p<0.0001 and $\rho$=0.5952, p<0.0001). In CSF, levels of monocyte/macrophage activation markers were positive correlated to plasma NfL levels (sCD163: $\rho$=0.5213, p=0.0026; sCD14: $\rho$=0.4992, p=0.0250). Finally, CSF TIMP-1 levels were positive correlated with plasma NfL levels ($\rho$=0.4075, p=0.0282) and plasma GFAP levels ($\rho$=0.4180, p=0.0300). Compared to control group, bacterial meningitis and PML groups showed higher CSF NfL levels (p=0.0091 and p=0.0003, respectively). Higher CSF GFAP levels in PML and HIV-associated neurocognitive disorder groups compared to control group were observed (p=0.0003 and p=0.0390, respectively). CSF GFAP levels were higher in herpesvirus encephalitis (p=0.0071), neuro-COVID (p=0.0155), HIV-associated neurocognitive disorder (p=0.0003) and bacterial meningitis (p=0.0005) compared to control group. Otherwise, CSF sCD14 levels were higher only in bacterial meningitis compared to control group (p=0.0172). CSF MMP-9 levels were higher in bacterial meningitis and PML groups (p=0.0145 and p=0.0321, respectively) compared to control group. Finally, in bacterial meningitis group higher levels of CSF TIMP-1 were found (p=0.0005).

Conclusion: Our data showed that CSF and plasma biomarkers of neuronal and astrocyte damage or inflammation may vary during CNS infections according to different causative agents. The observed correlations between CSF and plasma samples underscore the possibility of measuring CNS markers in an easily accessible source such as blood. The prognostic value of these biomarkers needs to be assessed in prospective studies.

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## NEUROLOGICAL REHABILITATION AND NEUROTRAUMATOLOGY

## FEASIBILITY STUDY OF A NEW EXTENDED REALITY SYSTEM IN PARKINSON'S DISEASE

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Objectives: Recent research has been indicating eXtended Reality (XR) as a promising tool for innovative and tailored therapeutic-rehabilitative intervention in Parkinson's Disease (PD). XR refers to the application of immersive technologies that allow users to submerge in a virtual world and/or interact with it. Our aim was to assess the feasibility of a new XR system in PD patients.

Materials: We enrolled 22 PD patients (17M/5F; mean age±SD 62.7±8.7 years) with MMSE>23 (mean±SD 28.8±1.8). All participants underwent neurological examination using UPDRS-III and Hoehn & Yahr scale (HY) for disease staging. They were administered for a game session using the Hololens2 XR viewer.

Methods: The experimenter started the game by the remote connection between the PC and the viewer applied to the subject's head. The patients performed the game session (which consists in popping virtual balloons) while sitting in a fixed position. The XR application was organized in two training sessions(one for each side) lasting one minute each, and eight experimental game sessions(four for side,

maximum of three minutes for each session) carried out respectively in "free" condition, during a simple cognitive task, during a contralateral motor task(finger tapping) and during complex cognitive task(mathematical calculation).At the end of the game session the System Usability Scale(SUS) to assess the level of perceived usability, and the User Experience Short Questionnaire(UEQ-S) to assess the immediate impressions, were administered.

Results: Overall, patients have not encountered any issues during the game session, showing a significant interest in the application proposed. The mean±SD of the SUS score was 77.9±18.1(SUS score>70 suggests good usability). At UEQ-S, the scores for both the pragmatic and the hedonic quality were high. We did not find any significant differences between the scores obtained by the more affected hand for all game levels except for a trend towards statistical significance in the difference between level 1 and level 2 performance(p=0.057). No significant differences were observed between the more affected and the less affected side in all game sessions. Furthermore, there was not any significant relationship between the questionnaire scores, the game results, and the demographic and clinical data, such as age, disease duration, motor subtype, UPDRS-III, and HY.

Discussion. The usability, acceptance and tolerability of our XR system have been good. The application was considered easy, clear, interesting, inventive and innovative by most of the patients. Although some subjects had complained fatigue during the third and fourth level of play, difficulty maintaining concentration did not significantly impact game performance.

Conclusions: Our XR system could be considered a tool for use in research settings and in clinical-rehabilitative practice.

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## THE DIAGNOSTIC ACCURACY OF PLASMA GFAP AND UCHL1 LEVEL: AN ANALYTICAL SUPPORT TO CT IMAGING IN MILD HEAD INJURY


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Head trauma is a common cause of admission in emergency departments (ED) and computerized tomography (CT) is the gold standard to diagnose trauma brain injury (TBI). Head trauma is classified in three degrees according to the obtained Glasgow Coma Scale (GCS) score: mild for patients with GCS 14-15, moderate for GCS 9-13 and severe for score of 8 or less. However, head CT reveals TBI in patients with mild head trauma in only 10% of cases, of which 1% needs neurosurgical treatment. Considering the risk of exposing patients to unnecessary radiation, the Canadian CT Head Rule was introduced in 2001 for identifying the pool of mild head trauma patients who needs a cranial CT. The possibility of matching these criteria with other brain injury markers (such as optic nerve echography and specific plasmatic biomarkers) is crucial for the early diagnosis of mild head trauma. The aim of this study is to assess if the combination of further different brain injury markers can predict a TBI. For our purpose, we verified the diagnostic accuracy of a new test for measurement of two specific proteins, glial fibrillary acidic protein and ubiquitin carboxy-terminal hydrolase L1 (GFAP and UCHL1 respectively). These proteins are released into plasma after brain damage. Further parameter of this study includes the evaluation of optic nerve dilation as a sign of intracranial hypertension for likely TBI. We enrolled 98 patients with mild head trauma who arrived in ED in the last 9 months. Each patient underwent a nerve optic echography and a head CT to verify a possible TBI, a blood sample to measure GFAP and UCHL1 levels via with chemiluminescent microparticle immunoassay (CMIA). Analysing the data, 76.53% of patients presented a normal value of GFAP and UCHL1 and a negative head CT (with a specificity and sensitivity equal to 72.21% and 40%). The remaining 23.47% had an increased of protein levels within 12 hours of the injury and a head CT confirmed a TBI in 8.8% of this patients' group. A possible correlation between proteins level and dilation of optic nerve is still under evaluation. These statistics showed that the GFAP and UHCL1 plasmatic levels have a high negative predictive value and it can be a valid support for excluding the need of CT scan, especially if it is matched with other parameters. Further studies are required to confirm the efficacy of these biomarkers.

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## INSTRUMENTAL EVALUATION OF POSTURAL CONTROL IN PATIENTS WITH PARAPROTEINEMIC NEUROPATHIES


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Objectives: Peripheral neuropathies associated with paraproteinemia cause several neurological disturbances, ranging from sensory symptoms to gait ataxia. The objective of the present study is the prospective assessment of the posturographic features of this rare condition in a cohort of patients.

Materials and Methods: The postural analysis represents a secondary analysis of the main study, which is intended to assess clinically and instrumentally a cohort of 17 patients for 3 years, every 6 months. The experimental protocol consists of an instrumental postural evaluation using a force platform (BTS P-Walk, Milan, Italy) with the patient in an upright comfortable standing position. We will evaluate the parameters of the motion of the center of gravity (COG), namely the COG area, length, speed of oscillation and sway density (SD) in two conditions: eyes open (EO) and eyes closed (EC) (three 50-second and three 10-second recordings per condition). The instrumental evaluation will be conducted also in a group of healthy controls (HC).

Results: At the state of art, 17 patients (mean age 71.3±11.4 years, 6 females) and 5 HC (mean age 58.0±9.1 years, 4 females) completed the baseline evaluation. The parameters of the COG area were significantly different in the EC condition when compared to the EO session. More specifically: COG area (EC 133.5±245.7 mm2; EO 30.5±44.4 mm2; p=0.004), length (EC 113.8±145.6 mm; EO 49.1±20.8 mm; p=0.004), speed of oscillation (EC 11.4±14.6 mm/s; EO 4.9±2.0 mm/s; p=0.004) and sway density (EC 3.0±2.1 mm/s; EO 5.0±2.0 mm/s; p=0.004). By contrast, in the HC group we did not find significant differences in the two conditions: COG area (EC 10.3±12.6 mm2; EO 9.7±6.4 mm2; p=0.9), length (EC 35.2±9.6 mm; EO 34.5±6.9 mm; p=0.9), speed of oscillation (EC 3.5±0.9 mm/s; EO 3.4±0.7 mm/s; p=0.9) and sway density (EC 6.2±3.2 mm/s; EO 7.7±1.7 mm/s; p=0.72).

Discussion: The observed significant worsening of parameters in the EC condition indicates an impaired proprioceptive regulation of postural stability in patients.

Conclusion: Posturography represents an easy to use and reliable tool to assess postural stability of patients with polyneuropathy. Hopefully, we will be able to use posturographic indexes as an instrumental marker for sensory ataxia and monitor treatment response, although conclusive results will come from the complete longitudinal evaluation.

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## DESIGN OF A GLOBAL INTER-RATER RELIABILITY STUDY OF THE POST-STROKE SPASTICITY REFERRAL TOOL

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Objectives: Post-stroke spasticity (PSS) occurs in ≈58% of stroke survivors. The simple, 1-page PSS Referral Tool was developed to facilitate PSS early identification and referral by clinicians involved in stroke rehabilitation.

Materials: In PSS Referral Tool, red, yellow, and green colors indicate urgent referral to a spasticity specialist, routine referral with a recommendation for multidisciplinary team consult, or periodic monitoring, respectively. To validate the PSS Referral Tool use in clinical practice, an inter-rater reliability (IRR) study will be conducted.

Method: This 3-part observational, prospective study will use the PSS Referral Tool to assess and classify patients up to 1-year post-stroke with varying degrees and types of spasticity. Part A will consist of investigators at 2 sites recording 30 clinical assessment videos using a semi-structured script based on PSS Referral Tool categories. In Part B, 4 clinicians will select 15 videos (5 each for red, yellow, and green) for IRR assessment. In Part C, stroke rehabilitation clinicians recruited from 6 global regions will classify 5 randomly assigned videos into appropriate categories in 3 separate sessions.

Results: This study will report the intraclass correlation coefficient (ICC) for IRR of the PSS Referral Tool, using a 2-way random effect model ICC with 95% confidence intervals. Sample size calculation for 80% power (alpha=0.05) determined a need to recruit 270 clinicians stratified by 2 categories or 540 for 4 categories of PSS Referral Tool experience. ICC values range from 0.0 to 1.0, with higher scores indicating a more stable instrument.

Discussion: PSS Referral Tool will facilitate PSS early identification and referral by clinicians involved in stroke rehabilitation.

Conclusion: This study aims to ensure that the PSS Referral Tool possesses sufficient sensitivity and specificity for meaningful use by clinicians regardless of experience.

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## PREDICTORS OF SHORT-TERM RECOVERY OF CONSCIOUSNESS IN PATIENTS WITH DISORDERS OF CONSCIOUSNESS

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Aims: Disorders of Consciousness (DoC) include Unresponsive Wakefulness State (UWS), Minimally Conscious states minus (MCS-) and plus (MCS+) and often lead to permanent disability with huge ethical and economic consequences [1]. Reliable prognostic markers are critical in planning tailored care pathways and optimizing the use of resources in compliance with ethical and social issues. Our aim was to explore the prognostic value of demographic, anamnestic, clinical, and neurophysiologic findings on consciousness recovery at the discharge from an intensive rehabilitation unit (IRU).

Population: The present multicenter prospective, observational longitudinal study was conducted in the framework of the PRABI study [2]. All patients admitted to one of the three involved Fondazione Don Gnocchi units from January 2020 to January 2022 and fulfilling the following inclusion criteria were included: 1) age >18 years; 2) clinical diagnosis of DoC of any etiology; 3) time post-onset (TPO) < 3 months.

Methods: Within 1 week from enrollment, all patients underwent a clinical and neurophysiological assessments including: Coma Recovery Scale revised (CRS-R), Disability Rating Scale (DRS), a standard Electroencephalography (EEG) reported according to the terminology of the American Clinical Neurophysiology Society of Critical Care EEG [3] and Somatosensory evoked potential (SEPs). The independent variable included in the multivariate logistic regression analysis were: age, sex, TPO, etiology, CRS-R sub-scores (Auditory, Visual, Motor, Oro-verbal, Communication, and arousal), DRS total score, presence of SEP, and EEG patterns (Frequency, Antero-posterior Gradient, Cortical reactivity, Symmetry, Voltage). The dependent variable was the complete recovery of consciousness at discharge from the IRU.

Results: We included 104 patients: UWS:38 (36.5%), MCS- : 28 (26.9) and MCS-+: 38 (36.5); females: 46 (44.2%), Traumatic etiology: 35 (33.7%), median age: 67.5 years [IQR = 20] and median TPO: 40 days [IQR = 21]. After a median length of stay in the IRU of 90.5

days [IQR = 71], 102 patients were discharged from the IRU (2 deaths) including 61 (58.7%) emergent from DoC. Traumatic etiology (OR: 6.23, p=0.04), a higher CRS-R visual sub-score at admission (OR: 7.75, p<0.001) and presence of EEG cortical reactivity to eye opening (OR: 9.611, p<0.002) predicted the complete recovery of consciousness at discharge with R2 0.638.

Conclusions: The study suggests that the visual subscale of the CRS-R and cortical reactivity to eye opening on at admission are the best predictors of short-term consciousness recovery in patients with DoC. This data confirmed that the multimodal diagnosis of consciousness would allow a better neuroprognostication in patients with DoC.

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## LONG-TERM EVOLUTION OF POST-ANOXIC PROLONGED DISORDERS OF CONSCIOUSNESS: AN INDIVIDUAL PATIENT META-ANALYSIS

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Prognosis of patients with severe anoxic brain injury and prolonged (28 days to 3 months post-onset) Disorders of Consciousness (pDoC) is usually considered poor, but solid prognostic indications for long-term clinical evolution are still lacking. In this study we performed a systematic review and meta-analysis of longitudinal studies on patients with post-anoxic pDoC addressing: 1) long-term clinical evolution (i.e., at least 6 months after the brain injury) in these patients, in terms of rates of mortality, any improvement in clinical diagnosis, and recovery of full consciousness; 2) demographic and clinical characteristics more likely associated with each of the above three outcomes. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; PROSPERO ID: CRD42021264692), we performed a literature search on PubMed, Scopus and PsycINFO databases until 25th January 2023. The quality of evidence of included studies was evaluated using the Quality In Prognosis Studies (QUIPS) checklist. Then, meta-analyses of proportions were performed to estimate the rates of mortality, clinical improvement, and recovery of full consciousness. Furthermore, we used cross-sectional meta-analyses to investigate whether significant differences in demographic and clinical variables could be observed across outcomes. We identified 27 studies including a total sample of 357 (289 in Unresponsive Wakefulness Syndrome, UWS and 68 in Minimally Conscious State, MCS) individuals with pDoC due to anoxic brain injury with a follow-up diagnosis at least 6 months after injury. We found that 26% of included patients deceased, 26% showed any clinical improvement, and 17% recovered full consciousness. Higher likelihood of survival and of clinical improvement was associated with younger age, baseline diagnosis of MCS vs. UWS, higher baseline level of responsiveness as assessed by the CRS-R total score, and earlier admission to intensive rehabilitation units. These same variables, but time of admission to rehabilitation, were also associated with recovery of full consciousness. Our findings showed that anoxic pDoC is associated with a sizeable percentage of recovery and that clinical variables can help to predict clinical evolution. This study raises important ethical issues about the need for solid predictive factors, particularly in relation with decisions about withdrawal of life support or discontinuation of long-term management.

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## STUDY OF NEUROPLASTICITY BY HIGH-DENSITY EEG IN POST-STROKE PATIENTS FOLLOWING ROBOT-ASSISTED UPPER-LIMB REHABILITATION

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Objective: Stroke is the second leading cause of death and the leading cause of disability in the world. In recent years, an increasing number of end-effector robots have been developed for the treatment of the upper limb [1], while only a bilateral exoskeleton is currently available. In addition to clinical assessment, monitoring of brain electrical activity, using Electroencephalography (EEG), has emerged for longitudinal assessment of patients with stroke outcomes. The proposed study is an RCT aimed at evaluating recovery in post-stroke patients after unilateral or bilateral robot-assisted upper limb rehabilitation using an EEG quantitative index.

Materials and Methods: Nineteen patients with ischemic stroke in the subacute phase underwent a 30-session upper limb neurorehabilitation program using the Arm Light Exoskeleton Rehab Station (ALEx RS). Each patient was randomly assigned to the experimental group (bilateral treatment) or the control group (unilateral treatment). In addition, neurophysiological evaluation was performed at the following time points: before the start of the first session (T0), immediately after the end of the first session (T1), at the end of the 30 treatment sessions (T2), and at 1-week follow-up (T3). From the acquired EEG data, the Brain Symmetry Index (BSI), one of the most used EEG parameters for the purpose of stroke prognosis, was calculated [2]. It is a metric that

quantifies the symmetry of Power Spectral Density between the two cerebral hemispheres. BSI index values obtained before (T0) and after (T2) the intervention were compared by a two-way repeated measures ANOVA, with time (2 levels: T0 vs T2) as the intragroup factor, and treatment group (2 levels: unilateral vs bilateral) as the intergroup factor, considering the eyes open and eyes closed conditions, separately.

Results: Statistical analysis showed an increase in the symmetry between the cerebral hemispheres (injured and healthy) following rehabilitation treatment in both the eyes open and eyes closed conditions (p=0.006 and p=0.01, respectively). This trend showed no difference in the two groups (unilateral vs bilateral), being the timeXgroup interaction factor statistically non-significant in both conditions (p=0.499 and p=0.997, respectively).

Discussion: The results show a progressive "normalization" of symmetry between the two cerebral hemispheres (injured and healthy) following robotic rehabilitation treatment, also accompanied by a clinical improvement in the upper extremity.

Conclusion: The results, therefore, show the change in the index following the intervention, suggesting its use as a means of investigating the mechanisms of neuronal plasticity involved in stroke rehabilitation.

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## INFLUENCE OF CARDIORESPIRATORY FITNESS AND MRI MEASURES OF NEUROINFLAMMATION ON HIPPOCAMPAL VOLUME IN MULTIPLE SCLEROSIS PATIENTS

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Objectives: The hippocampus is a clinically relevant region characterized by neuroplasticity and neurogenesis that occur throughout the whole lifespan and contribute to functional preservation and restoration, making this structure an appealing potential target for treatment. Neuroinflammation and cardiorespiratory fitness (CRF) may influence hippocampal integrity by modulating the processes promoting neurogenesis and neuroprotection. This study aimed to investigate the effects of neuroinflammation and CRF on hippocampal volume in multiple sclerosis (MS) patients and to evaluate whether these differed according to MS clinical phenotypes (i.e., relapsing-remitting [RR] or progressive [P]). The influence of CRF and neuroinflammation on brain, grey matter (GM) and thalamic volumes was also evaluated to determine whether these effects were specific for the hippocampus.

Materials and Methods: 3D T1-weighted and fluid attenuation inversion recovery (FLAIR) MRI sequences were acquired from 81 MS patients (27 RR and 54 P) and 45 age- and sex-matched healthy controls (HC) using a 3.0 Tesla scanner. White matter T2-hyperintense lesion volume (T2-LV) and choroid plexus volume (CPV) were quantified as neuroinflammatory measures. Moreover, patients underwent cardiopulmonary exercise testing to assess maximum oxygen consumption (VO2max), a proxy of CRF. Associations of demographic, clinical, neuroinflammatory and CRF measures with normalized brain, GM, thalamic and hippocampal volumes in RRMS and PMS patients were assessed using Shapley and best subset selection regression.

Results: RRMS and PMS patients did not differ significantly in age (p=0.174) and sex (p=0.623). Compared to RRMS, PMS patients had higher Expanded Disability Status Scale (EDSS) score (p<0.001), longer disease duration (p=0.003), and a lower value of VO2max (p<0.001). For most volumetric outcomes, largest portions of variance were explained by T2-LV (variable importance [VI]=9.4-39.4) and CPV (VI=4.5-26.2). VO2max explained the largest portion of variance of normalized hippocampal volume in RRMS patients (VI=16.9) and was retained as a relevant predictor of this outcome (Std. β=0.374, p=0.023) together with T2-LV (Std. β=-0.330, p=0.016). However, it explained only a small amount of variance of normalized hippocampal volume in PMS subjects (VI=0.1) and of all the other volumetric outcomes in both groups (VI from 0.3 to 2.2).

Discussion: The positive association between hippocampal volume and VO2max is specific for this structure, and it is present only in patients with RRMS.

Conclusions: By exerting beneficial neurotrophic effects, a higher CRF may play a specific neuroprotective role on MS patients' hippocampal integrity, mainly in the RR phase of the disease.

## EXERGAMING INTEGRATED WITH AUTOMATED MOTOR ASSESSMENT IN PARKINSON'S DISEASE FOR REHABILITATION PURPOSES: A PILOT STUDY USING AZURE KINECT

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Objectives: Healthcare facilities traditionally employ targeted physiotherapy treatments to improve motor conditions in Parkinson's disease. Nevertheless, these treatments are underused because of the costs and resources involved in hospital settings. The paper presents an integrated solution suitable for home settings, targeted to stimulate physical activity through exergames in a virtual game environment, and integrated with the automated assessment of motor performance.

Patients and Methods: 12 patients with idiopathic Parkinson's disease were enrolled (Hohen & Yahr score: 2.5 ± 0.9; UPDRS part III: 29.5 ± 12.3; age: 69.5 ± 8.1 years; disease years: 7.3 ± 5.0; 7 males, 5 females. The new Azure Kinect DK camera (TM) and 3D non-contact body tracking libraries were used for real-time capture of body motion through a 3D skeletal model, both for motor assessment and avatar control during execution of exergames. Automated motor assessment was performed according to tasks derived from the UPDRS scale and included leg agility (LA), sit-to-stand (S2S), gait (G), posture and postural stability (PoS). Specific virtual exergames was developed and integrated: skiing, airplane, keyboard, bouncing ball (a gamified version of traditional leg agility). A two-week, exergaming-based experimental protocol was defined to evaluate its potential for future use in home environments, including the automated motor assessment before (T0) and at the end of the protocol (T1).

Results: The average clinical UPDRS score changed from 28.8 ± 4.7 (T0) to 27.1 ± 6.3 (T1). Similarly, the automated assessment of motor tasks (LA, S2S, PoS, and G), showed a slight improvement at T1 in 8 subjects, most parameters appearing stable in the other subjects. The improvement was evidenced for the exergames: the time to complete the level slightly decreased in T1, the number of points increased, and the errors decreased. Even if a significant proportion of participants was almost devoid of habits in using technologies (57%), all participants indicated medium to high overall system usability.

Discussion: This pilot study confirms the overall participants' significant engagement and enjoyment in the exergaming rehabilitation program, which demonstrated its feasibility and suitability for prolonged use, i.e., multiple daily sessions for several consecutive weeks. A more extended period is needed to quantify and evidence the benefits of exergaming through the assessment tasks.

Conclusion: These preliminary results are therefore encouraging and support the feasibility of the protocol, with proper adjustments, to deploy an automated motor assessment integrated, in real-time, with virtual exergames, in home settings, for rehabilitations purposes in Parkinson's disease.

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## STRUCTURAL AND FUNCTIONAL CORRELATES OF DISABILITY AND GAIT IN MULTIPLE SCLEROSIS: FOCUS ON THE GLOBUS PALLIDUS


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Objectives: The globus pallidus (GP) is divided into an internal (GPi) and an external (GPe) component. Previous works have reported associations between GP atrophy and gait impairment in people with multiple sclerosis (pwMS). In this work we explored the structural and functional alterations of the GP and its components in pwMS compared to healthy controls (HC). We also analyzed the relationship with clinical measures of disability and gait impairment.

Materials and Methods: Sixty pwMS and 30 age- and sex-matched healthy controls (HC) underwent 3T magnetic resonance imaging (MRI) including 3D-T1-weighted, dual-echo and resting state (RS) functional MRI. The timed 25-foot walk (T25FW) test and Expanded Disability Status Scale (EDSS) were administered. Two operators segmented left and right GP into GPi and GPe starting from FSL FIRST masks. Whole-GP, GPi and GPe normalized volumes and T1/T2 ratio were extracted, and seed-based RS functional connectivity (FC) was analyzed.

Results: PwMS had a higher T25FW than HC ($p<0.001$). The GP and its components were not significantly atrophic in pwMS ($p=0.08$-$0.73$). Compared to HC, pwMS had higher T1/T2 ratio in GP regions ($p=0.01$-$0.09$), which correlated with EDSS scores ($r=0.26$-$0.39$, $p=0.003$-$0.05$). Whole-GP RS FC analysis showed that pwMS had decreased connectivity between the left GP and right insula and between the right GP and frontal cortices. They also showed increased connectivity between the right GP and thalamus. When looking at RS FC of individual pallidal components, pwMS exhibited decreased connectivity between bilateral GPe and frontal cortices, as well as decreased intra-pallidal and increased thalamo-pallidal connectivity of the GPi. Lower RS FC between the GPe and frontal areas correlated with worse walking abilities and higher disability.

Discussion: Structural involvement of the GP in pwMS was similar across the two segmented portions. Our results confirm previous reports of increased iron accumulation in the GP of pwMS, which increases with disability. Regarding fMRI, the GPi and GPe showed component-specific RS FC alterations, which correlated with walking impairment and global disability.

Conclusion: Segmentation of the GP in its components might be useful in the study of functional correlates of walking impairment in pwMS.

## A DIGITAL PLATFORM FOR NEUROVISUAL REHABILITATION


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Objectives: Rehabilitation of visual deficits is crucial for improving cognitive and motor functions and quality of life, however, the influence of visual-sensory and oculomotor disorders on patient's outcome is often ignored in neurorehabilitation. The idea of creating a digital platform for neurovisual rehabilitation comes from our clinical experience with patients affected by neurovisual deficits. Our conventional home-based rehabilitation program for patients with these conditions lead to increased performance in various tasks; we needed an instrument that allowed us to constantly monitor the improvements of our patients, creating personalized rehabilitation programs with an increasing difficulty.

Materials: A digital rehabilitative platform was designed to include specific tasks for each deficit: saccadic tasks in patients with diplopia and alterations of extraocular muscles. Various levels of difficulties in visual search tasks, Benton's line and antisaccade task were designed for peripheral visual field deficits and Neglect rehabilitation. Visual search and visual sequential search tasks, visual recognition and identification of figures, 2-3D shapes, objects, facial expression recognition and colors (Stroop test) were designed for rehabilitation of visual perception, visual attention and visual agnosia.

Methods: The platform is accessible from both clinical and remotely; the clinician assigns the exercise to the patient from the platform, who receives an e-mail notification with a link that takes him to perform the exercise. A final report of each rehabilitation cycle is redacted and it allows a constant monitoring of patient's results but it is also used for obtain statistics data and for customizing rehabilitation on patient.

Results: We tested 46 patients: 21 patients with central visual deficits: 9 patients with diplopia, 2 patients with USN, 3 patients with hemianopia and 7 patients with visual perception deficits. The results

showed a significant improvement in subjective and objective visual functions.

Discussion: Our digital platform for neurovisual rehabilitation allows the clinician to personalize and monitor the treatment's progression and ensures an easily accessible instrument for patients and it showed an efficacy in improving neurovisual performance in neurological patients.

Conclusions: Neurovisual rehabilitation platform represents a valid instrument for rehabilitation of visual deficits in neurological patients.
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## NEUROMOTOR REHABILITATION IN PARKINSONIAN SYNDROMES: OUTCOMES AND DISABILITY AFTER HIP FRAC TURE

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Objective: To investigate the clinical outcome of neuromotor rehabilitation after hip fracture in patients with clinically diagnosed parkinsonism.

Materials: 59 patients diagnosed with parkinsonism (45 patients with Parkinson's Disease and 14 patients with atypical parkinsonism) and 59 age and sex matched patients without parkinsonism underwent clinical assessment at neuromotor rehabilitation unit admission and at discharge (mean 40.77 days) after hip fracture surgery.

Methods: Demoghraphic, anamnestic, clinical and functional data were retrospectively collected. Modified Barthel Index (MBI) and modified Rankin Scale (mRS) were used as measures of disability. Demographic and clinical variables were compared between groups using Student's t-test, Mann-Whitney test and Pearson's chi-squared test when appropriate. Linear mixed-effects models were used to study the association between outcome, clinical and demographic variables. Statistical analyses were used to compare data between the two main groups (parkinsonism vs non-parkinsonism groups) and among parkinsonian patients (patients with Parkinson's Disease vs those with atypical parkinsonism).

Results: MBI was significantly lower and mRS was significantly higher in parkinsonism group at both admission and discharge, compared to non-PD group ($p<0.001$). MBI and mRS at discharge were significantly associated with group appartenence corrected for age and sex. Among parkinsonian patients MBI scores at admission ($p=0.02$) and at discharge ($p=0.04$) were lower in atypical parkinsonism (AP) group compared to Parkinson's Disease (PD) patients. Disability, defined by MIB and mRS scores, was significantly associated with the presence of AP ($p<0.001$), dementia ($p<0.001$), dysphagia ($p=0.01$) and postural instability ($p<0.001$), correcting for age, sex and disease duration.

Discussion: PD patients showed higher risk of hip fracture compared to non-parkinsonian patients [1], even though the outcome was controversial [2, 3]. In our knowledge, this is the first study that investigated the outcome of neuromotor rehabilitation in parkinsonian patients after hip fracture, showing higher disability in patients with parkinsonism, compared to those without. Among parkinsonian patients, those with AP, cognitive decline, dysphagia or postural instability showed the worst functional outcome.

Conclusions: According to our results parkinsonian patients, especially with AP, showed a worse outcome after rehabilitation for hip fracture compared to patients without parkinsonism. Cognitive decline, dyspagia and postural instability may represent relevant factors worsening the global outcome, with relevant prognostic implications.
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## OXIDATIVE STRESS AND NUTRITIONAL STATUS IN POST STROKE PATIENTS UNDERGOING REHABILITATION TREATMENT: GENDER DIFFERENCES

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After a stroke insult, even in the subacute phase [1], there is an overproduction of free radicals which overpower antioxidant defenses, causing oxidative stress (OS) and further tissue damage. Nutritional status is crucial for stroke-associated malnutrition [2] and for the metabolic antioxidant system. The aim of the study was to evaluate in men and women: i) the systemic OS marker and nutritional status parameters in patients at admission and after a rehabilitation treatment; ii) the correlation of these parameters with functional outcome. We enrolled 87 subacute stroke patients (42 women, 45 men; mean age $69 \pm 12$ years; NUTRISTROKE project: NCT04923165) admitted to our department and evaluated both at admission (T0) and after a six-weeks rehabilitation program (T1), which included a conventional and robotic physical therapy. Functional independence in activities of daily living was assessed by the modified Barthel Index (BI). The nutritional status was assessed by anthropometric measurements, the Geriatric Nutritional Risk (GNRI), and daily estimation of food consumption, together with a Mini Nutritional Assessment screening (MNA-SF®) at admission. Serum samples of patients were collected and analyzed for albumin, hydro-peroxides, total antioxidant defenses, and thiol content. Mann-Whitney U test, chi-squared test, or Paired Wilcoxon's signed-rank test were used to compare data. Correlation between variables was performed with Spearman rho correlation coefficients (JASP v.0.16.4). Women and men did not differ for parameters recorded, except for anthropometric measurements, as expected. Hydroperoxides levels were very high in men and women at T0 and T1, and antioxidants were apparently in the normal range, but the Oxidative Stress Index (BAP/d-ROMs ratio) was very low. Hydroperoxide levels decreased at T1, in parallel to an increase of OSI, in the whole group, and in men. Albumin and GNRI increased at T1 only in women. We found a correlation between MNA-SF®, GNRI (T0 and T1), food consumption, and recovery in terms of delta BI (BI T0-BI T1) in the whole group; women showed all these correlations, even stronger. Oxidative stress status is very high in subacute patients even three months after the stroke insult. The antioxidant defense is insufficient to counteract this condition and an inappropriate nutritional condition could contribute to exacerbating this scenario. Moreover, women are more impaired in terms of oxidative stress and seems that recovery is more related to nutritional status. This suggests that more efforts should be done

to assess the OS, so that to opportunely improve antioxidant intake, especially in women.

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## NEUROMUSCULAR DISEASES - MYOPATHIES AND NEUROPATHIES

### A NOVEL MUTATION IN MYH14 IN A ITALIAN FAMILY WITH AUTOSOMAL DOMINANT DISTAL SPINAL MUSCULAR ATROPHY

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Introduction: Distal spinal muscular atrophy (dSMA) is a rare genetically and clinically heterogeneous group of disorders characterized by slowly progressive distal muscular weakness and atrophy without sensory abnormalities [1]. To date, at least 20 genes and 4 loci associated with dSMA have been reported [2,3].

Case Report: We report the case of an Italian family with autosomal-dominant dSMA with eight affected members. In all patients the first sign was abnormal ambulation, due to weakness and atrophy in distal lower limbs. Later in disease course the same pattern of distal weakness and atrophy involved upper limbs. Electromyography was neurogenic in distal muscles with reduced compound muscle action potential (CMAP) amplitudes. Sensory conduction was normal. Muscle MRI in III-(2) and III-(3) documented muscle atrophy of legs and forearms with fibrous-adipose replacement. Three patients (II-(3), III-(2), III-(3)) were also affected by sensorineural hearing loss confirmed by audiometry. We completed an exome sequencing of 136 genes in all affected members still alive, II-(3), III-(2), III-(3), III-(4), IV-(1) and IV-(2) to identify the causative variant in this family. Genetic analysis identified in all of them the heterozygous c.291G>T variant in gene MYH14, which was classified as likely pathogenic by genome aggregation database (gnomAD).

Conclusion: Although variants in MYH14 gene are yet known to be associated with progressive dSMA, the direct correlation between clinical phenotype and the c.291G>T variant confirms the pathogenicity of this mutation in dSMA. Our findings broaden the genetic spectrum of MYH14 associated dSMA and could improve molecular diagnostics of dSMA.

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### OFTEN MISDIAGNOSED AND TREATABLE IMMUNE MEDIATED AUTONOMIC NEUROPATHY

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Objectives: Autoimmune autonomic neuropathies (AAN) are a group of disorders characterized by an autonomic failure triggered by a dysimmune mechanism. Here we report two cases of AAN characterized by a diagnostic delay with negative consequences for patients and by a good response to intravenous immunoglobulin (IVIg) therapy.

Methods: A 24-year-old woman presented with a 10-year history of gastroparesis, urinary retention, sicca syndrome, paresthesia, and orthostatic hypotension following vaccination. The symptoms were interpreted as a spinal cord dysfunction, and she was implanted with a spinal cord stimulator. The patient was sent for a gastroenterological and then surgical evaluation, and she was offered a colostomy procedure. Autonomic tests showed the presence of autonomic failure. The laboratory and instrumental tests led to a diagnosis of Sjogren's for which IVIg therapy was performed with benefit. A 35-year-old man was evaluated for a history of altered sensitivity to heat and cold in the four limbs, gastroparesis, urinary retention, and orthostatic hypotension, which had occurred approximately 20 years earlier and resolved after plasmapheresis and steroids, and recurred following vaccination. The patient was prescribed laxatives and given the limited benefit he had to resort to numerous visits at the emergency department before being hospitalized. Autonomic tests showed the presence of autonomic failure and he was given IVIg with benefit.

Results and Conclusion: AAN are often misdiagnosed and that this can lead to important consequences for the patients. Several reports confirm a response to therapy with immunomodulatory drugs, in particular IVIg, in AAN.

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### WHEN WEAKNESS IS NOT ALL: PORPHYRIA MIMICKING A CIDP

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Introduction: Porphyria is a rare but treatable genetic disease caused by alteration of heme metabolism. Even if several types of porphyria had been described so far, porphyria may be dived into acute and chronic disease. Chronic syndromes include porphyria with skin manifestation and without acute attacks. Acute diseases include syndromes with acute manifestations such as pain, psychosis, neuropathy and coma. Porphyria may begin at any age, however only few cases with a late onset had been described.

Materials and Methods: We report a case of acute porphyria mimicking an inflammatory neuropathy. A 60 years old woman was referred to neurologist for a lower limb distal weakness. Her medical history was unremarkable except for a depression, treated with paroxetine. The patient underwent to nerve conduction studies, revealing a demyelinating sensory neuropathy. Hospitalization in our neurology department was suggested. At first the patient refused but after three months, in April 2023, the patient was referred to our department due to a worsening of symptoms. Another nerve conduction study showed a worsening of the demyelinating sensory neuropathy; motor nerve studies and needle EMG were normal. Brain and spinal MRI were unremarkable. Lumbar puncture showed an albumin-cytological dissociation. A CIDP was hypothesized and intravenous immunoglobulin was administered. During the treatment, the patient showed a worsening of neuropathy with an involvement of motor nerves. Moreover hyperCKemia and hypertransaminasemia were observed. A myopathy was hypothesized, however patient suddenly developed an hypercapnic coma and was transferred to the intensive care unit where she was intubated. In the intensive care unit a new intravenous immunoglobulin treatment was administered without benefit; a muscle MRI was performed and it was unremarkable. Patient underwent to steroid treatment: hyperCKemia was resolved where hypertransaminasemia was persistent. In few days the patient developed a severe pancytopenia. In the meanwhile her neuropathy further worsened. Even if patient never complained of abdominal pain, the association with neuropathy, pancytopenia and psychiatric disorders suggested porphyria. Urine porphobilinogen and elevated values of urinary porphyrins led to the diagnosis of acute intermittent porphyria. Patient was treated with heme arginate with a marked improvement of symptoms: actually the patient came out of coma and even neuropathy sowed a mild improvement.

Conclusions: Ancient physicians said: "if you don't know what it may be, think about porphyria". Actually, due to the broad spectrum of manifestation, porphyria may be underdiagnosed and it should be suspected in those kinds of inflammatory neuropathies unresponsive to treatment.

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## FRIEDREICH ATAXIA IN A YOUNG WOMAN PRESENTING AS POLYNEUROPATHY


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Case Presentation: A 29-years-old woman came to our attention for the sudden onset of gait disturbance at 26. Personal history was unremarkable, besides spinal scoliosis treated with a corset. Family history was negative for neuromuscular diseases; parents were consanguineous (first-grade cousins). At 27 she had performed a brain and spine MRI that found no abnormalities (except for the known scoliosis). She also lamented tinnitus in the right ear; an audiometric examination evidenced sensorineural hearing loss in the right ear. Neurological examination evidenced bilateral pes cavus and bilateral dysmetria at the finger-nose and heel-to-shin tests. An ENG showed a sensitive polyneuropathy, with absence of SAPs from median, ulnar and sural nerve. Routine blood tests, cerebrospinal fluid analysis, autoimmunity serum panels and anti-neuronal antibodies were normal. Anti-ganglioside serum panel revealed a weak positivity of anti-GD 1b and anti-GT 1b IgM. Suspecting an inflammatory polyneuropathy, she was treated with prednisone 50 mg. Even if she reported a subjective improvement, neurological evaluation did not change. After two weeks, she presented serous retinal detachment at the right eye and the treatment was suspended, with rapid improvement of eyesight. However, gait and balance worsened. Suspecting a genetic syndrome, an NGS panel for spino-cerebellar ataxias was inconclusive, while a homozygous GAA triplets expansion was demonstrated in the FRDA gene. Her parents were found to be carriers for the expansion. To evaluate any subclinical cognitive impairment, neuropsychological tests were administered, with normal results.

Discussion: FRDA is the most common autosomal recessive spinocerebellar ataxia in Europe. It usually presents between 10 and 16 years with a multisystem involvement, affecting both the central and peripheral nervous systems, the musculoskeletal system, the myocardium and the endocrine pancreas. Late-onset forms (>20 y) occur rarely and often typical symptoms such as dysarthria, gait ataxia and cognitive impairment may be absent. [1] In our case, clinical presentation and family history pointed to an inflammatory etiology; clinical signs that could suggest a genetic etiology were subtle (namely, bilateral pes cavus and scoliosis).

Conclusion: Genetic testing should be considered even in mild suspicion of a genetic disorder to avoid misdiagnosis.

Reference:


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## MITOCHONDRIAL CARDIOMYOPATHIES: A CLINICO-PATHOLOGICAL STUDY


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Objective: The aim of this study is to describe the clinical and pathological findings of three unrelated patients presenting with cardiomyopathy and different mitochondrial syndrome (PEO and MELAS associated with m.3243A>G mutation, MERRF and m.8344A>G).

Materials and Methods: In order to elucidate the etiology of the heart dysfunction, all patients underwent extended cardiac evaluations, including endomyocardial biopsy.

Results: Histologic analysis revealed different features in the three hearts' patients: in the m.3243A>G-PEO patient we observed classical focal accumulation of mitochondria with COX defect, while in the other two patients COX was slightly reduced. In the MELAS patient cardiomyocytes were hypertrophic and showed sarcoplasmic vacuoles filled with PAS-positive granules analogous to those

observed in storage disease and mitochondrial proliferation; in the patient affected by PEO and MERRF there was only mitochondrial abnormalities without cytoplasmic vacuolation.

Discussion: There was a good correlation between the histopathological finding and the severity of the clinical conditions. In fact, the 24-year old MELAS has been showing an acute heart failure that happened suddenly without warning and she passed away two weeks after the endomyocardial biopsy. On the contrary PEO and MERRF patients presented a long history of chronic cardiomyopathy diagnosed many years before histological investigations.

Conclusions: Our results show a histopathological variability of endomyocardial biopsy. The severity of histological findings reflects the clinical conditions of the patients and their prognosis.

## FATIGUE AND ASSOCIATED FACTORS IN PRIMARY MITOCHONDRIAL MYOPATHIES: A SINGLE-CENTRE COHORT SURVEY EXPERIENCE

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Introduction and Objectives: Muscle pain and fatigue are commonly reported complaints in Primary Mitochondrial Myopathies (PMMs). We aim to investigate the prevalence of these disturbances and to stratify the different domains of fatigue in our cohort of patients affected by PMMs and tried to compare the possible relation between these conditions and others potentially influencing factors such as sleep disturbances or psychiatric comorbidities.

Materials and Methods: We administered self-reported or perceived fatigue and muscle pain routinely scales such as Modified Impact Fatigue Scale (MFIS), Fatigue Severity Scale (FSS), Back Pain Inventory scales in 50 patients affected by PMM and controls. PSQI (Pittsburgh Quality Index), ISI (Insomnia Severity Index), Hamilton Anxiety Rating Scale (HAM-A), BDI (Beck depression Inventory), NMDAS were also performed. Linear regression analysis was performed to evaluate the associations between the different variables.

Results: Fatigue resulted to be very common in our population (42/50; 84%). 11/50 (22%) reported muscle pain. Higher fatigue and pain scales rates relates with anxiety, depression and altered sleep quality ($p<0.05$). Higher age and NMDAS score were related with higher fatigue perceived and muscle pain.

Discussion: The burden of pain and fatigue in PMM seem to be associated to increased age and to overall clinical involvement. Pain and fatigue appear to influence sleep disturbances in this population and vice-versa. Anxiety and depression are likely contributing factors of fatigue and pain perceived.

Conclusion: Anxiety, depression and sleep quality questionnaire should be assessed routinely to PMM patients claiming fatigue and pain for a better assessment and management. Considering the different fatigue scales available, MFIS and MFI-20 appear to be more selective in the evaluation of these patients.

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## MYASTHENIA GRAVIS, MULTIFOCAL MOTOR NEUROPATHY, AND ANTI-GBM NEPHRITIS: THREE AUTOIMMUNE DISORDERS IN ONE PATIENT

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Objectives: The coexistence of multiple autoimmune diseases in patients with a chronic autoimmune disease is common and known as "multiple autoimmune syndrome". The acute, simultaneous onset of multiple autoimmune disorders is rarer and has often been explained by the exposure of a genetically predisposed individual to a triggering factor. We present a case of three new-onset autoimmune disorders occurring simultaneously: anti-GBM nephritis, Myasthenia Gravis (MG), and Multifocal Motor Neuropathy (MMN).

Patient and Methods: We describe a 69-year-old man, affected by arterial hypertension and diabetes mellitus. He was hospitalized due to the subacute onset of tetra-hyposthenia, dysphagia, ptosis, and ophthalmoparesis rapidly evolved in few days. Two months before he had presented a lack of strength in the left upper limb. Early in the hospital stay, the patient presented progressive impairment of respiratory function and motor skills until he developed cardio-respiratory arrest. He was then admitted to the intensive care unit where after intravenous Ig therapy he progressively improved in motor skills. The patient underwent lumbar puncture which was negative for infectious and inflammatory diseases. He also underwent neurophysiological investigations (ENG, EMG, and SFEMG). Several autoimmunity laboratory tests were performed. An ultrasound study of the nerves has been carried out.

Results: At the beginning of the hospital stay, the patient's clinical and neurological picture rapidly deteriorated within a few days. He presented with a concomitant increase in gammaglobulin, serum IgG and IgA, and nonselective proteinuria. Therefore, high-dose Ig ev therapy was undertaken. Neurophysiological exams revealed peripheral motor trunks pathology with conduction blocks and altered neuromuscular junction. Screening tests for autoimmunity showed positivity of ARAB, anti-GBM, ABTG, ABTPO and ANA antibodies. CT scan of the chest excluded expansive masses or thymic hyperplasia. After the initial acute phase, the patient progressively improved with complete remission of the nephritic syndrome and progressive motor recovery. In all, two courses of Ig ev therapy were performed subsequently corticosteroid and azathioprine therapy was continued.

Discussion: To our knowledge, no other cases like this have been described. The concomitant occurrence of membranous glomerulonephritis and MG has been sporadically reported, especially associated with thymic pathology. In our case, we couldn't find a putative trigger cause explaining such abnormal immune response.

Conclusion: The present case of MMN, MG, and anti-GBM nephritis occurring in one patient indicates a common underlying immune mechanism, including the involvement of autoantibodies, complement activation and T cells.

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## CO-OCCURRENCE OF OCULOPHARYNGEAL MUSCLE DYSTROPHY AND MYASTHENIA GRAVIS: AN ASSOCIATION OR AN INCIDENTAL FINDING?

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Introduction: Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant late-onset myopathy, characterized by progressive ptosis, dysphagia and limb muscle weakness. Myasthenia gravis (MG) is an autoimmune neuromuscular junction disease, most commonly caused by antibodies against the acetylcholine receptor (AChR), leading to fatigable and fluctuating weakness that variably affect ocular, bulbar and limb muscles. Since both diseases may affect the same muscular groups, overlap and misdiagnosis can occur.

Case Description: A 80-year-old Italian man with a 30-years history of slowly progressive ptosis referred to our hospital for a recent onset of dysphagia and lower limbs weakness with difficulties in walking and climbing stairs. Seven of nine siblings shared similar symptoms since the age of 50 years. Neurological examination showed severe ptosis with upward gaze limitation, hypophonic speech, proximal muscle weakness involving pelvic and scapular girdle. Concentric needle EMG showed patchy myopathic abnormalities without spontaneous or insertional activity in proximal muscles but was normal in distal ones. Genetic testing for OPMD was significant for PABPN1 gene mutation with 14 GCN repeats. Given the fluctuating fatigability, expecially in the lower limbs associated to shortness of breath, a coexisting neuromuscular junction disease was suspected. High AchR antibodies titre was found in two different determinations. Repetitive nerve stimulation revealed a significant decrement from the accessory nerve. Pyridostigmine therapy was added to therapeutic regime, with immediate response and fast clinical improvement.

Discussion and Conclusions: Only few cases of genetic myopathies coexisting with AchR MG have been reported. This occurrence may be coincidental, but it could also indicate a disruption of immune tolerance to AChR due to autoinflammation (innate immunity) triggered by muscle fiber degeneration, rather than through adaptive immune processes in the thymus. Our case aims to suggest that even in patients with a confirmed genetical diagnosis, the presence of unusual clinical features forces to investigate additional overlapping condition, especially when a treatable disease like MG is suspected. Further case reports will be needed to better understand the mechanism underlying this association, in order to define the most effective and tailored therapeutic approach in these patients.

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## A CASE OF TREATMENT-REFRACTORY ANTI-NUCLEAR-RIM NECROTIZING AUTOIMMUNE MYOSITIS

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Objectives: We report on a case of a 30-year-old patient affected by treatment-refractory necrotizing autoimmune myositis with predominantly bulbar symptoms and positivity for anti-nuclear-rim antibodies.

Methods: We report the case detailing medical and clinical history together with histological, genetic and autoimmune tests.

Results: A 30-year-old male was referred to our department due to onset of dysphagia and dysarthria. High CPK levels and electromyographic test were consistent with acute autoimmune myositis. Despite the presence of an anti-nuclear-rim pattern of antinuclear antibodies, myositis-specific autoantibodies panel tested negative. Muscular biopsy was then performed and showed a necrotizing autoimmune myositis. Patient was then treated with high-dose steroids, with a rapid, but incomplete, response. Due to persistent clinical and biochemical abnormalities, intra-venous immunoglobulins (2g/kg over 5 days) and cyclophosphamide (1 g/m^2) were administered. Due to a clinical and biochemical relapse patient was re-treated with high-dose steroids followed by rituximab (two 1 g infusions 15-day apart). A complete and long-lasting response was then achieved. Genetic analysis tested positive for HLA DPA1 (01:03), HLA DQA1 (02:01, 03:01) and DQB1 (02:01, 03:02) haplotypes that have been associated with cases of autoimmune myositis with antibodies anti-nuclear pore complex.

Discussion: The anti-nuclear-rim ANA pattern has only been described in four cases of myositis-overlap syndrome, each of them presenting a relapsing-remitting course with poor response to steroid therapy; moreover, it was described the association with HLA DPA1 (01:03), and DQA1 (05:01) haplotypes, the latter identified as the most probable risk allele for anti-nuclear-rim associated myositis [1]. However, our patient's genetic analysis showed only the presence of HLA DPA1 (01:03) haplotype, disproving such hypothesis. Additionally, we report that most first line treatments (i.e.: steroids, intravenous immunoglobulin, cyclophosphamide) resulted in transient disease remission, while rituximab administration resulted in a long-lasting disease remission with steroid discontinuation. Thus, the case we described highlights the possibility of achieving a complete and sustained therapeutic response in MSAs-negative necrotizing myositis, even after failure of conventional therapies, and underlines both the role of genetics, and the importance of recognizing an atypical ANA pattern as a guide to the correct therapeutic management.

Conclusion: In this report we show a case of anti-nuclear-rim autoimmune myositis showing that, albeit rare, this autoimmune pattern reflects the presence of a necrotizing myositis that could be refractory to conventional treatment and might need rituximab administration to induce a long-lasting remission.

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## LONG-TERM OUTCOME IN GUILLAIN-BARRÉ SYNDROME WITH ANTI-PARANODE ANTIBODIES: A 5 YEAR FOLLOW-UP STUDY

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Objectives: The aims of this study were to evaluate clinical and neurophysiological characteristics of patients affected by Guillain-Barré syndrome (GBS) that tested positive for antibodies directed against paranodal proteins neurofascin-155 (NF155), contactin-1 (CNTN1) and contactin-associated protein-1 (CASPR1), evaluating their long-term follow-up.

Materials: We retrospectively collected data of patients with diagnosis of GBS, hospitalized from 2013 to 2022, positive for paranodal antibodies. Patients with follow-up of $< 12$ months and diagnosed with acute onset chronic inflammatory demyelinating polyradiculoneuropathy (A-CIDP) were ruled out.

Methods: NF155, CNTN1, and CASPR1 antibodies were determined with in-house ELISAs. GBS variants were distinguished based on Wakerley classification [1]. Electrophysiological distinction between demyelinating and axonal forms was based on Hadden criteria [2]. Disability was assessed according to the GBS disability scale (GBS-DS).

Results: 21 patients (15 males, 6 females) with GBS confirmed at follow-up, tested positive for CNTN1, or CASPR1 antibodies (no seropositivity for NF155 antibodies). Mean age was 65.6 years (range 40-91). 18 patients had classic GBS: 12 acute inflammatory demyelinating polyneuropathy (AIDP), 3 acute motor sensory axonal neuropathy (AMSAN), and 3 acute motor axonal neuropathy (AMAN). Two patients were diagnosed with Miller-Fisher syndrome (MFS), and one with a GBS-MFS overlap. We excluded five patients with a follow-up of $\leq 6$ months. Of the remaining 16 patients, 5 had CNTN1 (classic GBS, 4; MFS, 1), 6 CASPR1 antibodies (classic GBS, 4; MFS, 1; overlap GBS-MFS, 1), and 5 had a double positivity (CNTN1/CASPR1, all classic GBS). Long-term follow-up data from onset was available in 76,2% of the patients (mean 4.68 years, range 1-9 years). At the disease nadir, 25% of the patients had a GBS-DS of $< 3$ and 75% $\geq 3$. At the last follow-up visit, 81.25% showed a GBS-DS of $< 3$.

Discussion: While the association of CIDP and paranodal antibodies is well described, cases of GBS seropositive are still scarcely known. Moreover, literature data regarding long-term follow-ups of these patients are lacking. Our cohort showed considerable follow-up period, phenotypic variability and good average recovery. Although our study presents some limitations, particularly the lack of a standardized laboratory assay for paranodal antibodies and confirmation with cell-based assays, the results highlight the importance of correlation between seropositivity, clinical phenotype and long-term follow-up data.

Conclusions: This is the first study evaluating the long-term follow-up of GBS with positivity for paranodal antibodies. More insights on the role of these antibodies in shaping GBS phenotypes require further studies on larger series.

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## PHENOTYPIC SPECTRUM OF A SERIES OF TEMPORALLY CLOSE CASES OF GUILLAIN-BARRÉ SYNDROME

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Objectives: We report here some temporally close cases of Guillain-Barré-Syndrome (GBS) [1] with remarkable unexpected clinical characteristics, which were consecutively observed in our clinic over a period of nine weeks.

Materials: Patients with a diagnosis of GBS admitted to the Neurology ward of the Policlinic Hospital in Milan from January 12th to March 16th, 2023, were included.

Methods: Clinical features, diagnostic evaluations as well as treatment responses were collected.

Results: Among the five patients enrolled (four male, mean age 61,4 years), two presented as typical clinical variant, both with a likely antecedent viral febrile event; two as Miller Fisher syndrome although without seropositivity to antibodies against GQ1b; one as pharyngeal-cervical-brachial variant. All patients showed markedly sustained increase of arterial blood pressure and heart rate over the previous weeks, with three of them reporting recent starting of antihypertensive medication. Laboratory testing were normal. Cerebrospinal fluid analysis (CSF) (performed in 4/5) revealed elevated CSF protein with a normal white blood cell count in the two with typical forms, whereas normal values were found in the two with Miller Fisher variants. Serially performed electrodiagnostic studies showed demyelinating features in 4/5 of patients. Treatment response was overall sufficient. Of those patients, one received only intravenous immune globulin (IVIG) (0.4 g/kg per day for five days), whereas four received plasma exchange (PLEX) (four to six treatments over 8 to 10 days). Out of these four, two failed to improve and they subsequently received IVIG. These two were a woman with Miller Fisher variant who developed impending respiratory failure, while the other was a man with typical clinical variant with progressive severe weakness. Prognosis was poor (GBS-disability score, $\geq 3$) in 2/5 patients.

Discussion: We outlined the clinical features of 5 temporally close consecutive patients admitted in our clinic, which serves, alongside other centers, an area of about 1.352 million inhabitants. Notably three patients displayed GQ1b syndromes phenotypes. Interestingly, all patients suffered from subacute increase of arterial blood pressure and sustained increased heart rate starting two weeks before the onset of neurological symptoms, often requiring treatment modifications with good response.

Conclusions: This cluster of temporally close consecutive patients with GBS showed instead that cardiovascular autonomic dysfunction may represent a common early feature. Alongside supportive management, valuable immunomodulatory treatments are nowadays available [2], but outcome strictly depend from their use at an early stage. Therefore, this unusual clinical feature deserves prompt recognition.

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## MYELIN PROTEIN ZERO MUTATIONS: CMT CLUSTERS ACROSS ITALY

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Background: To investigate the clinical features of a large cohort of Charcot-Marie-Tooth patients with *MPZ* (myelin protein zero) mutation, focusing on the main clusters across Italy.

Materials and Methods: We retrospectively gathered a minimal dataset of clinical information, including type of mutation, disease onset, milestones timeline, disease severity (CMTES-CMT Examination Score), motor/sensory symptoms, cranial nerves involvement and use of orthotics. We performed Fisher's exact test/ANOVA/Spearman's Rank-Order Correlation, as appropriate, to compare patients with different mutations and analyze correlations between age and disease severity.

Results: We collected data from 180 patients: 58 had the p.Ser78Leu mutation (demyelinating CMT; from Sicily), 40 the p.Pro70Ser (axonal form; from Lombardy and Emilia Romagna), 38 the p.Thr124Met (axonal CMT; from Veneto), 24 the p.Ser44Phe (axonal type; from Sardinia), and 20 the p.Val102fs (intermediate form; from Campania and Puglia). Disease severity (CMTES) was highest in p.Thr124Met patients (9.4±6.6), followed by p.Pro70Ser (8.4±6.0), p.Ser44Phe (8.3±6.4), p.Ser78Leu (7.1±4.4), and p.Val102fs (1.6±1.7). Disease onset, determined by both the onset of walking difficulties and the age at first assessment, differed among the five clusters ($p<0.001$), namely earlier in the demyelinating p.Ser78Leu group (34.6±20.3; 49.0±21.3, respectively) and later in the axonal p.Pro70Ser cohort (56.4±5.8; 61.8±13.6, respectively). However, disease progression was faster for p.Pro70Ser patients ($rs=0.82$, $p<0.001$) as compared to those with p.Ser78Leu mutation ($rs=0.61$, $p<0.001$). In the p.Val102fs cohort, no patient reported walking difficulties ($p<0.001$), AFO use ($p<0.001$) or walking support need ($p<0.001$), and no correlation between age and disease severity was found. However, p.Val102fs patients more frequently experienced neuropathic pain as compared to other clusters (76%, $p<0.001$). In the other four groups, orthotic aid use ranged between 39-57% (17-33% for shoe inserts; 24-48% for AFOs), walking difficulties were reported by 70-74% of patients while walking supports were used by 16-25%. Sixteen percent of patients with the p.Ser78Leu mutation reported delayed autonomous walking (beyond 15 months), more than in the other four groups ($p<0.001$). Upper limb involvement, observed in the 12-42% of patients, did not differ across the five cluster. Hearing loss and pupillary abnormalities were almost exclusive of patients with p.Thr124Met (43% and 71%, respectively; $p<0.001$ for both) mutation.

Discussion and Conclusions: This is the largest Italian cohort of MPZ patients, reporting the five most frequent clusters and the comparison among them. The region of origin and some clinical peculiarities, reflecting different pathomechanisms, must help the clinician to guide the genetic analysis.

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## USE, TOLERABILITY, BENEFIT AND SIDE EFFECTS OF ANKLE-FOOT ORTHOTICS IN CMT

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Introduction: Shoe inserts, orthopaedic shoes and ankle-foot orthoses (AFOs) are important tools in the management of Charcot-Marie-Tooth disease (CMT) patients, but data about frequency of use, benefits and tolerance are scanty.

Materials and Methods: We administered to patients of the Italian CMT Registry an online *ad hoc* questionnaire investigating use, complications and (through VAS scale, 0-10) perceived benefit, tolerability and emotional distress of shoe inserts, orthopaedic shoes, AFOs. Mann–Whitney U test was performed to analyse the impact of different determinants on orthoses tolerability.

Results: We analysed answers from 266 CMT patients (136 females; mean age 47.5±12.9 years, range 20-77): 185 (70%) subjects were prescribed lower limb orthoses but 19% did not used them. Among the 150 users, only 69% reported current use. Overall, 39% subjects wore shoe inserts, 18% orthopaedic shoes, 23% AFOs. Among AFOs, Codivilla spring (41%), Toe-off (28%) and Peromed (24%) were the most frequently used. Complications were reported by 59% of patients. AFO users complained mostly of skin reddening (52%) and moderate-to-severe pain (41%) while calluses were a more frequent issue in both shoe inserts (36%) and orthopaedic shoes (36%) wearers. Complications accounted for the 37-42% of orthosis abandonment. AFO users showed greater emotional distress (5.5±3.5) and reduced tolerability (5.9±3.2) as compared to both shoe inserts (2.5±3.2, $p<0.001$; 7.1±3.1, $p=0.001$) and orthopaedic shoes (3.7±3.5, $p=0.003$; 6.8±3.1, $p=0.045$) users. Concerning AFOs, patients with moderate-to-severe CMT (CMTES>8 vs CMTES<=8) and moderate-to-severe (MRC<3 vs MRC≥3) weakness on foot dorsiflexion reported higher tolerability (6.6±2.9 vs 4.5±3.2, $p=0.002$; 6.3±3.1 vs 5.0±3.2, $p=0.038$, respectively) and perceived benefit (6.9±3.2 vs 5.1±3.3, $p=0.005$; 6.9±3.1 vs 5.0±3.4, $p=0.007$, respectively) to their device. Customization was

required for 60% of the orthotics and was related to higher compliance since those who personalized their orthotics were more prone to use it outdoor as compared to those who did not (75% vs 52%, p=0.001). Moreover, delayed customization was associated to lower tolerability (5.7±2.2 vs 7.3±2.0, p=0.006) and perceived benefit (6.2±1.9 vs 7.2±2.1, p=0.031), and to higher emotional distress (5.5±2.1 vs 3.2±1.7, p=0.004) with respect to quick personalization.

Conclusions: Orthoses are frequently used in CMT. However, 19% of subjects never used the prescribed device and abandonment was frequent. Although perceived benefits and tolerability are rather good, there is a high rate of complications and considerable emotional distress, which make their use problematic. A patient-based approach and employment of personalised/customised AFOs must be encouraged.

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## EVALUATING THE EFFECTIVENESS OF ECULIZUMAB IN THE MANAGEMENT OF REFRACTORY MYASTHENIC CRISIS

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Introduction: Myasthenia gravis (MG) is a chronic autoimmune disorder caused by autoantibodies targeting different components of the neuromuscular junction (NMJ), which results in muscle fatigability up to respiratory failure in severe cases. Myasthenic crisis (MC), a life-threatening condition that requires hospitalization in ICU, with ventilatory support and treatments with intravenous immunoglobulins (IVIg) and plasma exchange (PLEX). We report the case of MC in a patient with Acetylcholine receptor antibodies (AchR-MG), refractory to standard treatments, responding to Eculizumab as rescue therapy with a rapid and complete recovery.

Case description: A 74 years-old Italian man previously diagnosed with MG, referred to our hospital for 10-days history of worsening eyelid and head drooping, double vision, feeding difficulties, limb weakness and dyspnea. Upon admission he promptly received IVIg infusion and high-dose prednisone, but his conditions worsened, requiring transfer to the Intensive Care Unit (ICU) and mechanical ventilation. Despite several attempts to wean him off the ventilator, his condition did not improve, and pneumonia was discovered. Given the high risk of sepsis despite adequate antimicrobial therapy, a second cycle of IVIg and PLEX were excluded. Hence, the disease was deemed refractory to conventional rescue therapies and, a month later, Eculizumab was initiated. The patient was successfully weaned-off ventilation and moved back to neurology department within 5 days from the first infusion. Over the next few weeks, he gradually regained independent breath and the ability to feed autonomously. Prednisone dosage was reduced, and he was discharged home after five weeks. Currently, he keeps receiving Eculizumab on outpatient basis, with excellent clinical condition and ongoing steroid tapering.

Discussion: Eculizumab is a humanized monoclonal antibody that selectively prevents the activation of the complement component C5, recently approved for refractory generalized AchR-MG. The observation of a complete terminal complement inhibition by the end of the first dose, and the significant reduction of the MG-ADL score during the first week of treatment in the REGAIN study support the evidence of its rapidity of effect. Our case aims to suggest that Eculizumab could also be considered as a fast-acting option in the emergency setting, when conventional treatments fail or are unfeasible. Of note, other reports suggest that delayed initiation of Eculizumab may reduce its effectiveness, leading to incomplete clinical recovery. Further clinical studies are needed to fully understand the role of Eculizumab in the management of refractory MC.

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## LAMBERT-EATON MYASTHENIC SYNDROME IN A SINGLE CENTRE COHORT OF PATIENTS: CLINICAL, NEUROPHYSIOLOGICAL FEATURES AND THERAPEUTIC MANAGEMENT

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Introduction: The Lambert-Eaton myasthenic syndrome (LEMS) is a rare neuromuscular junction disorder, mediated by paraneoplastic (P-LEMS) or primary auto-immune mechanisms (NT-LEMS). Patients typically present proximal muscle weakness, autonomic dysfunctions, and reduced tendon reflexes. High frequency repetitive nerve stimulation (RNS) shows an incremental response of compound muscle action potential (CMAP) amplitude. Furthermore, antibodies against presynaptic P/Q-type voltage-gated calcium channels (VGCC-Ab) are detected in 85–90% of patients.

Patients and Aim: We report herein a cohort of 12 patients affected by LEMS to describe clinical, neurophysiological, and therapeutic features along a median follow-up of 7,5 years (range 1-25 years).

Results: Our cohort includes 8 males and 4 females, with a mean age of 51,3 years old (SD ±17,5; range 10-80 years) at onset, characterized by difficulty in raising from a chair and in climbing stairs (12/12 patients), and dysautonomia (10/12 patients). Small cell lung carcinoma was diagnosed simultaneously with LEMS in one patient, who died for cerebral metastasis 2 years later. Interestingly, another patient developed xerostomia, bulbar symptoms, and lower legs muscle weakness three months after SARS-CoV-2 infection. All patients presented an increase of CMAP amplitude from a distal muscle after muscle maximum contraction. Six patients were tested positive for VGCC-Abs. All patients have been treated with 3,4-diaminopyridine, in addition with prednisone in eight cases and azathioprine in two of them. Moreover, two patients needed rescue therapy such as plasmapheresis and immunoglobulin at the onset or during the disease. After therapy, 58% of patients presented an improvement of at least 2 points in MG-ADL.

Conclusions: LEMS is a rare and insidious disorder, frequently misdiagnosed due to the non-specific clinical features. Neurophysiological studies and VGCC-Abs can allow a correct diagnosis to early detect a possible associated neoplasm and to start therapy, impacting positively on patients' quality of life and survival.

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## EFFECT OF AGE ON METABOLOMIC CHANGES IN A MODEL OF PACLITAXEL-INDUCED PERIPHERAL NEUROTOXICITY

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Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common dose-limiting side-effects of paclitaxel (PTX) treatment. Many age-related changes have been hypothesized to underlie susceptibility to damage or impaired regeneration/repair after nerve injury. The results of these studies, however, are inconclusive and other targets, which might be used as potential biomarkers of nerve impairment, need to be investigated.

Methods: Twenty-four young (2 months of age) and 24 adult (9 months of age) Wistar male rats were randomized to either paclitaxel (PTX) treatment (10 mg/kg i.v. once/week for 4 weeks) or vehicle administration. Neurophysiological and behavioral tests were performed to investigate nerve damage at baseline, after 4 weeks and the 2-week follow-up period. Skin biopsies from sacrificed animals were examined for intraepidermal nerve fiber (IENF) density assessment. Blood and liver samples were collected for targeted metabolomics analysis using Ultra-Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS/MS).

Results: At the end of treatment, the neurophysiological studies revealed a reduction in sensory nerve action potential amplitude ($p<0.05$ ) in the caudal nerve of young PTX-treated animals, and in both the digital and caudal nerve of adult treated animals ($p<0.05$). Behavioral tests revealed a significant decrease in the mechanical threshold in young PTX-treated animals ($p<0.001$), while adult treated rats showed no significant difference in mechanical threshold compared to controls. Concerning IENF assessment, both young and adult PTX-rats had reduced IENF density ($p<0.0001$), which persisted at the end of follow-up. Targeted metabolomics analysis showed significant differences in the plasma metabolite profiles between PTX-treated animals developing peripheral neuropathy and age-matched controls, with triglycerides, diglycerides, acylcarnitines, carnosine, long chain ceramides, sphingolipids, and bile acids playing a major role in the response to PTX administration.

Conclusions: Our study identifies for the first time multiple related metabolic axes involved in paclitaxel-induced peripheral neuropathy and suggests age-related differences in CIPN manifestations and in the metabolic profile.

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## CONCOMITANT PERIPHERAL AND CENTRAL NERVOUS SYSTEM DEMYELINATION AFTER INFLIXIMAB THERAPY IN CROHN'S DISEASE: DOUBLY RARE, DOUBLY TROUBLE

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Background: Infliximab is a monoclonal antibody belonging to Tumor necrosis factor-alpha (TNF-alpha) blockers, approved for treatment of several inflammatory diseases. However, side effects related to their use are described, including also uncommon cases of central or peripheral neuroinflammatory disorders.

Case Description: A 40-year-old female patient suffering from Crohn's disease since 2020 and treated with Infliximab since October 2022, came to our attention due to paresthesias in the four limbs. Hands paresthesias have been present since February, while feet paresthesias appeared after the third infusion of Infliximab in March 2023. At neurological evaluation, tactile hypoesthesia below knee level bilaterally and both proximal and distal weakness in the lower limbs were showed, in association with brisk deep tendon reflexes at four limbs. Electrophysiological study documented a diffuse sensitive-motor demyelinating pattern. CSF analysis revealed mild damage of the blood-CSF barrier, with pathologically increased albumin quotient and intrathecal IgM synthesis. Searching for peripheral antinerve and anti-onconeural antibodies showed low positive antibody titer for Anti GT1a and Anti GQ1b IgM gangliosides. A diagnosis of chronic inflammatory peripheral neuropathy was done. Due to the presence of unusual headache, in the suspicion of CSF hypotension, a brain MRI was performed with the unexpected finding of non-enhancing hypointense diffuse multiple areas in T1 sequences. No further lesion on cervical and upper dorsal spine were found. The patient was initially treated with high-dose corticosteroids, without significant benefit and subsequently with intravenous immunoglobulins at the standard dosage of 0.4 grams/kg/day for 5 days, with improvement of the clinical picture.

Discussion and Conclusions: Some cases of inflammatory demyelinating lesions of the peripheral or central nervous system are described in literature in patient treated with Infliximab. The mechanism of developing disymmune disorders is not clear, nevertheless some evidences support the hypothesis of a causal association. Co-incidence of peripheral and central demyelinating signs, as here reported, is more rare, underlying the importance of strict therapy surveillance and caution in use of TNF-alpha blockers.

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## RAPIDLY PROGRESSIVE CRANIAL MULTIPLE NEUROPATHY: A TOUGH DIAGNOSIS, WHILE THE TIME IS RUNNING OUT

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Getting to a diagnosis when a cranial multiple neuropathy occurs may not be easy, especially considering how frequent are overlap cases.

Case-report: A 42-year-old man was admitted to Neurology clinic of Policlinico Tor Vergata for subacute onset of saddle anesthesia

and cranial multiple neuropathy. The latter begun with unilateral left lower face paralysis, sensorineural hearing loss, vertigo, diplopia, and nystagmus. The patient had a 12-year clinical history of multiple sclerosis currently on Teriflunomide 14mg/d, primary intracerebral hemorrhage 8 years before, lung adenocarcinoma in remission treated with surgery, chemo- and radiotherapy the previous year. Two weeks before he had been vaccinated against SARS-CoV-2 and influenza. The symptomatology rapidly evolved within a month, causing dysphagia, dysarthria, facial diplegia, right hemifacial dysesthesia, and tongue, pharyngeal, and sternocleidomastoid unilateral weakness. In addition, he complained paresthesia with tingling-like sensation in hands and feet, tendon reflexes in the lower limbs were absent. The brain MRI showed enhancement of the optic nerves, optic chiasm, left oculomotor, trigeminal, statoacoustic and facial nerves, and the nerve roots of the cauda equina. Furthermore, there was evidence of tissue thickening in both ear canals and Meckel's cave. The demyelinating lesions were the same as those of previous MRIs, in absence of contrast-enhancement. Whole-body 18F-FDG-PET/CT was unremarkable. Serum ACE level was within normal range. The Cerebrospinal Fluid (CSF) analysis excluded infectious causes and showed hyperproteinorrachia (184.00 mg/dl), and mild pleocytosis (32.0 mmc), with CD4/ CD8 ratio equal to 4 and CD19+ cells. In the CSF were later identified isolated atypical epithelioid cells, suggestive of localization of lung adenocarcinoma. Eventually Anti-Glutamic Acid Decarboxylase (GAD) and Anti Glutamate Receptor 3 (GluR3) Antibodies were identified in both serum and CSF.

Discussion: Considering the subacute onset, the clinical and paraclinical picture, suspicion of Miller-Fisher or paraneoplastic syndrome were raised, and the patient was treated with methylprednisolone, intravenous immunoglobulins and eventually plasmapheresis, without benefits. The diagnostic workup was carried on, ultimately considering as the most reasonable the neoplastic or dysimmune etiopathogenesis [1]. Considering the results that came out later, the signs were attributed to meningeal carcinomatosis [2] and treatment with pemetrexed was set up [3].

Conclusion: The lack of standardized laboratory analysis for CSF, retrospective trials, and systematic nervous tissue biopsies made the diagnostic process so complicated. The presence of atypical epithelioid cells in CSF suggested a neoplastic etiology, nonetheless the detection of antiGluR3 and antiGAD antibodies, so far not associated with lung adenocarcinoma, should be considered as a culprit or a bystander?

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## A NOVEL MISSENSE VARIANT IN THE ACADVL GENE IN A PATIENT WITH VLCAD DEFICIENCY: A CLINICAL AND GENETIC STUDY

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Objectives: Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is a rare autosomal recessive long chain fatty acid oxidation disorder caused by mutations in the ACADVL gene. The myopathic form presents with exercise intolerance, exercise-related rhabdomyolysis and muscle pain usually starting during adolescence or adulthood. We report clinical and genetic findings of a VLCAD subject carrying a novel pathogenic mutation in ACADVL.

Patients and Methods: A 17-year-old boy presented with exercise-induced muscle pain and fatigue since his childhood. In the recent clinical history, episodes of exercise-related severe hyperCKemia and myoglobinuria were reported. A neurophysiological, myopathological and biochemical assessment was carried out. A 34 gene panel NGS analysis for metabolic myopathies and a familial segregation analysis were conducted.

Results: Electromyography and electroneurography were normal. Muscle biopsy showed "moth-eaten" fibers, and mild increase in lipid storage in muscle fibers. PAS staining was normal. NGS analysis displayed the already known heterozygote c.1769G>A (p.Arg590Gln) variant and the unreported heterozygote c.523C>T (p.Gly175Arg) change in ACADVL both having disease causing prediction. Healthy mother and father were heterozygous for c.523T>C and c.1769G>A respectively. Plasma acylcarnitine profile revealed high long chain acylcarnitine species levels, especially C14:1.

Discussion: The very long-chain acyl-CoA dehydrogenase is an enzyme that catalyzes most of the dehydrogenation of mitochondrial palmitoyl-CoA in liver, heart, and skeletal muscle. Clinical, histopathological, biochemical and genetic tests support the diagnosis of VLCAD deficiency in our patient. The report of a novel pathogenic missense variant in ACADVL expands the allelic heterogeneity of the disease.

Conclusions: VLCAD is a very rare metabolic myopathy; prompt diagnosis is essential for early starting a specific diet and avoiding prolonged fasting and strenuous exercise in order to minimize muscle damage and slow the disease progression.

## FOCAL NERVE ENLARGEMENT AND HYPERVASCULARIZATION IN COMPARTMENTAL SYNDROME: A SINGLE CENTER RETROSPECTIVE STUDY

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Background: Compartmental syndrome (CS) is a potentially highly disabling but treatable disease defined by increased intramuscular pressure within a defined anatomic fascial compartment. In addition to muscular injury, elevated pressure around the nerve can inhibit local vascular flow resulting in nerve ischemia. The role of electrodiagnostic studies in differentiating nerve injury from muscle damage is limited. Data on nerve morphology by ultrasound techniques are still scarce.
Aim: To characterise the ultrasound features of peripheral nerve involvement in CS.

Methods: Retrospective study on patients with CS referred for nerve ultrasound from January 2016 to May 2023. Demographic, clinical and ultrasound parameters were collected.

Results: We identified 9 patients (median age 57.7, IQR 44.7-61.3; 7/9 men). Lower limbs were involved in 6/9 cases, 1 case presented a bilateral involvement. The following etiologies were identified: ischemic reperfusion injury (n=4), trauma (n=2), regional hematoma (n=1), complex regional pain syndrome (n=1), intensive care unit

(n=1). Ultrasound showed evidence of focal nerve injury (oedema, increased cross-sectional area) in all patients (peroneal nerve=7, tibial nerve=5, sciatic nerve=4, median nerve=3, ulnar nerve=2, posterior interosseous nerve=2). The median cross-sectional areas of the involved nerves were: peroneal nerve, 17 sqmm [IQR 14.5-18.5]; tibial nerve, 51 [IQR 50-52]; sciatic nerve, 72.5 [IQR 55-90]; median nerve, 12.5 [IQR 11.75-13.25]; ulnar nerve, 12 [IQR 12-12]; posterior interosseous nerve 6.5 [IQR 6.3-6.8]. All patients developing CS after an ischemic-reperfusion injury, and one patient who presented CS in intensive care unit during COVID infection, showed large tortuous vascularization located within the nerve and adjacent to the epineurium. In 4/5 patients, these abnormalities were proximal to the CS site. Hypervascularization was observed early after the CS (median time of first evaluation, 1.37 months [IQR 1.1–2.3]) and was persistent at follow-up in all patients (median, 12.5 moths [IQR 57.7-61.8]).

Conclusion: Nerve damage after CS appear as a focal increase in CSA. A subgroup of patients with ischemic-reperfusion injury shows vascular abnormalities in the affected nerve. This finding can possibly be related to the release of vascular growth mediators during the hypoxic phase and the increased downstream resistance in the distal vessels during CS. The impact of our findings on treatment and prognosis of CS needs further studies.

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## ACUTE ONSET ANTI-MAG NEUROPATHY WITH PARADOXICAL RESPONSE TO RITUXIMAB: A CHALLENGING CASE


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Introduction: Anti-myelin-associated glycoprotein (anti-MAG) neuropathy is typically a chronic, progressive, predominantly sensory distal and demyelinating neuropathy, with ataxia and postural tremor. Herein we describe an atypical case of anti-MAG neuropathy.

Case Report: A 60-year-old man developed acute lower limb weakness and severe ataxia with difficulty in stance and walking. He was admitted to ER where received a diagnosis of Guillain-Barrè Syndrome (GBS) and was treated with intravenous immunoglobulin (IVIG) with mild improvement. Nerve conduction study (NCS) was consistent with a demyelinating GBS. After 6 months the patient worsened and was treated again with IVIG that were uneffective. Neurological examination showed severe sensory ataxia, marked lower limb distal muscle weakness, and gait was possible with unilateral aid. Deep tendon reflexes were reduced at upper limbs and absent at lower limbs. Distal postural tremor was observed at upper limbs. NCS confirmed demyelinating sensory-motor neuropathy and highlighted disproportionate distal nerve conduction slowing. Cerebrospinal fluid analysis showed mild protein increase (78 mg/dl) and laboratory testing revealed an IgM k monoclonal component. A diagnosis of paraproteinemic neuropathy with anti-MAG was advanced. Anti-MAG antibodies tested positive at high titer (88000 BTU; ELISA assay). The patient underwent intravenous methylprednisolone (500 mg/die for 5 days) unsuccessfully and after having received anti-MAG antibodies results, Rituximab treatment was started (1000-mg IV infusion at Day 1 and Day 15). Few days later the second infusion the patient experienced a dramatic clinical worsening and the patient became wheelchair-bound. Therefore, Plasma Exchange (PE) was started with neurological improvement that persisted at 6-month follow-up. Genetic analysis for MYD88 gene mutation was negative.

Conclusions: The present case shows some atypical features: the GBS-like onset that is uncommon (2%) in anti-MAG neuropathy and the paradoxical response to Rituximab that is the choice treatment for anti-MAG neuropathy. Such worsening is probably due to IgM flare related to B-lymphocyte lysis with resultant release of intracellular paraprotein and PE is typically the rescue therapy. Looking for MYD88 gene mutation (L265P) (60% of anti-MAG neuropathy) may be useful in case of unsatisfactory response to rituximab since alternative treatments are available (BTK inhibitors).

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## MYOFIBRILLAR AND DISTAL MYOPATHY: NATURAL HISTORY OF AN ITALIAN COHORT OF PATIENTS


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Introduction: Myofibrillar myopathy (MFM) identifies a group of hereditary myopathies characterized by disorganized myofibrils with cytoplasmic inclusions. Distal myopathies (DM) are a genetically heterogeneous group of muscle disorders with prevalent weakness in the distal part of upper and lower limbs. Both diseases showed phenotypic heterogeneity and variable natural history. Aim of this study is to longitudinally assess the disease progression of MFM and DM in an Italian cohort of patients.

Methods: Patients diagnosed with MFM and DM were prospectively enrolled in three Italian neuromuscular centre, and they were evaluated on a yearly basis. The evaluation included full neurological examination with North Star Ambulatory Assessment and timed tests (get up from floor and chair) and IBM-FRS.

Results: We present here the data for the first year (T1) of follow-up of the included cohort. A total of 58 patients, 26 males and 32 females, were enrolled. Mean age at first evaluation was 49.3 years (range= 18-84) and we collected data at baseline, and T1 (1 years follow up) and T2 or T3 (2 and 3 years follow up respectively). The most common mutated genes were DES and GNE (n=8 pts), followed by DNAJB (n=7 pts) and DYSF and PLIN4 (n= 6 pts). Mean IBM-FRS and NSAA scores at baseline were 30,5 ±9,2 and 20 ±12,1, respectively. At baseline 44 patients (75,8%) were able to get up from the floor and the mean time was 7,19” (1,38”- 45,36”), 14 patients (24%) were unable to perform the test. At baseline only 8 patients (13,7%) can’t get up from the chair, mean time was 2,66“(0,58”- 27,51”) for the others 50 (86%). 31 patients reach T1 follow-up. We consider T1 follow up: IBM-FRS improved in 7 patients, 22,5% of the cases (+ 3,375, range of 1-8), remain stable in 9 patients, 29%, and had a reduction of -2,2

points (range 1-8) in 15 patients, 48,3%. NSAA score remain stable in 14 patients, 45%, has a reduction of 3pts (range 1-7) in 15 patients, 48,3%, and improve of 1 points in 2 patients, 6,4%. 3 patients at T1 visit lost capability to get up from the floor, mean time was 5,25" (1,24-16,96"), and 2 patients lost the ability to get up from the chair, the remain patients have a mean time of 3,11" (0,71"-8,47").

Conclusion: Our preliminary data suggest a disease stability or mild worsening according to NSAA and, to a lesser extent, IBM-FRS at one-year follow-up.

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## ACUTE ONSET OF DYSESTHESIAS AND PARESTHESIAS


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Introduction: Multiple cases of small fiber neuropathy following acute infection due to COronaVIrus Disease 2019 (COVID-19) have been reported in literature. Multiple case reports also described peripheral neuropathies after administration of the COVID 19 vaccine, including Guillain Barrè syndrome and small fiber neuropathy (SFN). The latter represents a peripheral neuropathy involving A-delta and C nerve fibers causing neuropathic pain and autonomic complaints. It can develop due to primary (genetic) or secondary causes. Main symptoms include sensory alterations, pain, dysautonomia. SFN patients can become disabled with relevant economic, familiar and psychological consequences. As the time of February 2023, 13 case reports of post-vaccination small fiber neuropathy had been reported.

Materials and Methods: Our patient, a 48 year old Caucasian man, was hospitalized due to acute tingling paresthesias and burning-stabbing dysesthesias involving four limbs distally and simmetrically, starting seven days after first dose administration anti COVID 19 vaccine (Cominraty). He also referred generalized weakness and hypotension. He performed routine blood tests, resulting all normal. His medical history was normal and he denied family history of neuromuscular disorders. Neurological examination showed mild thigh-to-pelvis flexion (3/5 according to the Medical Research Council-MRC scale) and leg-to-thigh extension (4-/5 bilateral MRC) weakness. He complained of dry mouth and reduced tearing. He performed brain and spinal cord magnetic resonance, screening tests for peripheral neuropathies, a thoraco-abdominal computed tomography, an esophagogastroduodenoscopy, electromyography, lumbar puncture, somato-sensory evoked potentials. which resulted all normal.

Results: Thigh small fiber biopsy showed a reduction in intraepidermal nerve fiber density (IENFD). Symptoms slightly improved to a combination therapy including gabapentin, amitriptylline and supplements.

Discussion: In our opinion temporal correlation between COVID 19 vaccine administration and the development of neuropathic symptoms seems to demonstrate its role in the pathogenesis of SFN, thus expanding existing literature. In previously reported cases SFN can be mild or severe and may or may not require treatment.

Conclusions: We suggest to consider small fiber neuropathy as a possible, even rare side effect of COVID 19 vaccinations in order to promptly recognize and treat it.

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## ACTN2-RELATED MYOPATHY: EXPANDING PHENOTYPING, HISTOPATOLOGICAL AND GENETIC SPECTRUM


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Background: The ACTN2 gene encodes the alpha-actinin-2 protein expressed in skeletal and cardiac muscle. Variants in ACTN2 have been first associated with cardiomyopathy and with an adult-onset form of distal myopathy named Adult-Onset Distal Myopathy 6 (MDP6; OMIM #618655) and a more severe condition named Congenital Myopathy with Structured Cores and Z-Line Abnormalities (Myocoz; MSCD; CMYP8; OMIM #618654).

Patient and Methods: A 48-year-old male presented with progressive distal lower limb and facial weakness since the age of 25. His mother has had scapulo-peroneal myopathy since the age of 40. They were diagnosed as having atypical FacioScapuloHumeral Muscular Dystrophy by a 32 kb D4Z4 fragment on chromosome 4. Proband's neurological examination showed limb muscle weakness and atrophy predominantly involving the distal segments associated with moderate upper and lower facial muscle weakness. A neurophysiological, myopathological, and imaging assessment was carried out. An NGS analysis for distal myopathies and a familial segregation analysis were conducted.

Results: Electromyography showed diffuse myogenic signs, more evident in the distal segments of the lower limbs. CK, LDH, and lactic acid were within normal limits. Cardiological examinations did not show signs of structural heart disease. Muscle MRI showed fat infiltration and atrophy of leg muscles. Multiple fibers with single central core-like abnormalities and rimmed vacuoles were observed on muscle biopsy. The NGS study highlighted the presence of the 2624_2625dup

(Pro876Cysfster26) mutation in the ACTN2 gene, resulting in a change in the reading frame and a prediction of pathogenicity.

Discussion: Myocoz is a congenital condition with facial weakness, a cleft palate, and diffuse muscle weakness. Muscle biopsy usually shows rimmed vacuoles and central cores. MDP6 usually presents in adulthood and is characterized by slowly progressive distal muscle weakness primarily affecting the lower limbs and resulting in gait difficulties, drooping foot, and muscle atrophy. Facial, respiratory, and cardiac muscles were usually unaffected. Some patients may develop proximal and upper-limb muscle weakness. Muscle biopsy may show increased numbers of internal nuclei, rimmed vacuoles, and fibrotic or fatty replacement. Our patient presents clinical and histopathological features of intermediate severity between Myocoz and MDP6, characterized by a predominantly distal involvement associated with facial weakness and central cores and rimmed vacuoles on muscle biopsy.

Conclusions: Our study helps to further expand the ACTN2-related disease spectrum of manifestation, suggesting that it is a complex and more heterogeneous condition than previously believed. Phenotypes intermediate between the severe congenital and adult distal forms may be observed and easily misdiagnosed as other myopathies.

## LAMOTRIGINE AS AN ANTI-MYOTONIC AGENT IN MYOTONIC DYSTROPHY TYPE 1: AN OPEN-LABEL SINGLE-CENTER PILOT STUDY

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Objectives: The primary objective of our study was to evaluate the safety and efficacy of lamotrigine in treating myotonia in patients affected by Myotonic Dystrophy type 1. Secondary objectives were to assess the impact of treatment with lamotrigine on quality of life and the lowest effective dose for treating myotonia.

Patients: In this open-label pilot study, we included adult patients with clinical myotonia affecting daily living and genetically confirmed DM1. Myotonia was observed in eye orbicular muscles, hands, and/or leg muscles and affected daily living with a MBS score greater than or equal to 1. We excluded patients with concomitant treatment with mexiletine.

Methods: All patients received lamotrigine at an increasing dosage every 3 weeks, starting from 50 mg/daily up to 400 mg/daily. The primary outcome was a change in the severity score of myotonia (Myotonic Behavior Scale -MBS) as reported by the participants. The 9-Hole Peg Test (9HPT), the SF-36 questionnaire, and other tasks of daily living, such as disassembling a coffee maker and putting some coins in a wallet, were also assessed.

Results: We enrolled 14 DM1 patients. The medium age at enrollment was 43, and the latest follow-up available was after 12 months. The medium MBS score at baseline was 3.21, while at the last follow-up it was 2.43 ($p<0.05$). At baseline, medium 9HPT time was 38.7 seconds in the dominant hand and 49.6 seconds in the other hand, while at 200 mg daily, we found an improvement in both the dominant (32.1 seconds, $p<0.05$) and non-dominant hands (40,6 seconds, $p<0,05$). Clinical improvement in the other daily-living tasks tested was also observed. No further improvement was detected at 400 mg daily. The SF-36 questionnaire showed a statistically significant improvement in all domains. No significant adverse events were recorded; only a patient with a mild skin rash was reported.

Discussion: Our study showed that lamotrigine was safe in DM1 patients. Our data demonstrated a global improvement in both motor tasks and quality of life assessment that was evident already at the dosage of 200 mg daily. These improvements were not correlated to a further dose increase to 400 mg, suggesting a possible "ceiling effect".

Conclusions: Our pilot study shows very encouraging findings on using lamotrigine as an anti-myotonic agent in DM1 patients and should lead to the confirmation of these results on a large scale in controlled studies.

## BAD THINGS COME IN THREES: KEEP ALERT FOR GUILLAIN-BARRÉ SYNDROME

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Objective: Guillain-Barré syndrome (GBS) is a rare neurological disorder characterized by progressive muscle weakness and paralysis, often triggered by an antecedent infection, but an increasing number of reports suggests that surgery could be a potential trigger event.

Materials and Methods: We describe the case of a 64-year-old woman with a history of multiple sclerosis (MS), who underwent a craniotomy for left middle cerebral artery aneurysm clipping. The surgery was further complicated by a subdural hematoma and a subsequent mild right hemiparesis with hyperreflexia. Five days after surgery, the patient developed subacute dysarthria, dysphagia, and gait difficulties. One week later, neurological examination was remarkable for progressive paraparesis, areflexia, and autonomic dysfunction characterized by tachycardia, poor blood pressure control, constipation, and bladder dysfunction.

Results: Diagnostic procedures included brain and spinal cord magnetic resonance imaging (MRI) with gadolinium, which showed new T2-lesions without enhancement, compatible with MS; the subdural hematoma remained stable, and lumbar rootlets enhancement was observed. Electrophysiological studies demonstrated acute axonal and demyelinating, motor and sensory polyradiculopathy. These radiological and neurophysiological findings support our clinical hypothesis of GBS. Lumbar puncture was not performed due to the presence of the subdural hematoma. Intravenous immunoglobulin treatment (2g/kg) was administered, and within two weeks significant clinical improvements were observed in terms of lower limb strength, dysphagia, and autonomic dysfunctions.

Discussion: This case underscores the potential association between surgery and the onset of GBS, emphasizing the need to consider GBS as a possible diagnosis, particularly in patients with pre-existing neurological conditions, even in the absence of recent infections.

Conclusion: Timely recognition and appropriate management of GBS can significantly improve patient outcomes and prevent potential complications associated with delayed diagnosis or misdiagnosis. Further research is warranted to better understand the underlying mechanisms and risk factors associated with the development of GBS following surgery.

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## CYTOKINES IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY AND MULTIFOCAL MOTOR NEUROPATHY: FROM PATHOGENESIS TO POTENTIAL BIOMARKERS AND TARGET OF IMMUNOMODULATORY THERAPIES. A SYSTEMATIC REVIEW

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Objectives: Advances in cytokines understanding revolutionized treatment of rheumatoid arthritis and other autoimmune diseases. The aim of the study was to investigate the role of cytokines in Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) and Multifocal Motor Neuropathy (MMN) through a systematic review of the literature.

Material and Methods: Ovid Medline, EMBASE and Web of Science were searched until August 31st 2022 for studies investigating cytokines levels in CIDP or MMN patients. Data were extracted according to a predefined protocol.

Results: Fifty-five articles on 1061 CIDP patients and 86 MMN patients were included (median of 18 patients per study, range 3-71). Studies differed in type of assay, manufacturer and control subjects. A minority of studies reported data on disease activity. Thirty studies tested cytokines in peripheral blood, 9 in cerebrospinal fluid, 10 in both, and 6 in nerve biopsy. IL6, IL17, CXCL10, and TNF-alfa, resulted increased in CIDP patients in most of the studies compared to controls. IL-6 and TNF-alfa levels also correlated with disability, TNF-alfa with therapeutic response and CXCL10 with clinical phenotypes in CIDP. In MMN patients, IL-1Ra resulted elevated in majority of studies.

Discussion and Conclusions: Our results suggest that IL6, IL17, CXCL10, and TNF-alfa might have a role in CIDP pathogenesis, and that more data are needed in MMN. The major limits or the review are the small sample size, particularly in MMN, and the wide heterogeneity of the studies. Further investigations on larger cohorts with a prospective design are needed to evaluate selected cytokines as pathogenic factors, biomarkers for disease monitoring and possible therapeutic targets.

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## ATTENUATED TOTAL REFLECTION-FOURIER TRANSFORM INFRARED SPECTROSCOPY (ATR-FTIR) IN MUSCLE DISEASES

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Objectives: Inherited muscle diseases are a heterogeneous group of clinical conditions, characterized by histological and functional abnormalities of skeletal muscle. Attenuated Total Reflectance (ATR) is one of the sampling technologies used for infrared spectroscopy and, as a rapid and non-destructive technique, it is increasingly used in different biological applications. The aim of this study was to evaluate whether the biochemical profile determined by the ATR-Fourier transform infrared (FTIR) spectroscopic technique would allow to distinguish patients affected by late-onset Pompe disease (LOPD), Becker muscular dystrophy (BMD), limb-girdle muscular dystrophies (LGMD), and healthy subjects (HS).

Methods: A total of 40 participants were included: 11 LOPD, 10 BMD, 10 LGMD, 9 HS. For ATR-FTIR, muscle samples were cut at 10 μm in cross-section and placed onto diamond/ZnSe crystal for spectral analysis.

Results: The results obtained show that the spectroscopic fingerprint embeds sufficient information to allow a correct classification of the majority of participants in three groups: dystrophic (BMD and LGMD) and metabolic (LOPD) myopathies, healthy subjects (accuracy 88.4±7.1%). The ATR-FTIR analysis was also effective in classification rates using a two-class model: LOPD vs LGMD (accuracy 95.7±3.2%), LOPD vs BMD (accuracy 82.9±4.6%) and LOPD vs BMD+LGMD (accuracy 93.4±3.0%).

Discussion and Conclusion: In conclusion, our data suggest that ATR-FTIR profile is a reliable diagnostic biomarker for LOPD, BMD and LGMD. Future directions will include evaluating its role as a prognostic biomarker in these genetic diseases, also analyzing biofluids, and the ability of this technique to shed light on the underlying pathogenic mechanisms.

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## DESCRIPTION OF A CASE OF WIEACKER-WOLFF SYNDROME IN A FEMALE PATIENT WITH A NEW MISSENSE MUTATION IN ZC4H2 GENE

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Objectives: Wieacker-Wolff syndrome is an X-linked neurodevelopmental disorder, caused by hemizygous or heterozygous mutation in the ZC4H2 gene. The clinical features are characterized by severe intellectual disability and symptoms of central and peripheral nervous system involvement, such as spasticity, hyperreflexia, muscle weakness and arthrogryposis in male. Female may be asymptomatic or often mildly affected. ZC4H2 is a gene subject to X-inactivation. The variable clinical manifestations of heterozygous carrier females with a "de novo" variant may be explained by the X-inactivation status within specific affected cells and tissues.

Materials and Methods: The patient was extensively investigated performing neurological examination, blood analysis including endocrinologic and profile as well as autoimmunity, Whole genome sequencing, neuropsychological evaluation using Weschler Intelligence Scale of Children (WISC-III), Electromyography with nerve conduction studies, acoustic, visual, motor and sensory Evoked Potentials, peripheral nerve ultrasound and muscle MRI.

Results: The patient has a phenotype characterized by mild axonal polyneuropathy with cranial nerves involvement and some CNS signs. She also has markedly curly hair and metabolic dysfunctions. Whole genome sequencing showed a missense mutation in ZC4H2 gene that results in the substitution Pro201His. Nerve ultrasonography highlighted reduced cross-sectional area of upper and lower limbs nerves.

Conclusions: We described the phenotype of a new mutation in ZC4H2 never reported before. The clinical phenotype of our patient extends the spectrum of this syndrome being different from the ones already present in literature. Considering the described phenotype, Wieacker-Wolff syndrome is a possible differential diagnosis with Charcot-Marie-Tooth and Congenital myasthenic syndrome.

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## SEARCH PROGNOSTIC FACTORS IN GUILLAIN-BARRÉ SYNDROME

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Objective: We retrospectively collected the data of 69 patients (49 M; 20 F) with definite Guillain Barré syndrome according to Brigthon Criteria, admitted in neurological unit of AOU San Giovanni di Dio e Ruggi D'Aragona (Salerno, Italy) between January 2009 and December 2022. This study aims to compare our cohort with those already reported in current literature and to research possible prognostic factors that may be useful to the clinician in managing the disease.

Methods: We collected: clinical findings, previous infectious disease history, routine laboratory examination, autoantibodies classically correlated to GBS and its variants, autoimmune screening. Furthermore we have evaluated the two neurophysiological studies (first within 7 days from onset and second after treatment or within 14 days from onset), CSF analysis, lumbosacral MRI and outcome at discharge.

Results: In 37 (54%) patients, clinical onset was preceded by infectious symptoms: diarrhea (11/37), upper respiratory tract infection (13/37), other infections (11/37), sars-cov2 vaccination (1/37), sars-cov2 infection (1/37). In 52/69 albumino-cytological dissociation was found (proteins > 45 mg/dl, cells < 5). Anti-ganglioside autoantibodies were found in 7/35 patients. Axonal pattern was found in 15/69 and the demyelinating in 47/69 patients. Typical phenotype was found in 59/69 patients (87%), atypical in 13/69 (13%). 68/69 received intravenous immunoglobulin (IVIG). Plasmapheresis was performed as first line treatment just in 1 case due to IgA deficiency; as second line, 3 out of 5 cases received IVIG, while the other two went through plasmapheresis. According to GBS Disability Scale, the prognosis was largely favorable at discharge (0-2 score in 71%), especially in patients with demyelinating pattern, severe disability was 19% (3-5 score), mortality was almost 10%. At 12 months follow up, about 70% of patients walked without any support.

Discussion and Conclusion: Our results are largely comparable with the Western series: male prevalence (70%), demyelinating pattern (71%), typical phenotype (87%), respiratory and gastrointestinal infections were the most common preceding the clinical onset, without any prognostic correlation with one of them or with the time from infection to clinical onset. We found no correlation between albumino-cytological dissociation, MRI roots enhancement or anti-ganglioside autoantibodies and prognosis. The IVIG remain a pillar of GBS treatment and the more-timely administration could correlate with a better prognosis. Long term outcome analysis confirmed that if GBS is rightly treated had a good prognosis.

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## NFL AS A BIOMARKER FOR ATTRV AMYLOIDOSIS: A SINGLE CENTRE EXPERIENCE

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Background: Hereditary transthyretin amyloidosis (ATTRv) is an autosomal dominant, adult-onset progressive systemic disease predominantly involving the peripheral nervous system and the heart [1]. Previously, biomarkers of peripheral nerve disease have focused on neurophysiological parameters. Even if these remain necessary for the diagnosis of peripheral neuropathies, due to the high expertise required, inter-operator variability and lack of sensitivity and responsiveness, its use as a biomarker of disease progression over time is limited [2]. Neurofilament light chain (NfL) are a neuronal protein that is released into the serum and cerebrospinal fluid when damage to the nervous system occurs. A few studies show NfL has been proved to be a promising biomarker to assess the state of the disease in ATTRv amyloidosis [3].

Aim of the work: Our work aimed to highlights any correlations between the serum concentration of neurofilaments and the severity of the disease in patients with ATTRv amyloidosis.

Materials: We selected 38 patients with ATTRv undergoing treatment with Patisiran, Inotersen, and Tafamidis, along with 10 carriers and 7 healthy controls. Patients and carriers were divided into 4 groups based on the main mutations present (Glu89Gln, Phe64Leu, Phe84Leu, and Thr49Ala). Serum NfL concentrations were determined using the ultrasensitive single-molecule array assay (Simoa) analysis.

Methods: For each subject, we collected two serum samples, on which neurofilament measurements were taken at 3 different time points: baseline, after 6 months, and after 12 months. At each collection, patients were evaluated using mNIS (Modified Neuropathy Impairment Score) CMTES, FAP stage and PND score (familial

amyloidotic polyneuropathy), CADT (compound autonomic dysfunction test) to assess the neuropathy status, and BNP and Troponin to assess cardiac function.

Results: We observed that the serum concentration of neurofilaments is well correlated with the severity of neuropathy manifested by the patients, regardless of the type of treatment they undergo or the expressed mutation.

Discussion: NfL has recently garnered interest as a reliable biomarker in neurodegenerative diseases, particularly in ATTRv V30M amyloidosis [3]. This study confirms previous reports and extends the utility of NFL as biomarkers even in non-Met30 patients.

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## A RARE CASE REPORT OF TICK-BORNE ENCEPHALITIS (TBE) CAUSING PHARINGO-CERVICO-BRACHIAL BILATERAL PALSY, WITH NO CLINICAL INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM

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Objectives: We describe the case of a 74-year-old healthy man who met clinical and laboratory criteria of neuroinvasive tick-borne encephalitis (TBE) infection involving laryngeal recurrent, accessory, sovrascapular, axillary, muscolocutaneous, longus thoracicus, and phrenic nerves.

Materials and Methods: At the end of May, 2022, the patient started complaining of fatigue, drowsiness, and nausea. On 1st June he was admitted to our Neurology department, presenting with fever, headache, diffuse myalgia and polyarticular arthralgia. The IgM and IgG TBE antibodies were present in blood; anti-Borrelia Burgdorferi antibodies were negative. The patient lived in a rural area, anyhow he denied any tick borne. After 10 days from hospital admission, he presented severe weakness of the cervical paraspinal muscles with dropped head syndrome, hypophonia without dysphagia, bilateral upper cingulus palsy, and he was unable to walk autonomously. He had no alteration of consciousness, nor any meningeal sign. Brain and spinal magnetic resonance imaging (MRI) and EEG were unremarkable. Cerebrospinal fluid (CSF) analysis performed on 13th June revealed hyperproteinorrachia (144 mg/dL) without pleiocytosis and negative PCR test for TBE, confirmed also in blood and urine examinations. Repeat serological test for TBE was positive. Routine and standard electroneurographic (ENG) examination, including motor and sensory nerve conduction studies (Median, Ulnar, Radial, Tibial, Peroneal, and Sural nerves), F-waves, Blink reflex testing, and low-frequency repetitive stimulation, was normal. Unconventional nerves conduction studies from sovrascapular, axillary, muscolocutaneous, longus thoracicus, and phrenic nerves and ultrasound guided-electromyography (EMG) of sternocleidomastoid muscle and scaleni muscles revealed axonal damage and acute denervation. Patient was promptly treated with intravenous immunoglobulins (dosage of 2 g/kg), with a good clinical recovery. He underwent intensive rehabilitation treatment, obtaining further clinical improvement. After two months from hospital discharge, he was able to walk autonomously, to hold his head, and to raise his arms. He also had a complete recovery from hypophonia. The follow-up ENG examinations revealed progressively increased amplitudes of the compound motor action potentials (CMAPs) in the involved nerves.

Discussion and Conclusions: A 70 to 98% of TBE infections are asymptomatic. Meningitis or meningoencephalitis are most frequent clinical forms of TBE, whereas the cranial nerves involvement is rare and often asymmetrical [1,2]. When occurring with unusual clinical presentations and unremarkable routine diagnostic examinations, TBE diagnosis may be difficult, with increased risk of incomplete recovery and long-lasting morbidity.

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## CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY AND OPTIC NEUROPATHY: A CHANCE ASSOCIATION?

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Objective: Combined central and peripheral demyelination (CCPD) is a disease characterized by chronic inflammatory demyelination of peripheral nerves (CIDP) and central nervous system (CNS) involvement, mainly associated to N155 antibodies.

Methods: We report two CCPD patients presenting at the onset clinical and neuroradiological signs of monolateral optic neuritis (ON). In both patients it was performed brain and orbital MRI, neurophysiological study, visual acuity evaluation, tonometry, visual evoked potentials.

Case report: Case 1. A 59-year-old female reported acute onset of lower limb paresthesias and numbness, bilateral facial palsy. She also reported low visual acuity and pain during movements of left eye. The first dose of COVID-19 vaccine (ChAdOx1 nCov- 19) was administrated 15 days before. Cerebrospinal fluid examination (CSF) was consistent with albumino-cytologic dissociation (protein 74 mg/mL; 3 cells/1/4L). Repeated nerve conduction studies were consistent with CIDP (EAN criteria). Anti-gangliosides and nodal/paranodal autoantibody screening was negative. Brain MRI showed severe left ON (marked swelling with contrast enhancement). IVIG treatment slightly improved symptoms, high dosage of IV steroid did not improve visual acuity. Peripheral neuropathy was under control (25 mg of prednison), no visual function was recovered. Case 2. A 70-years-old male, with sars-cov2 infection about 2 months earlier, admitted to our department for progressive generalized hyposthenia, painful and tingling-type paresthesias at the lower limbs, low visual acuity in left eye. He progressively worsened becaming chairbound in 3 months. CSF examination revealed albuminocytologic dissociation (protein>50 mg/mL, cells<5/1/4L). Brain MRI demonstrated signs of left ON. Neurophysiological study was performed after six months from clinical onset and fullfied EAN criteria for CIDP. No anti-gangliosides or nodal/paranodal autoantibodies were found. IVIG and steroids treatment improved motor and sensory symptoms, but visual recovery remained poor. The patient required IVIG monthly.

Discussion: We report two CIDP patients (according EAN criteria) who developed also an ON. Few cases were reported in current literature of CCPD, usually associated with NF155 antibodies. We reported two CCPD patients not NF155 related. In both case, the peripheral phenotype improved regardless severity of onset, while the visual loss

did not respond to treatment (IVIG and prednison), and remained the major disability.
Conclusion: ON may be associated to CIDP, but the absence of NF-155 autoantibodies in our cases may suggest the possible involvement of new antigen that need to be studied.
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## ACUTE MULTIPLE CRANIAL NEUROPATHY: AN UNEXPECTED CASE


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Objective: Botulism is a rare, neurotoxin-mediated, life-threatening disease caused by a neurotoxin elaborated by Clostridium botulinum. The most know typical clinical syndrome of botulism refers to the foodborne form caused by ingestion of food contaminated by preformed botulinum toxin. Foodborne botulism intoxication is often underdiagnosed; the initial symptoms are not pathognomonic and can be confused with more common clinical conditions (i.e., stroke, myasthenia gravis, Guillain–Barré syndrome in Miller–Fisher variant, Eaton–Lambert syndrome, tick paralysis and shellfish or tetrodotoxin poisoning). The diagnosis of botulism is based on clinical suspicion, as well as the decision to apply the specific antidote. It is important to recognize symptoms and formulate an early diagnosis to not delay treatment.

Case Report: A 60-year-old woman with no risk factors was admitted in the Emergency Department (ED) with a 1-day history of nausea, vomiting and dizziness followed by diplopia. In the ED the neurologist evaluating her asked for CT and CT angiography scan that showed no abnormalities. Blood tests showed only mild anaemia and hyponatremia. Toxicology screening resulted negative. Few time later the patient presented with bilateral ptosis, fixed bilateral mydriasis and dysphonia. Botulism intoxication suspicion was made despite the patient denied exposure to contaminated foods and no other family members reported symptoms. Serum and stool samples were collected, and the botulinum antitoxin administrated. The day after the patient developed dysarthria, dysphagia, and urinary retention. During hospitalization electroneuromyography and lumbar puncture were not performed due to the patient's opposition. Few days later the patient remembered eating vacuum-packed zucchini bought in a superstore. During the hospitalization, the patient presented a progressive improvement of the symptoms and was discharged home after 15 days in good general conditions. Botulinum toxin was found in stool sample only.

Discussion: Botulism should be suspected in a patient who develops acute symmetric cranial nerve palsy followed by flaccid paralysis. The diagnosis is based on clinical presentation and epidemiological context. The identification of toxin is not necessary to definitive diagnosis. Therefore, is important to avoid delay in treatment and even to ensure the detecting and the best clinical management of any subsequent cases.

We presented a case of food botulism with rapid evolution and total clinical response to antidote in which diagnosis was promptly made based only on clinical suspicious, despite the patient denied in a first moment a history of exposure to contaminated foods.
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## UNCLASSIFIED CLINICAL PRESENTATIONS OF CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY


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The 2021 EAN/PNS guidelines have refined the diagnostic criteria for typical CIDP and its variants, posing more stringent clinical definition [1]. The efficiency of these criteria to successfully classify each patient into a specific category remains however unclear. To assess the

ability of the 2021 European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) clinical criteria for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) to include within their classification the whole spectrum of clinical heterogeneity of the disease and to define the clinical characteristics of the unclassifiable clinical forms. The 2021 EAN/PNS clinical criteria for CIDP were applied to 329 patients fulfilling the electrodiagnostic (and in some cases also the supportive) criteria for the diagnosis of CIDP. Clinical characteristics were reviewed for each patient not strictly fulfilling the clinical criteria (unclassifiable). At study inclusion, 124 (37.5%) patients had an unclassifiable clinical presentation, including 110 (89%) with a typical CIDP-like clinical phenotype in whom some segments of the four limbs were unaffected by weakness (incomplete typical CIDP), 10 (8%) with a mild distal, symmetric, sensory or sensorimotor polyneuropathy confined to the lower limbs with cranial nerve involvement (cranial nerve predominant CIDP), and 4 (1%) with a symmetric sensorimotor polyneuropathy limited to the proximal and distal areas of the lower limbs (paraparetic CIDP). Eighty-one (65%) patients maintained an unclassifiable presentation during the entire disease follow-up while 13 patients progressed to typical CIDP. Patients with the unclassifiable clinical forms compared to patients with typical CIDP had a milder form of CIDP, while there was no difference in the distribution patterns of demyelination. A proportion of patients with CIDP do not strictly fulfill the 2021 EAN/PNS clinical criteria for diagnosis. These unclassifiable clinical phenotypes may pose diagnostic challenges and thus deserve more attention in clinical practice and research.

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## BOTULINUM TOXIN TYPE A FOR NUMB CHIN SYNDROME

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Goal: Numb chin syndrome is a rare pain disorder characterized by decreased sensation and paresthesia in the territory of the mental nerve [1]. We describe a case of bilateral numb chin syndrome, secondary to Burkitt's lymphoma and characterized by the presence of persistent burning neuropathic pain, treated with Botulinum toxin type A (BoNT/A).

Materials: BoNT/A has proven to be effective in many neuropathic pain disorders [2]; however, there are no cases of neuropathic pain secondary associated with numb chin syndrome treated with BoNT/A.

Methods: The patient was treated with subcutaneous injections of BoNT/A (incobotulinumtoxinA, 100U/ml dilution), 10U on each side in the cutaneous territory of the mental nerve. The treatment was performed 12 times with a time interval between one injection and the other of 3-4 months.

Results: Each treatment was able to reduce basal pain significantly (8/10 vs 3/10 NRS) for 3-4 months. The procedure was well tolerated; the patient reported incomplete closure of the mouth of minimal entity that initiated 20 days after each treatment and lasted for 15 days.

Discussion: There are no cases of neuropathic pain associated with numb chin syndrome treated with BoNT/A. BoNT/A modulates neuropathic pain through the interference with the expression of TRPV1 on the plasma membrane of sensory fibers, dorsal root ganglia, and neurons in the central nervous system; moreover, it inhibits the release of CGRP and substance P in both the peripheral and central nervous system, interfering with the central and peripheral sensitization mechanism, and enhances the inhibitory opioid and GABA systems located in the dorsal horn and brainstem [3].

Conclusions: BoNT/A could be a safe and effective therapy for neuropathic pain associated with numb chin syndrome.

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## CHANGING PERSPECTIVES: NEW INSIGHTS FROM NERVE ULTRASOUND IN FRIEDREICH'S ATAXIA

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Background: Friedreich's ataxia (FRDA) is the most common cause of hereditary ataxia. It is a multisystem disease encompassing a wide spectrum of clinical manifestations. Frataxin mutation leads to a damage of the Peripheral Nervous System producing a sensory neuropathy, a key clinical feature in FRDA. Though Nerve Conduction Study (NCS) can easily detect a sensory neuropathy in FRDA, sensory nerve action potentials are usually severely reduced or absent thus implying a floor effect that hampers the utility of NCS in the diagnostic follow-up of FRDA patients (Creigh et al., 2019). In this clinical, neurophysiological and nerve ultrasound study we tested the usefulness of nerve ultrasound in the assessment of peripheral neuropathy in Friedreich's Ataxia.

Method: We prospectively enrolled 10 consecutive patients with a defined diagnosis of Friedreich's Ataxia. In the same day anamnestic data, neurological examination with functional and disability scales assessment (Scale for the Assessment and Rating of Ataxia (SARA), Inflammatory Neuropathy Cause and Treatment Disability Score (INCAT), Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL)), Nerve Conduction Study and peripheral nerves high-resolution ultrasound (HRUS) findings were collected. For each patient 24 nerve sites were quantitatively evaluated (Cross Sectional Area (CSA) assessment). CSA values were compared with 20 healthy volunteers.

Results: All the patients had a severe sensory axonal neuropathy (1 patient had a reduction of all sensory action potentials, the other 9 had absent sensory nerve action potentials). In FRDA, HRUS showed a significant nerve enlargement of the Median and Ulnar nerves at the axilla and at the arm ($p<0.001$). The total number of altered nerve sites directly correlated with clinical disability as assessed by SARA and INCAT score and inversely correlate with ADL and IADL.

Conclusions: Nerve ultrasound can highlight alterations along the nerves in Friedreich's Ataxia, mostly at the level of upper limbs. Nerve Ultrasound can provide information where NCS is no longer informative. Nerve ultrasound can be a valuable tool in the assessment of Friedreich's Ataxia.

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## EXPANDING THE CLINICAL SPECTRUM OF MYOTONIC DYSTROPHY TYPE 2: A CASE SERIES

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Introduction: Myotonic dystrophy (DM) type 2 (DM2) is an autosomal dominant condition caused by an expanded tetranucleotide repeat [cytosine-cytosine-thymine-guanine (CCTG)] within the first intron of the ZNF9 gene (CNBP gene). Usually, DM2 involves proximal muscles, therefore, it is also named Proximal Myotonic Myopathy (PROMM). The limb-girdle weakness is often the presenting feature of DM2 with progressive involvement of other muscles, including the facial district. Myotonia is also a frequent feature, affecting 75% of DM2 patients. Muscle pain, stiffness, and fatigue are variably associated with the main features. Furthermore DM2, like DM1, has a multisystemic involvement with ophthalmological, endocrinological, cardiac interest, while in DM2 cognitive impairment is absent.

Objective: We want to describe the clinical spectrum of DM2 in a case series of patients from the Neuromuscular outpatient clinic of the University of Genova.

Results: We evaluated 11 patients, 5 females and 6 males, with a mean age of 56.1 and an average disease duration of 15 years. 6 patients had already been diagnosed, while 5 have been tested in our laboratory. The presenting symptoms were muscle pain in three patients (27%), paroxysmal supraventricular tachycardia in one (9%), frontal balding in two subjects (18%), proximal weakness (18%) in two patients, and hearing loss around age 50 was in one case (9%). Myotonia was rarely reported as presenting feature. Interestingly, a 47-year-old man had an acute DM2 presentation with two episodes of severe hyperCKemia and muscle pain, with subsequent complete remission and unspecific mild signs of myogenic damage at electromyographic tests. We applied our diagnostic algorithm for hyperCKemia, which includes multiplex ligation-dependent probe amplification for Duchenne muscular dystrophy gene and DM1-DM2 genetic test, before next generation sequencing target gene panel for hyperCKemia, reaching an early diagnosis.

Discussion and Conclusions: In our outpatient clinic, DM2 is not uncommon (13% of patients with hyperCkemia or limb-girdle muscular dystrophy), likely because of our protocol which rules out myotonic dystrophies before further NGS tests. Moreover, we want to highlight uncommon presentations of DM2 such as recurrent rhabdomyolysis or early hearing loss, to expand the spectrum of clinical presentation.

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## BLOOD TESTS MATTER: A RARE CASE OF MULTINEUROPATHY

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Background: Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome) is a systemic necrotizing vasculitis of small and medium-sized vessels characterized by the formation of extravascular granulomas, hypereosinophilia and eosinophilic infiltrates in various tissues. The neurological manifestations reported in the literature mainly concern the peripheral nervous system.

Case Presentation: A 21-year-old patient with history of chronic asthma, came to our observation for subacute onset of symmetric sensorimotor symptoms. We performed the following exams: lumbar puncture: protein 28 mg/dl (0.0-50); white blood cells 1/ml (0.0-5); MRI of the dorsal and lumbar spine with contrast medium: findings within normal limits; NCS: sensory-motor axonal multineuropathy; blood tests: eosinophilic leukocytosis (WB 28.20 10^09/L, of which 42% eosinophils), elevation of transaminases (AST 67 U/L, ALT 165 U/L) and troponin (54.6 ng/ml); chest-abdomen CT scan: pulmonary lesions of suspected granulomatous nature, groundglass bilateral thickenings and widespread thickening of the walls of the gallbladder. We suspected an axonal multineuropathy secondary to EGPA. We started a first line treatment with high-dose corticosteroids, followed by Rituximab. At the discharge, the patient was clinically stable and started a rehabilitation process.

Discussion: EGPA is one of the three anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, among which is the one with the highest incidence of involvement of the nervous system, in most cases in form of multineuropathy. In our case, the clinical-laboratory features (such as axonal involvement, the absence of dissociation to the CSF, the subacute onset and the asymmetry at NCS) together with the anamnestic finding of organ damage and hypereosinophilia, directed our diagnostic suspicion towards an axonal multineuropathy secondary to systemic disease in the setting of hypereosinophilias. In this context, the main differential diagnoses to consider are secondary eosinophilias (such as EGPA and parasitosis), clonal hypereosinophilic syndromes and idiopathic hypereosinophilic syndromes. We've ruled out other causes of hyperesoinophilia, in particular we performed a genetic analysis for the research of the fusion gene FIP1L1/ PDGFR, with negative result. The diagnosis of EGPA allowed the prompt beginning of specific treatment, therefore we started a immunosuppressive therapy with rituximab. A biopsy of the anterior tibial nerve, which revealed a focal ischemic process of the nerve with evidence of lymphocytic inflammatory infiltrate, supported our hypothesis.

Conclusion: EGPA is a rare cause of peripheral axonal multineuropathy associated with hypereosinophilia important to diagnose since

a specific treatment is available and effective in the management of other systemic complications.

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## A CASE OF AN ACQUIRED SENSORY GANGLIONOPATHY PRESENTED WITH A FIBROMYALGIA-LIKE PHENOTYPE

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We describe a challenging case of possible inflammatory or paraneoplastic sensory ganglionopathy with severe small nerve fibre involvement presented as a fibromyalgia at onset, with a good response to immunomodulatory therapy. A 40-year-old woman with history of hypertension, unspecified dermatitis, endometriosis, irritable bowel syndrome, depression, recent thyroid cancer undergoing surgical and radiometabolic treatment. She reported widespread pain, itching, burning feet and mouth, dry skin and photophobia onset in October 2022. After 2 months, symptomatology evolved in paresthesias, fatigue, severe gait disturbance, initial motor weakness and the patient was brought out to our attention. Neurological examination revealed feet-slapping gait ataxia, positive Romberg sign, pinprick and tactile sensory loss without length-dependent pattern, hyporeflexia, mild distal hypopalesthesia and weakness in limbs. She also reported widespread burning pain, asymmetric numbness in upper and lower limbs, blurred vision, constipation. We found increased CSF protein without oligoclonal bands. Neurophysiological exams showed a severe axonal sensory neuropathy including foveal involvement and abnormal motor nerve conduction studies in 1 nerve in lower limbs. Brain and Spine MRI was normal. Extensive assessment for secondary causes was negative, including autoimmune and infectious serology, vitamin deficiency, Fabry disease genetic test, radiological and laboratory screening for occult cancer research and onconeural antibody. We exclusively found a mild ANA positivity (1:100) and bilateral sacroiliitis. During hospitalization the patient underwent a cycle of IVIG, rehabilitation and started steroid therapy with regression of small fibre damage symptoms and only slight improvement in others. The clinical picture of the patient is suggestive of a possible acquired inflammatory or paraneoplastic ganglionopathy. The non-length-dependent small nerve fibers sensory and vegetative symptomatology associated with mood disorder at the onset, resemble fibromyalgia syndrome. The axonal damage involving the foveal component in visual evoked potentials suggests a possible involvement of retinal ganglion cells, however other tests are needed. The history of dermatitis, the finding of bilateral sacroiliitis and the mild positivity of the ANA suggest an inflammatory genesis. However the history of cancer, the presence of motor alterations and poor response to immunomodulatory treatments suggest a paraneoplastic syndrome. Futher investigations to complete screening and research autoimmune and paraneoplastic causes, including HLAB27, FDG PET body, skin biopsy are scheduled. Autoimmune or paraneoplastic ganglionopathy is a clinical challenge which might present like a fibromyalgia syndrome due to initial small nerve involvement which may respond to immunomodulatory treatments. A close clinical and instrumental follow-up is mandatory in order to reach correct aetiological diagnosis and adequate therapy.

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## COMPARISON OF EFFICACY OUTCOMES WITH VUTRISIRAN VS. PATISIRAN IN HATTR AMYLOIDOSIS WITH POLYNEUROPATHY: POST-HOC ANALYSIS OF THE HELIOS-A STUDY

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Objective: Assess the relative efficacy of RNAi therapeutics for hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy. hATTR amyloidosis is a progressive, life-threatening disease caused by amyloid deposits derived from misfolded variant and wild-type TTR protein. Vutrisiran and patisiran are approved RNAi therapeutics that reduce TTR protein production to treat hATTR amyloidosis with polyneuropathy.

Materials: In the Phase 3 HELIOS-A study (NCT03759379), patients with hATTR amyloidosis with polyneuropathy were randomized (3:1) to vutrisiran (25 mg subcutaneously, Q3M) or patisiran (0.3 mg/kg intravenously, Q3W). Prespecified comparisons previously established the clinical efficacy of vutrisiran versus external placebo (from the Phase 3 APOLLO study of patisiran). The HELIOS-A patisiran arm served as a reference group, and comparison of TTR reduction between vutrisiran and within-study patisiran was included as a secondary endpoint.

Methods: Here, additional post-hoc analyses comparing the HELIOS-A vutrisiran and patisiran arms on clinical outcomes are reported: neuropathy impairment (modified Neuropathy Impairment Score+7 [mNIS+7]), quality of life (Norfolk-QOL-DN), gait speed (10-meter walk test [10-MWT]), nutritional status (modified body mass index [mBMI]), and disability (Rasch-built overall disability scale [R-ODS]).

Results: HELIOS-A enrolled 164 patients (vutrisiran, n=122; patisiran, n=42). TTR reduction with vutrisiran was non-inferior to that observed with patisiran (median difference [vutrisiran-patisiran] [95% CI], 5.28% [1.17, 9.25], 95% CI lower limit >–10%). In the current analysis, least-squares mean (±SE) changes from baseline to Month 18 for vutrisiran and patisiran, respectively, showed similar treatment effects: mNIS+7 (0.06±1.48 vs. 1.53±2.59; p=0.6248),

Norfolk-QOL-DN (−2.5±1.8 vs. −0.8±3.0; p=0.6472), 10-MWT (−0.019±0.025 vs. −0.053±0.043 m/s; p=0.4936), mBMI (21.8±9.2 vs. 7.6±15.8; p=0.4378), and R-ODS (−1.2±0.5 vs. −1.3±0.9; p=0.9266).

Discussion: At Month 18, vutrisiran and patisiran showed numerically and statistically similar efficacy for treating the polyneuropathy manifestations of hATTR amyloidosis.

Conclusions: These post-hoc findings demonstrate comparable efficacy between vutrisiran and patisiran, which both target the key pathogenic protein and have similar pharmacodynamic effects in terms of TTR lowering.

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## CLINICAL AND PATHOLOGICAL FINDINGS IN A COUPLE OF ITALIAN GYPSY SIBLINGS WITH CHARCOT-MARIE-TOOTH TYPE 4D AND A REVIEW OF THE CURRENT LITERATURE


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Objectives: Charcot-Marie-tooth disease type 4D (CMT4D) is an early onset autosomal recessive form of CMT characterized by severe demyelinating motor sensory neuropathy, muscle weakness and atrophy leading to gait impairment and foot deformities and hearing impairment. It is caused by mutations in the N-myc downstream-regulated gene 1 (NDRG1). Eight different mutations in NDRG1 have been identified so far. We report the case of two siblings of Romani ancestry, a 38-year-old man and a 40-year-old woman, with a NDRG1 mutation (p.R148) and concurrently provide a review of the current literature.

Materials: Two adult patients affected by CMT4D admitted to the Neurology Department of the Policlinico Hospital in Milan were evaluated clinically and instrumentally.

Methods: Disease staging was assessed through a battery of clinical and instrumental examinations as CMT neuropathy score, electromyography, visual evoked potentials, fiberoptic endoscopic evaluation of swallowing and pulmonary function tests. The review includes all articles focusing on CMT4D available online, published from 1998 to 2022.

Results: Both patients showed severe distal-proximal motor sensory neuropathy, severe muscle weakness and atrophy, mild dysphagia with the need of modified consistencies, mild pulmonary restrictive syndrome and sensorineural deafness. Neurophysiological tests showed markedly impaired motor and sensory conduction parameters. 15 articles, published from 1998 to 2022, were included in the review.

Discussion: The age at onset, in the first decade of life, and the clinical features are in line with the clinical course described in the literature about this pathogenic variant. p.R148 accounts for the majority of CMT4D cases, almost all of Romani ancestry. Because of the lack of data regarding other pathogenic variants, it is difficult to provide a comparison between potential differences in clinical phenotypes and age at onset, but it is interesting to notice that all the patients who had an onset with delayed motor milestones, meaning a very early onset, were p.R148 variant carriers.

Conclusions: Additional research into NDRG1 mutations and phenotypic characteristics may provide further information about potential genotype-phenotype correlations and prognosis.

Reference:


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## CEREBROSPINAL-FLUID TAU LEVELS AS A MARKER OF AXONAL DAMAGE IN GUILLAIN-BARRÉ SYNDROME


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Introduction: Inflammatory neuropathies (INs) are a group of acquired disorders of peripheral nerves, typically classified as acute or chronic. The most common INs, the Guillain-Barré syndrome (GBS) and the chronic inflammatory demyelinating polyneuropathy (CIDP) are predominantly demyelinating. Since these diseases affect peripheral nerves and the proximal nerve roots, the pathogenic process may lead to cerebrospinal fluid (CSF) biomarker alterations. High CSF levels of neurofilament light chain have been reported in GBS and CIDP, while the role of other biomarkers, including the CSF total-tau (t-tau), is still uncertain. Tau is a microtubule-associated protein involved in microtubule assembly and stability and is considered one of the most established biomarkers of axonal injury. Nonetheless, few studies explored its role in INs, and none reported correlations with neurophysiological data. Therefore, we aimed to investigate the value of CSF t-tau levels in revealing neuronal damage in INs and its correlation with clinical and neurophysiological data.

Methods: We included n=17 patients with INs diagnosed at the Neurology Unit of the S. Andrea Hospital, Vercelli, Italy. All patients had evidence of CSF albumin-cytologic dissociation and were classified according to the clinical presentation in GBS (n=12) and CIDP (n=5). Nerve conduction studies (NCS) were conducted in the upper and lower limbs. T-tau levels were measured in the CSF.

Results: GBS and CIDP groups were similar in age and sex. NCS studies showed a predominant demyelinating involvement in 67% of GBS patients. T-tau levels were significantly higher in the GBS than in the CIDP (218.4±90.9 vs. 125.3±59.6 pg/ml). Also, in the GBS, CSF t-tau levels were inversely correlated with the ulnar compound motor action potential (cMAP) amplitude and the sural sensory action potential (SAP) amplitude.

Discussion: In this study, we analyzed the role of CSF t-tau as a marker of axonal damage in INs. The higher CSF t-tau levels in GBS than in CIDP patients suggest greater neuronal damage in acute than in chronic INs. This might be related to a temporary higher permeability of the blood-brain barrier with higher release of t-tau from proximal nerve roots. NCS also showed correlations between t-tau levels and the ulnar cMAP and sural SAP amplitude, supporting the hypothesis

of acute axonal damage, even in predominantly demyelinating forms. As known, an axonal involvement in GBS may be related to a worse outcome. Therefore, we could assume that CSF t-tau levels may have a prognostic value, but further longitudinal confirmation is needed.

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## LONG-TERM FOLLOW-UP STUDY OF MUSCLE MRI IN MYOTONIC DYSTROPHY TYPE 1: CORRELATIONS WITH DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

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Introduction: Muscle MRI is a useful biomarker of disease activity and severity in neuromuscular disorders. In the gene-therapy era, objective evaluation of natural history of progressive diseases and their correlations with clinical evolution are warranted. We recently reported data from 134 Myotonic Dystrophy type 1 (DM1) patients showing that Muscle MRI can detect muscle involvement also in the milder spectrum of disease (MIRS 1-2) and correlate with disease severity, and that STIR positivity and muscle atrophy could represent additional mechanisms for muscle wasting and weakness in DM11. Herein, we report on long-term follow-up data of muscle MRI study in 28 patients of this cohort.

Materials: Twenty-eight consecutive patients with genetically confirmed DM1 were included in this prospective, longitudinal study. Each patient underwent a complete neurologic examination including Muscular Impairment Rating Scale (MIRS) and a MRI study at baseline and at follow-up. Demographic and genetic characteristics of each patients were recorded.

Methods: We analyzed 32 couple of muscles of lower body (LB) and 16 couple of muscles of upper body (UB) by T1 and STIR sequences. T1-, STIR-, and atrophy-scores and their variations between MRIs were considered. Correlations between different MRI-sequences data and between MRI and demographic, clinical and genetic characteristics were analyzed.

Results: The median FU was 3 years (range 21-53 months). The average T1-score progression was +3.1% in LB (range 0-10.6%) and +0.8% in UB (range 0-4.2%). Patients with higher T1-score variation at FU showed an increase of MIRS rating at FU. 25% of patients did not show any progression in T1-score at FU regardless of disease severity and T1-score at baseline and time lapse between MRIs. Some patients with normal MRI study at baseline (T1 negative/STIR negative) showed STIR positivity in some muscles at FU (3.1-4.7%) and a minimal T1-score progression at FU (+0.3-0.6%) in certain of the STIR positive muscles. Muscle atrophy showed a progression regardless T1-score and STIR positivity or their progression at FU.

Discussion: Our results confirm that muscle MRI represents a useful tool to investigate disease severity and progression and can provide important information about muscle damage overtime. It can be able to detect alterations and progression also in clinically spared muscles. Moreover, MRI changes overtime have shown a good correlation with disease severity.

Conclusions: Muscle MRI is a sensitive biomarker to assess disease activity and progression in DM1.

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## CLINICAL REMISSION THOUGH MISSED DEFINITE DIAGNOSIS AND DIABOLICAL COMORBIDITY

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A 21-year-old male farmer came to observation for fever, arthralgias, hyposthenia of lower limbs, right lumbosciatalgia, urinary urgency. The onset of neurological symptoms and signs was one year ago with myalgia after vaccination against coronavirus 19, which worsened at the third dose, accompanied by paresthesias and hyposthenia of right lower limb. Because of mild anti-Borrelia burgdorferi IgG positivity, the diagnosis was suspected Lyme disease (LD). However, bug bite was denied and anti-Borrelia positivity was not confirmed. Right lower limb hyposthenia, with Wasserman and Lasegue positivity, diffuse muscular hypotrophy, deep hypoesthesia at lower limb extremities, deep tendon hyperreflexia with achilleus clonus, Romberg positivity, antalgic gait were observed. The following examinations yielded negative results (MEP; -ENG-EMG; - cerebrospinal fluid analysis). CT showed hepatosplenomegaly. Lack of relaxation of internal sphincter was described at urodynamic test. Mild neutrophilia, monocytosis, positivity of Abs anti-Epstein-Barr (anti-EBV IgM 12,3, EBNA IgG > 600, EBV VCA IgG > 750) were detected. Cerebral and spinal cord MRI showed: right parietal gliotic area; mild C4-C5, C5-C6, minimal L4-L5 and L5-S1 disc protrusions. The patient was already under ceftriaxone and doxycycline. Corticosteroids and multivitamins were added. An area of migrant erythema appeared. Antibiotic therapy was stopped because of erythematous rash, followed by papules and vesicles, increased levels of bilirubin, transaminases and gamma-GT. At improvement of neurological signs, the patient was transferred to rehabilitation. Migrant erythema is considered a peculiar sigh of LD, although humoral response was negative. Usually, anti-borrelias IgGs persist for long time, even years [1]. Abs anti-VCA and anti-EBNA-1, presence of hepato-splenomegaly oriented toward a diagnosis of concomitant suspected EBV infection, which may account for LD relapse. Although Abs finding may be expression of past infection, the virus may be not eradicated,

yet. Autoimmune processes may be ongoing. Chronic inflammation may result in immunological exhaustion with increased susceptibility and vulnerability to other infections and oncogenic transformation. Moreover, it may exacerbate neurological condition related to other causes. The diagnosis might be confirmed by PCR. However, positivity may not be related to ongoing infection, the number of etiologic agents may be too low to be detected. There is controversy regarding the ideal type of sample, value of repeated assessment, especially if invasive, in paucisymptomatic, stable or improved patients. DNA may become undetectable after few months in immunocompetent patients [2,3]. The conundrum of suspected infective etiopathogenesis needs definition of guidelines. Clinical observation remains the pillar of clinical practice and follow-up schedule.

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## ANTI-MAG NEUROPATHY WITH OVERLAPPING ANTI-CASPR2 RELATED PERIPHERAL HYPEREXCITABILITY SYNDROME

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Introduction: The myelin associated glycoprotein (MAG) is one of the main target antigen in autoimmune demyelinating neuropathy, which is mostly associated to IgM monoclonal gammopathies. Contactin-associated protein-like 2 (CASPR2) autoantibody disease is a very rare condition with a variable clinical phenotype. Most patients have autoimmune or limbic encephalitis, while peripheral hyperexcitability syndrome represents the third frequent presentation. An association of both conditions has never been described in literature, arising more considerations about pathogenesis and therapeutic options in this overlap syndrome.

Case Presentation: A 69-year-old man presented to medical attention for subacute onset of gait imbalance. A first neurological examination revealed sensory ataxia with absent tendon reflexes at lower limbs. A nerve conduction study (NCS) showed a demyelinating pattern with disproportionate involvement of the distal nerve segments, as revealed by diffusely prolonged motor distal latencies. EMG showed mild chronic neurogenic pattern in lower limb distal muscles. A distal acquired demyelinating symmetric (DADS) neuropathy was suspected, and high titer of anti-MAG antibodies (49671 BTU, n.v. <1000 BTU), as well as an IgM monoclonal gammopathy of undetermined significance (MGUS) were detected. The bone marrow aspirate examination resulted normal. A cycle of Rituximab (1 gr iv repeated after 2 weeks) therapy was administered to the patient without any significant improvement of symptoms and increased anti-MAG antibodies titer. After 6 months, the patients presented to our attention for new onset of proximal lower limb weakness, cramps and fasciculations. Neurological examination revealed severe symmetric bilateral ileo-psoas weakness, conspicuous bilateral quadriceps fasciculation with hypertrophy, and absent lower limb tendon reflexes. The gait was anserine with no signs of sensory ataxia. A new NCS showed diffuse reduction of motor and sensory responses with reduced conduction velocities at lower limb nerves. EMG revealed frequent fasciculations and myokymic discharges in lower limb muscles with neurogenic pattern, expecially in proximal lower limb muscles. High titer of anti-CASPR2 antibodies on cerebrospinalfluid and serum was detected, while anti-MAG antibodies were absent. An extensive screening for malignancies, including full-body CT-FDG-PET scan, was negative. Plasma Exchange was started with mild improvement of symptoms.

Conclusions: Anti-MAG titer slowly dropped after Rituximab administration, but several months later an anti-CASPR2 related peripheral hyperexcitability syndrome developed, with no obvious malignancies detected. This condition has never been linked to anti-MAG neuropathy, but the distribution of molecular components in the paranode and juxtaparanode of peripheral myelinated fibers may suggest a role of anti-MAG-induced structural changes, with CASPR2 antigen revealing for autoimmune response.

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## CONCURRENT GUILLAIN-BARRÈ SYNDROME AND IMMUNE-MEDIATED NECROTIZING MYOPATHY: A CASE REPORT

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Background: Guillain-Barrè syndrome (GBS) and inflammatory myositis (IM) may rarely occur together. This is the first report about coexistent GBS and Immune-mediated necrotizing myopathy (IMNM).

Case Report: An 84-year-old woman presented to the Empoli Hospital Emergency Room with progressive weakness, walking disability and limb numbness. She had a history of arterial hypertension and recent myocardial infarction treated with angioplasty and stenting. A neurological examination revealed symmetrical weakness in upper and lower limbs, absent deep tendon reflexes, distal hypopallestesia, dysarthria, dysphonia, diplopia, bilateral palpebral ptosis, isochoric pupils with normal light reflex, bilateral facial deficit, with intact consciousness. Her Erasmus GBS Respiratory Insufficiency Score (EGRIS) [1] was 5. A diagnosis of Guillain-Barré syndrome was made based on clinical presentation, albuminocytological dissociation in the cerebrospinal fluid, and electrodiagnostic studies (EDxs), that provided evidence of an acute inflammatory demyelinating polyneuropathy with signs of autonomic impairment. A cycle of intravenous immunoglobulin (IVIg) (0.4 g/kg for 5 days) was administered without improvement of neurological symptoms. She proceeded to have worsening respiratory function and lower level of consciousness, then developed tetraparesis and a progressive sinus bradycardia until sinus arrest. After cardiopulmonary resuscitation, she needed intubation and mechanical ventilation. Repetitive EDx confirmed GBS findings and showed features of diffuse muscle suffering. A diagnosis of co-occurrent myositis was made based on high serum creatine kinase level (2190 U/L) and positivity for specific PM-Scl75 antibodies. A muscle biopsy revealed features of an autoimmune necrotizing myopathy. Oral Prednisone (1 mg/kg/day) and an additional cycle of IVIg were started with neurological improvement. One month later, she received a further cycle of IVIg and prednisone was decreased. The outpatient evaluation at 3 months showed improved strength with mild dysphonia and palpebral ptosis. Few weeks later, the patient died of cardiological complications.

Conclusion: Just few case reports of coexistent GBS and IM have been published in the literature and this is the first one describing concurrent GBS and IMNM. After an initial diagnosis of GBS, the recognition of coexistent GBS and IMNM could be difficult since both can manifest with progressive motor weakness. Careful monitoring of response to therapy is essential in GBS, since worsening of symptoms despite an adequate therapy should raise the suspicion of a diagnostic error [2]. Nevertheless, GBS with severe presentation could be poorly responsive to an initial therapeutic approach [1] and these cases could represent a diagnostic challenge. In addiction, the use of serial EDxs, already recommended for diagnosis [3], may reveal useful additional elements for differential diagnosis.

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## ZASP/LDB3-RELATED CARDIOMYOPATHY UNVEILED BY COVID19 INFECTION: A CASE REPORT

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Introduction and Objectives: Z-band alternatively spliced PDZ-motif (ZASP)/Lim domain-binding 3 (LDB3) mutations represent a rare cause of cardiomyopathy [1]. We present a case of distal-onset myopathy who developed a severe cardiopathy rapidly after COVID19 infection at 55 years.

Materials and Methods: A cross-sectional evaluation of past medical history, muscle biopsy, cardiac evaluations, magnetic resonance imaging (MRI) and next-generation sequencing (NGS) was performed after obtaining informed consent.

Results and Discussion: A 57-year-old man first presented at age 34 with post-exertional rhabdomyolysis requiring dialysis. Family history was unremarkable. The patient presented congenital club foot and reported multiple episodes of pigmenturia after physical activities from adolescence. The quadriceps biopsy at age 34 showed mild myopathic features, with granular/rod-like deposits and disorganized myofibrils at ultrastructural study, normal biochemistry. A generic diagnosis of 'congenital myopathy' was made at that time. Regular follow-up was unremarkable until the age of 55 when, one month after COVID19 infection, a cardiac MRI identified low ejection fraction (45%) even worsened after two months (39%), and diffuse hypokinesia. At neuromuscular re-evaluation at 57, CK was 10X UNL, muscle MRI displayed distal > proximal degeneration; mild heel walking, dorsal scoliosis and hypotrophic medial gastrocnemii and distal thighs were observed. An extended NGS panel was performed, identifying a likely damaging heterozygous missense variant in LDB3 gene (c.985G>A, p.Asp329Asn). Conclusion: COVID19 is known to induce severe myocarditis, especially in cardiopathic patients [2]. In our case, previously diagnosed as 'atypical congenital myopathy', COVID19 acted as a precipitating factor, allowing the identification of a ZASP/LDB3-related cardiomyopathy, broadening the phenotypic spectrum of this rare condition.

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## A CASE OF TRANSTHYRETIN-RELATED FAMILIAL AMYLOID POLYNEUROPATHY WITH UNCOMMON BULBAR PRESENTATION AND CRANIAL NERVE INVOLVEMENT

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Objective: Transthyretin (TTR)-related familial amyloid polyneuropathy (FAP) is an autosomal-dominant disorder caused by deposition of TTR amyloid in various organs [1]. Although systemic involvement, progressive sensorimotor and autonomic neuropathy are FAP hallmarks, diagnosis might be very challenging, due to a variable clinical presentation, depending on geographic areas and genetic heterogeneity [2]. Furthermore, variable penetrance makes family history poorly informative.

Materials: We describe the case of a 70-year-old male patient admitted to our Neurology ward.

Method: Electronic medical records, neuroimaging, neurophysiological reports and laboratory results were reviewed.

Results: The patient came to our attention with a 2-year history of ascending upper and lower limbs dysesthesia and hypoesthesia, associated with predominant bulbar symptoms including rhinolalia, dysarthria and paradoxical dysphagia. Moreover, he complained of chronic dry cough and he reported a weight loss of 20 kg in less than two years. At the admission, the patient had already been diagnosed with symmetric and length-dependent axonal sensorimotor polyneuropathy (PNP) but blood tests for PNP were unremarkable. Family history was negative; he had a past medical history of occupational asbestos exposure and bilateral carpal tunnel syndrome. The clinical examination showed generalized weakness, superficial hypoesthesia, steppage gait, hyporeflexia, orthostatic hypotension and severe tongue atrophy with fasciculations.

Discussion: We performed lumbar puncture and total body CT scan to rule out secondary PNP causes. The patient also underwent neurophysiological tests, as well as brain and whole spinal cord MRI, to exclude alternative diagnosis such as a motor neuron disease; electroneurography confirmed a severe axonal PNP, whereas electromyography showed chronic neurogenic changes in V, VI and XII cranial nerves territory. Transthoracic echocardiogram and cardiac MRI corroborated the suspicion of amyloidosis and genetic testing confirmed TTR-FAP diagnosis, revealing a heterozygous p.Phe64Le mutation. The patient also underwent sural nerve biopsy, which revealed severe loss of myelinated fibers as well as active axonal degeneration, without a Congo Red staining positivity.

Conclusion: Our case exemplifies the FAP diagnostic challenge and suggests taking this diagnosis into consideration in cases of unexplained axonal PNP, including atypical presentations with predominant bulbar symptoms.

Disclosure: the authors have no competing interests to declare.

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## ASSESSING IMMUNOGLOBULIN TREATMENT DEPENDANCE IN CIDP AND MMN PATIENTS

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Introduction: Chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) are rare diseases, belonging to a spectrum of peripheral nerve disorders with complex dysimmune disease mechanisms. Several immune therapies have been reported to be variably effective in these neuropathies, including steroids, plasma exchange, and high-dose intravenous (IVIg) or subcutaneous (SCIg) immunoglobulins. Approximately two-thirds of patients remain treatment dependent in the long term, but remission can occur.

Methods: We present here clinical baseline data and 24 months follow-up of 20 CIDP or MMN patients, chronically treated with IVIg or SCIg, which underwent periodically attempts of treatment reduction/suspension. Neurological examination, with evaluation of MRC-SS, INCAT score, ONLS, ISS and R-ODS CIDP or MMN were performed at baseline and every six months, or in case of clinical deterioration.

Results: All patients periodically underwent 20% reduction of previously ongoing treatment. In about 25% of our cohort, IVIg or SCIg treatment was permanently reduced. Twenty-five% of patients experienced a relapse between 1 and 6 months after treatment reduction, but well recovered after treatment restabilization and periodically could afford temporary therapy decrease. The last 50% of patient were strictly IVIg or SCIg dependent. No adverse events due to IVIg or SCIg treatment were observed.

Conclusions: In conclusion, IVIg or SCIg treatment confirmed as a safe and effective long-term treatment for CIDP or MMN patients. However, it must be considered that a partial, or even complete, disease remission can occur in a quote of patient. So, periodically attempts of treatment reduction/suspension must be encouraged, with the aim of avoiding patient's overtreatment, with the relative consequences on health system costs, hospital care burden and patients' comfort and safety.

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## ATYPICAL PRESENTATION OF MYOPATHY LINKED TO FILAMIN C MUTATION

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Case Presentation: A 62-year-old lady complained of profound weakness in lower limbs and diffuse muscle pain after repetitive strenuous exercise. Serum creatine kinase and myoglobin levels were elevated, 6732.00 UI/L and 1718.00 ng/ml, respectively, so she was hospitalized to carry out further investigations.

Methods and Results: Clinical evaluation proved a reduction of strength in thigh extensor and adductor muscles bilaterally, for left worse than right (respectively MRC 4/5 and 4.5/5), and in the extensors of the right leg (MRC 4/5). She reported a paternal family history of undefined myopathy and a personal, mild reduction of lower limb strength since a few years. During hospitalization, serum creatine kinase increased to a maximum value of 12234 UI/L; therefore, intravenous hydration therapy was adopted to reduce serum biomarkers of rhabdomyolysis and improve muscle symptoms. ECG was unremarkable. Needle EMG demonstrated an incomplete interference recruitment pattern and increased polyphasia in the tibialis anterior muscles and reduced amplitude of motor unit potentials with early recruitment pattern in vastus lateralis and triceps brachii muscles. Muscle MRI showed mild to moderate fat infiltration of right semimembranosus muscle and of semitendinosus, gracilis, sartorius, biceps femoris, adductor magnum, medial gastrocnemius, soleus, tibialis anterior muscles of both inferior limbs. According to a possible diagnosis of primary myopathy, using a targeted resequencing gene panel and studying the coding exons of 241 "muscle genes", we detected a heterozygous missense variant in the FLNC gene: c.2084G>C, (p. Arg695Pro) whose analysis aggregate of different tools is: "deleterious".

Discussion and Conclusion: Filamin C is a structural protein, whose main role is to maintain the integrity of sarcomeres, crosslinking the actin filaments and anchoring sarcolemmal proteins to the cytoskeleton [1]. FLNC gene mutations may be associated with different muscular and cardiac phenotypes, including myofibrillar myopathy and distal myopathy [2]. In particular, the Arg695Pro mutation has been described in a single case of limb-girdle myopathy [3], whereas a different aminoacid substitution in the same residue has been associated with hypertrophic cardiomyopathy [2]. This case adds further muscle phenotype variability of FLNC mutations, which could manifest with both proximal and distal myopathy and even as an exercise-related rhabdomyolysis at presentation.

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## AN UNCOMMON OVERLAPPING PRESENTATION OF GUILLAIN-BARRÉ AND MILLER-FISCHER SYNDROME IN PEDIATRICS: CLINICAL PICTURE AND 6-MONTH FOLLOW-UP CASE REPORT AND LITERATURE REVIEW

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Background: Guillain-Barré Syndrome (GBS) is an immune-mediated, rapidly progressive polyneuropathy, with several clinical subtypes, such as Miller Fisher syndrome (MFS) and Bickerstaff brainstem encephalitis (BBE). These syndromes are usually diagnosed by means of clinical/neurophysiological evaluation, and cerebrospinal fluid examination. Brain-spine MRI and peripheral nerve ultrasound can be supportive. [1]

Case Report: Herein, we describe a case of a 11years old boy, who was admitted to Intensive Care Pediatric Unit of University Hospital of Messina for abrupt onset of respiratory failure, with the suspicion of a choking episode. Actually, clinical history and examination suggested an ascending paralysis with cranial nerves involvement. He underwent neurological examination, neurophysiological studies, cerebrospinal fluid analysis and brain/spine MRI, that revealed a GBS-MFS-BBE overlapping syndrome, with meningeal irritation. This little patient was treated with multiple intravenous immunoglobulin (IVIG) cycles with immediate benefit, substantial improvement of the respiratory failure and progressive remission of neurological deficits. At 6-month follow-up visit, the clinical picture nearly reached normality.

Discussion: Literature review showed that, while GBS incidence linearly increases with age, the disease is much rarer in children and adolescents, with the exception of some geographical area (East-Asia), with an incidence of 0.62 cases per 100,000 per years (PYs) in 0-9-year-olds, and 0.75 cases per 100,000 PYs in 10-19-year-olds. [2] As regards as therapeutic interventions, there are currently no specific differences between various GBS subtypes. Previous studies mainly suggest the use of IVIG to obtain relevant benefits. Plasma exchange is recommended in children IVIG therapy is contraindicated, or this turns out to be ineffective. [3]

Conclusion: We presented here a rare, especially in Western countries, GBS-MFS-BBE overlapping syndrome in pediatrics. Although clinical presentation suggested a respiratory failure due to a choking episode, neurological examination revealed areflexia that arose the suspicion of neuromuscular disorder. Prompt diagnosis and IVIG treatment resulted in rapid improvement of the clinical picture.

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## EXPLORING THE ROLE OF MOBILE HEALTH TECHNOLOGIES IN DETECTING SUBTLE MOTOR IMPAIRMENT IN PAUCISYMPTOMATIC LATE-ONSET POMPE DISEASE: A PRELIMINARY STUDY

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Introduction: The sensitivity of standard assessment of motor performance for evaluating progression and response to treatment in Late Onset Pompe Disease (LOPD) in clinical practice and clinical trials is still a controversial issue. Mobile health technologies (MHT) have been demonstrated to improve diagnostic accuracy in several conditions with motor impairment by enabling detection of subtle motor dysfunctions. Aim of our study was to test whether MHT could improve the evaluation of motor impairment in LOPD patients.

Patients and Methods: Eight LOPD patients which were able to walk without aids and treated with enzyme replacement therapy (ERT) were enrolled. Six-minute walking test (6MWT), "Timed Up and Go Test" (TUG) and speed in one time and repeated rising to chair were evaluated in all the patients by MHT-based gait analysis (Rehagait, Hasomed). Data were compared to healthy controls (HC, n=96) with ANOVA model age and sex-adjusted.

Results: LOPD patients showed greater angle in raise from chair task (p=0.03) compared to controls with reduced extension velocity (p=0.05), which may reflect trunk involvement of PD. Turning task revealed a reduced global and peak-force angular velocity in LOPD patients (p=0.01), which may reflect proximal lower limbs weakness and fragmentation of turning task. Overall, LOPD patients require longer step time (p=0.01) and perform shorter steps (p=0.05) with greater variability in length (p=0.04). Walking analysis of young LOPD patients (n=3) compared to controls aged $\leq$ 30 years old (n=21) did not differ in number of steps or distance performed in 6MWT, but young LOPD patients still showed greater step time variability (p=0.03) and shorter step lenght (p=0.01) with greater variability in length (p=0.02). Gait parameters analyzed by MHT consistently correlate with clinical motor impairment scales.

Conclusion: Our preliminary results suggest that wearable technologies can identify subtle walking abnormalities in paucisymptomatic patients not otherwise evident by usual clinical evaluation. These findings may have important implications for management, follow-up and treatment decisions in clinical practice. Importantly, our results suggest that MHT deserve to be evaluated as promising outcome measures for clinical trials. Further studies in a larger population are warranted to confirm our findings.

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## LONG-TERM SAFETY AND EFFICACY OF ECULIZUMAB IN GENERALIZED MYASTHENIA GRAVIS: A 7 YEARS' EXPERIENCE

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Objectives: Generalized myasthenia gravis (MG) is an autoimmune disorder that leads to disabling weakness via damage to the neuromuscular junction. In most patients, the disease is mediated by autoantibodies to the acetylcholine receptor, which activate the complement cascade. Eculizumab, a complement inhibitor, demonstrated its therapeutic efficacy in these patients, however, data regarding its long-term impact

is limited. Our aim was to describe safety, tolerability and efficacy of 7-year treatment of eculizumab in one patient with refractory anti-AChR-positive generalized MG.

Methods: We describe the case of one patient with refractory generalized MG who was finally treated with Eculizumab and subsequently followed at our institution over 7- year period.

Results: A 62-year-old man with refractory anti-AChR-positive generalized MG experienced several relapses although multiple therapies administration. Therefore, 7 years ago, Eculizumab was started leading to an optimal control of symptoms and sustained efficacy until now.

Discussion: Eculizumab has been recently approved in the United States, Europe and Japan for the treatment of anti-AChR-positive MG. In our 7 years' experience with one patient, Eculizumab has been shown to lead to a satisfactory control of the disease, in the absence of new exacerbations or adverse events. This case provides evidence for the long-term safety and sustained efficacy of Eculizumab for refractory gMG.

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## MITOCHONDRIAL PATHOLOGY IN MYOSITIS: A MULTICENTRIC CASE SERIES

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Objectives: Mitochondrial alterations represent a classic finding in sporadic inclusion body myositis (s-IBM) and in polymyositis with mitochondrial pathology (PM-Mito), although they have been occasionally reported in dermatomyositis (DM) and immune-mediated necrotizing myopathy (IMNM). However, while DM and IMNM usually show good treatment response, PM-Mito and s-IBM present a variable clinical course and poor response to treatments. The prevalence and significance of mitochondrial pathology in non-IBM myositis has not been deeply investigated, particularly if it could be a reliable marker of progression to IBM from PM-Mito and/or an index of treatment unresponsiveness and worse clinical outcome.

Methods: We reviewed clinical and histopathological data from 22 patients, followed in 4 Italian and 1 French institutions, with clinical and histological diagnosis of myositis and presence of COX-negative fibers at muscle biopsy.

Results: 16 patients [72,7%] were women; mean age was 65.7 years [range 39-78 years]. 4 patients had IMNM, 2 DM, 10 non-specific myositis (NSM), 6 Overlap myositis (OM). The mean number of COX-negative fibers was 3.5%. Mean age at muscle biopsy was 62,3 years. Only 5 patients [22,7 %] showed a complete recovery after treatment while the others had variable residual weakness. Treatment refractory and worst clinical outcome were observed in patients with higher percentage of COX-negative fibers.

Conclusions: These findings suggest that the presence of mitochondrial pathology could represent a marker of disease severity in non-IBM myositis patients, predicting a worse response to treatment.

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## QUANTITATIVE SENSORY TESTING AND SKIN BIOPSY IN AN ITALIAN COHORT OF ATTRV PRESYMPTOMATIC CARRIERS: CROSS-SECTIONAL ANALYSIS AND PRELIMINARY LONGITUDINAL DATA

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Introduction: Hereditary transthyretin amyloidosis polyneuropathy (ATTRv-PN) pre-symptomatic carriers often show preclinical abnormalities at small fibre related diagnostic tests. However, no biomarker is still available to follow-up pre-symptomatic carriers, thus helping therapeutic decision making. Our study aimed at assessing nerve conduction study (NCS), quantitative sensory testing (QST), and skin biopsy parameters in a cohort of late-onset ATTRv pre-symptomatic carriers, and to evaluate whether they correlated with predicted age of disease onset (PADO).

Methods: consecutively enrolled late-onset ATTRv pre-symptomatic carriers underwent NCS, QST, and skin biopsy with intraepidermal nerve fibre density (IENFD) evaluation from a distal and a proximal site. Douleur Neuropathique-4 (DN4) and Small Fiber Neuropathy-Symptoms Inventory (SFN-SIQ) were used to assess painful and small fibre neuropathy related symptoms. PADO and time-to-PADO (delta-PADO) were estimated for each carrier, and correlations with diagnostic test measures were analysed. A subset of ATTRv carrier completed a lingitudinal evaluation of at least 1 years.

Results: Forty ATTRv pres-symptomatic subjects (M/F: 18/22; V30M/non-V30M: 26/14; age 49, IQR 42.5-59) were enrolled. Twenty carriers (50%) had distal IENFD reduction, with a non-length dependent distribution in 73% of cases. Eleven subjects (27.5%) had cold and/or warm detection threshold (CDT and/or WDT) abnormalities at QST. Delta-PADO positively correlated with sural sensory nerve action potential (SNAP) amplitude (r=0.416, p=0.004), and QST parameters like CDT (r=0.337, p=0.0017), WDT (r=-0.293, p=0.047), and mechanical detection threshold (MDT) (r=-0.462, p=0.003). Simple linear regression models showed a linear correlation between

delta-PADO and sural SNAP, CDT, and MDT. Six subjects completed a longitudinal anylisis at at least 1 year: 2/6 subjects showed a relevant modification at QST/Skin biopsy and were considered affected.

Conclusions: Our findings show that IENFD reduction and QST abnormalities may occur early in ATTRv pre-symptomatic carriers, often with a non-length dependent pattern. However, only sural SAP amplitude and QST parameters correlated with delta-PADO, suggesting that serial combined QST and NCS evaluation could be useful in ATTRv pre-symptomatic carriers' follow-up.

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## RECURRENT MILLER-FISHER SYNDROME OR PHARYNGEAL-CERVICAL VARIANT OF GBS? A CASE REPORT AND A REVIEW OF THE LITERATURE ALONG A PATHOPHYSIOLOGICAL CONTINUUM

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Objectives: Miller Fisher Syndrome (MFS) is a variant of Guillain-Barré Syndrome (GBS), and its prevalence is 1/1,000,000. The aim of this case report is to describe a recurrent case of MFS, which is very rarely seen in clinical practice.

Materials: In February 2005 a 27-year-old male developed subacute onset of MFS, treated with intravenous immunoglobulin with complete recover. In January 2023 the same patient developed distal paresthesia, difficulty in walking and double vision, a week after an upper respiratory tract infection.

Methods: Neurological examination revealed bilateral external ophthalmoplegia and moderate ptosis, loss of vertical gaze, mild rhinolalia, ataxic gait exacerbated by eye closure, and generalized areflexia. Considering the clinical findings and the similarity to the previous episode, MFS was suspected, and treatment with intravenous immunoglobulin (IVIg) has been undertaken.

Results: CT and MRI of the brain were both normal. Viral serology tested negative. Neurophysiological examination showed a mild reduction in SNAPs amplitude and conduction velocity in the right median nerve, and absence of H wave bilaterally registered from soleus muscle. Assessing the blink reflex, a higher latency of direct and contralateral RII was documented. GT1a and GD1b antibodies tested positive. In both episodes, there was a gradual but quick recover after immunoglobulin treatment. One month later, neurophysiological findings returned to normal, and after two months there was complete clinical remission.

Discussion: MFS accounts for 1-5% of all GBS cases in Western countries, it is considered a post-infectious autoimmune disease. Recurrencies are seen in approximately 10% of cases, which is higher compared to GBS. Based on a literature review, over 90% of MFS patients have anti-GQ1b present, while other forms of antibodies are less common but possible. GT1a alone has been associated with the Pharyngeal-Cervical-Brachial-variant (PCB) characterized by cranial nerve paralysis, whereas MFS or Bickerstaff's brainstem encephalitis (BEE) are likely to present both GQ1b and GT1a antibodies. GD1b antibodies are correlated with peripheral neuropathy symptoms. IVIg or plasma exchange are used as treatment for MFS.

Conclusions: Our patient had two episodes of MFS with an eighteen-year symptom-free interval in between. This case report illustrates the stereotypical nature of the recurrent episodes in MFS, its relatively benign prognosis, and the detection of a unique and new combination of antibodies, GT1a and GD1b. Whatever the diagnosis, our description could help to find novel markers, both clinical and immunological, able to predict recurrencies in the vast field of nodo-paranodopathies, as both MFS and PCB are now considered.

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## MULTIFOCAL MOTOR NEUROPATHY WITH CRANIAL NERVE INVOLVEMENT: A CASE REPORT

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Introduction: Multifocal motor neuropathy (MMN) is a rare neuropathy characterized by progressive, asymmetric weakness and muscle atrophy without sensory abnormalities. It is mostly associated with the presence of high levels of anti-ganglioside GM1 antibodies (Abs anti-GM1) and positive response to immunomodulatory treatment. The onset is typically subacute, often starting from a distal upper limb, asymmetrically. The diagnosis is based on clinical and electrophysiological criteria, with the evidence of conduction block and focal demyelination. In addition, high levels of Abs anti-GM1, slight increase of proteins in cerebrospinal fluid (CSF), hyperintense T2 signal and fascicular enlargement in affected nerves on magnetic resonance (MRI) and clinical improvement with IVIg treatment can support the diagnosis.

Case Report: A 56-year-old patient presented with ptosis in the left eyelid and diplopia, tongue deviated to the right and weakness in the left hand. Also, the patient reported a similar symptomatology three years before, spontaneously resolved. Patient underwent: 1) a brain and cervical MRI, unremarkable; 2) lumbar puncture, which showed a slight protein increase (, no cells, glucose in range); 3) an electrodiagnostic study, which showed conduction block with a reduction in the amplitude and area of the compound muscle action potential (CMAP) after a proximal stimulation, without abnormal temporal dispersion in the four limbs, without sensory abnormalities. The symptoms spontaneously remitted. Further examinations executed to the CSF found the presence of high level of Abs anti-GM1, supporting the diagnosis of MMN. We followed the patient for five months after the diagnosis. He did not report any weakness or other symptoms. An electrodiagnostic study after two months confirmed the conduction block with slight improvement of the proximal amplitude in the median and radial nerve bilaterally.

Discussion: MMN is a rare neuropathy, with an estimated prevalence of 0.6-2/100000. Onset with cranial nerve is an even more rare condition, but other sporadic cases are reported in the literature. We suggest further studies to identify any pathological mechanisms or cofactors in the patients, like antibodies subtypes or differences in GM1 concentration level or composition, that can lead to a more severe cranial nerve involvement than limb involvement.

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## MUSCLE PSEUDOHYPERTROPHY AS A PRESENTATION OF AMYLOID MYOPATHY

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Objectives: We describe a case of amyloid myopathy, a rare clinical presentation of Light chain (AL) amyloidosis.

Case Description: A 62-year-old woman developed proximal weakness and fatigability in lower limbs. In few months jaw claudication, dysarthria and upper limbs impairment appeared. Myasthenia Gravis was suspected but the research of anti-acetylcholine receptor (AChR) and anti-muscle-specific kinase (MuSK) antibodies were negative and repetitive nerve stimulation (RNS) test was normal. Six months after the onset, we observed diffuse muscle hypertrophy and macroglossia. A new electromyography (EMG) was performed and a myopathic pattern with early type recruitment was detected. Laboratory tests showed no elevation of serum creatine phosphokinase (CPK) level; the presence of IgG lambda monoclonal gammopathy monoclonal with elevation of serum free lambda light chains suggested multiple myeloma, confirmed by bone marrow biopsy. The muscle MRI showed a remarkable and diffuse thickening of the subcutaneous fatty tissue that appeared hyperintensity on STIR sequences, without muscular flogosis or fibrosis. Lately deltoid muscle and abdominal fat pad biopsies showed the diffuse presence of amyloid deposits with Congo red staining.

Results: The patient was treated with corticosteroids, daratumumab and bortezomib and three months later we observed a slight reduction in muscle pseudohypertrophy, whereas a moderate hyposthenia in intrinsic hand muscles, iliopsoas, and tibialis anterior bilaterally was documented.

Discussion: AL amyloidosis is a systemic disease with a poor prognosis, the mean survival is about 22 months. The onset with muscle impairment or belated muscular involvement is rare so amyloid myopathy can be easily misdiagnosed. Commonly it is characterized by fast, progressive, proximal muscle weakness and fatigability, myalgia, muscle hypertrophy and macroglossia, dysphagia and jaw claudication. Therefore myositis, Myasthenia gravis or muscular dystrophies such as limb-girdle dystrophy must be excluded. Normal or slight elevation of serum CPK and characteristic MRI muscle findings in presence of hematological abnormalities lead to the diagnosis. Conventional MRI sequences are not sensitive to detect muscle amyloid deposition, but a thickening of the subcutaneous fatty tissue with hyperintensity on STIR sequences is peculiar; moreover, muscle flogosis or fibrosis are not typical. In any case, a muscle biopsy demonstrating amyloid deposit with Congo red staining is mandatory.

Conclusion: This report highlights the importance of early diagnosis of amyloid myopathy, to promptly start therapy. In presence of a rapid evolutive history of muscle weakness, macroglossia and muscle pseudohypertrophy associated with myopathic EMG pattern without hyperckemia, haematological screening must be performed and amyloid myopathy suspected.

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## IMPACT OF BASELINE POLYNEUROPATHY SEVERITY ON VUTRISIRAN TREATMENT RESPONSE IN THE PHASE 3 HELIOS-A STUDY

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Introduction: Hereditary transthyretin-mediated (hATTR) amyloidosis, also known as ATTRv amyloidosis, is a rapidly progressive, multisystem disease. Vutrisiran, an RNAi therapeutic, improved neuropathy and quality of life (QOL) versus external placebo in patients with hATTR amyloidosis with polyneuropathy in the Phase 3 HELIOS-A study (NCT037759379). This analysis evaluates the impact of baseline polyneuropathy severity on response to vutrisiran treatment.

Methods: Patients were randomized (3:1) to vutrisiran (25 mg subcutaneous injection q3m) or patisiran (0.3 mg/kg intravenous infusion q3w), a reference group. The primary endpoint was change from baseline in modified Neuropathy Impairment Score+7 (mNIS+7) at 9 months versus an external placebo group from the APOLLO study (n=77). This post-hoc analysis divided patients into approximately equal quartiles of increasing baseline Neuropathy Impairment Score (NIS): Q1 ≥5.0—≤20.5; Q2 >20.5—≤44.1; Q3 >44.1—≤73.1; Q4 >73.1—≤127. Mean change from baseline to Month 18 was summarized by quartile for efficacy endpoints.

Results: Across NIS quartiles, vutrisiran demonstrated benefit in mNIS+7 versus external placebo (mean change from baseline in mNIS+7 at Month 9/18: Q1, -3.3/-3.0 [vutrisiran] vs +13.8/+18.4 [external placebo]; Q2, -0.6/-3.1 vs +12.1/+24.5; Q3, -2.1/+6.2 vs +16.5/+33.1; Q4, +1.6/+3.2 vs +16.5/+30.7). Vutrisiran also demonstrated benefit versus external placebo across NIS quartiles for endpoints of QOL (Norfolk QOL-DN), disability (Rasch-built Overall Disability Scale), gait speed (10-meter walk test), and nutritional status (modified BMI). Overall, patients in lower NIS quartiles (less severe disease) at baseline maintained better scores at Month 18 compared with those in higher NIS quartiles. The external placebo group progressively worsened in all measures at Month 18.

Conclusions: Vutrisiran demonstrated benefit in neurologic function and other key measures, versus external placebo, across all baseline polyneuropathy severities. Patients who initiated vutrisiran earlier in their disease course retained the highest level of neurologic function after 18 months, highlighting the importance of early diagnosis and treatment.

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## NFL LEVELS SIGNIFICANTLY DECREASE IN RESPONSE TO TREATMENT WITH PATISIRAN OR VUTRISIRAN IN HATTR AMYLOIDOSIS WITH POLYNEUROPATHY

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Background: Hereditary transthyretin-mediated (hATTR) amyloidosis, also known as ATTRv amyloidosis, is a rare, rapidly progressive, and fatal disease. Diagnosis is cumbersome and often delayed, and monitoring treatment response can be challenging. Neurofilament light chain (NfL) is a potential biomarker of disease progression and treatment response in patients with hATTR amyloidosis with polyneuropathy. NfL levels were analyzed in patients with hATTR amyloidosis with polyneuropathy from the Phase 3 APOLLO and HELIOS-A studies to further assess the potential utility of NfL in this disease.

Methods: NfL plasma levels were measured using the Quanterix® SimoaTM platform in healthy controls and in a subset of patients with hATTR amyloidosis with polyneuropathy who participated in the APOLLO or HELIOS-A studies, gave consent, and had sufficient volume of samples. Timepoints analyzed from APOLLO were baseline, 21 days, 4 months, and 18 months in placebo and patisiran groups, while samples from HELIOS-A were analyzed at baseline, 43 days, 4 months, 9 months, and 18 months in vutrisiran and patisiran groups.

Results: NfL levels measured at baseline were slightly higher in APOLLO than in HELIOS-A (69.4 pg/mL and 58.2 pg/mL, respectively) and did not differ significantly between treatment groups within each study. In the APOLLO placebo arm, NfL levels increased significantly relative to baseline at 4 months (+19.0 pg/mL, $p<0.001$), and there was a further increase at 18 months relative to baseline (+36.3 pg/mL, $p<0.001$). In the APOLLO patisiran arm, NfL levels decreased significantly at 4 months and 18 months relative to baseline (-20.0 pg/mL and -23.2 pg/mL respectively; $p<0.001$ for both). Similarly, in HELIOS-A, NfL levels in both patisiran and vutrisiran groups significantly decreased relative to baseline at 4 months (-9.7 pg/mL and -11.0 pg/mL, respectively; $p<0.05$ for both), and these decreases in NfL levels were maintained at 18 months post-treatment initiation (-16.4 pg/mL and -19.9 pg/mL, respectively; $p<0.001$ for both).

Conclusions: NfL may serve as a biomarker of treatment response as early as 4 months following initiation of treatment with patisiran or vutrisiran. The observed decreases in NfL levels from baseline are maintained through 18 months of treatment, in contrast to the significant increase in NfL levels observed in untreated patients, making it potentially useful for monitoring disease progression and treatment response over time in patients with hATTR amyloidosis with polyneuropathy.

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## A CASE OF STATIN-ASSOCIATED ANTI-HMGCR IMMUNE-MEDIATED NECROTIZING MYOPATHY (IMNM) WITH A VERY COMPLICATED COURSE

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Objectives: The purpose of this case report is to demonstrate the importance of early diagnosis and to begin proper treatment as soon as possible in statin-associated anti-hydroxymethylglutaryl-coenzyme A reductase (HMGCR) immune-mediated necrotizing myopathy (IMNM).

Materials: We report the case of a patient diagnosed with IMNM hospitalized at the Neurology department of the Policlinic Hospital in Milan from February 17th to March 23rd 2023. A comparison was made with similar cases in the Literature available on PubMed [1-3]. Method: We considered the clinical onset, the evolution of symptoms and especially the response to treatment.

Results: A 64-year-old male under atorvastatin treatment (80mg/day) from 2021 due to myocardial infarction (modified Rankin Scale, mRS=1) started to complain two years later progressive proximal weakness, at first in the lower limbs and then in the upper limbs. Discopathy was initially hypothesized in absence of CK's dosage. About a month after the onset, he developed dysphagia, dyspnoea, rhinolalia and head drop and he came to our emergency room where lab work showed an elevated creatine phosphokinase (CK) level of 6082 IU/L and the electromyography showed proximal and bulbar myopathic suffering. Atorvastatin was discontinued in IMNM suspicion, which was then confirmed by muscle biopsy and high HMGCR antibodies. He was treated with intravenous steroids, oral prednisone, a cycle of immunoglobulins and methotrexate; rhinolalia, dyspnoea and head drop gradually improved except for compromised segmental strength, particularly the lower limbs, actually the patient is no longer able to walk (mRS=4). Dysphagia progressively worsened and a percutaneous endoscopic gastrostomy was placed. The course was also affected by the development of gallbladder stones, bacterial mumps, elevation of transaminases and hypokalemia.

Discussion: Side effects of statins include myopathy, myositis, or rhabdomyolysis; all of which usually resolve with statin cessation [1]. Alternatively, an uncommon condition is IMNM with positive

anti-HMGCR antibodies, that is often difficult to diagnose because symptoms may appear years after initiation of therapy, and it is complicated to treat due to the continued production of antibodies long after discontinuing the incriminating agent. The goal for treatment is to induce complete remission, defined as normal strength and normalization of CK. However, treatment response tends to be heterogeneous as evidenced by this case and the reason remains unknown [2,3].

Conclusions: Our case emphasizes the importance of timely IMNM recognition as early diagnosis may allow a prompt start of treatment to prevent debilitating complications and mortality.

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## ACQUIRED TRANSTHYRETIN AMYLOIDOSIS IN DOMINO LIVER TRANSPLANTATION TREATED WITH PATISIRAN

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Hereditary transthyretin amyloidosis (ATTRv, v for variant) is an autosomal dominant disease, due to a mutation in the transthyretin (TTR) gene. The mutated TTR protein misfolds in amyloid deposits affecting multiples organs, mainly nerves, eyes, kidneys and heart. Hereditary ATTRv polyneuropathy is the most serious hereditary polyneuropathy of adult onset for which, until recently, the only therapeutic option was liver transplantation. We report on a 75-year-old man who, following a liver transplant, experienced a progressively worsening of neurological dysfunction impairing his quality of life. The patient had undergone underwent liver transplantation, after an incidental finding of HCV positivity with associated liver cirrhosis and hepatocarcinoma. Ten years later, the patient began to experience paresthesias distally in the upper limbs and in the right lower limb. The fine motility was affected, with difficulty in performing fine movements with hand fingers. Subsequently, dysautonomic symptoms occurred with orthostatic hypotension, erectile dysfunction, and an episode of urinary incontinence. Dysesthesias and weakness worsened over the months causing gait instability. Severe weight loss also occurred. Neurotoxicity of the immunosuppressants taken for the liver transplant was hypothesized, so tacrolimus was discontinued and cyclosporine started, with no benefit. A neurophysiologic study showed severe axonal sensory-motor polyneuropathy with signs of carpal tunnel syndrome bilaterally. On neurological examination, the patient had a wide base gait, with right foot drop; strength loss was present also at first interosseous muscles of the hand bilaterally; glove-shape hypoesthesia in the upper limbs and up to the knees in the lower limbs was present; vibration sense was absent at lower limbs, where there was also areflexia. An echocardiogram showed left ventricular hypertrophy with infiltrative cardiomyopathy. High-resolution ultrasound nerves examination showed no changes in nerves morphology or echogenicity. Molecular analysis of TTR gene mutations was negative. In view of the medical history and clinical picture, the possibility of an acquired TTR amyloidosis in domino liver transplantation was considered. Analysis of the medical records confirmed that the liver donor was a patient affected with ATTRv, carrying the Glu54Gln mutation, variant known to cause severe progression of neural and cardiac damage, which is further accelerated in iatrogenic forms. The patient immediately started treatment with a transthyretin gene silencing agent, patisiran, with benefit. In polyneuropathies, a thorough medical history is mandatory to foster a proper diagnostic workup. In the present case, it would have allowed early initiation of therapy, preventing disease progression and improving patient's quality of life.

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## MULTIFOCAL RECURRENT NEURALGIC AMYOTROPHY AFTER SARS-COV-2 INFECTION IN AN IMMUNOCOMPROMISED PATIENT

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We describe an immunocompromised patient who developed multifocal recurrent neuralgic amyotrophy after COVID infection. A 68-yr-old woman in September 2022 had successfully undergone allogeneic transplant for acute myeloid leukemia. No major infections occurred during aplasia, and complete response was obtained. After recovering from a mild SARS-CoV-2 infection during immunosuppressive therapy, she developed excruciating pain at left thigh with subsequent severe thigh weakness that forced the patient to stand and walk only with support. EMG revealed denervation in left rectus anterior and vastus medialis of the quadriceps femoris muscle, secondary to femoral nerve damage. Lumbosacral MRI was unremarkable. At neurological evaluation two months later the patient still had severe weakness (left iliopsoas and quadriceps femoris 2.5/5 MRC). Reduced tactile sensitivity at lateral aspect of left thigh was present. Lumbosacral plexus MRI with 3D neurographic sequences showed hypertrophy and hyperintensity of L3 and L4 roots and of left femoral nerve in its intrapelvic course up to the inguinal canal with slight contrast enhancement. Muscle MRI revealed muscular hypotrophy of left quadriceps femoris, related to denervation phenomena. Three months later, while immunosuppressive therapy was withdrawn, the patient complained of sudden acute pain at right arm and loss of strength at right hand that she was not capable of opening or stretching (right wrist extensor 2.5/5 MRC, fingers extensor 0/5, right interosseous and flexors fingers muscles 0/5, right thumb abductor 2/5). Sensation was preserved. Right winged scapula was present. EMG showed subacute denervation at triceps brachii, short abductor of the thumb, first interosseous and abductor of

the fifth finger, common flexor of the fingers muscles. At lower limbs, signs of subacute denervation at left ilio-psoas, vastus lateralis, vastus medialis and anterior rectus muscles of the quadriceps femoris were present. Nerve ultrasound and MRI neurographic of brachial plexus showed findings consistent with amyotrophic neuralgia. After pain subsided, the patient continued physical therapy with progressive strength improvement at left thigh, but still severe distal weakness at the right arm. Neuralgic amyotrophy after COVID infection has occasionally been reported. Generally, it is a monophasic episode although long-term functional deficits are common, and recurrence may occur. In our patient right brachial plexus involvement occurred 3 months after the onset at left lumbosacral plexus. It is possible that the immunological recovery secondary to the transplant might have delayed the healing or favored an early relapse.

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## CYTOKINE FINDINGS IN CHECKPOINT INHIBITOR-RELATED POLYNEUROPATHY REVEAL A PATTERN DISTINCT FROM GUILLAIN-BARRÉ SYNDROME AND CIDP


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Objectives: To compare clinical, immunological, and neurophysiological features of immune-related peripheral neuropathy following immune checkpoint inhibitors (ICI-PN) to those of patients with (i) Guillain-Barré syndrome (GBS) or (ii) chronic inflammatory demyelinating polyneuropathy (CIDP).

Materials: case report.

Methods: A patient with lung cancer was treated with two courses of iplimumab-nivolumab before developing a subacute peripheral neuropathy with distal limb weakness, paresthesia, and sensory ataxia. A large panel of cytokines was analyzed on serum and cerebrospinal fluid (CSF) samples using an ultrasensitive multiplex immunoenzymatic assays (Ella instrument, Bio-Techne, USA) and compared to those of a cohort of GBS (n=7) and CIDP (n=3).

Results: The patient showed complete oncological response according to RECIST v 1.1. The neurological symptoms did not improve after oral steroid therapy (1 mg/kg) but he regained the ability to walk without assistance after intravenous immunoglobulin (2 g/kg over 5 days). Compared to mean values of cytokines in GBS and CIDP patients, respectively, ICI-PN patient's serum showed a notable increase of IL10 (33.4 pg/mL vs 5.92 GBS; 2.69 CIDP), IFNgamma (7.9 pg/mL vs 1.3; 0.51), TNFalfa (40 pg/mL vs 17.91; 8.93) and CXCL10 (878 pg/mL vs 229.7; 127). Cerebrospinal fluid analysis showed a notable increase of TNFalfa (19,2 pg/mL vs 1.74; 0.87), CXCL10 (145959 pg/mL vs 373; 355.7), IL 10 (19.8 pg/mL vs 1.8; 1) and NfL (12686 pg/mL vs 950; 4645). Neurophysiology showed a mixed pattern with mainly axonal damage while a demyelinating pattern predominated in the other groups. The CSF and serum indirect immunofluorescence assay showed a patchy reaction of granular layer and diffuse reaction of molecular layer of primate cerebellum, absent in the other groups.

Discussion: Neurologic immune-related adverse events (irAEs) occur in 1-5% of patients receiving ICIs and their mechanisms have been poorly understood. [1,2] These neuropathies are commonly described as GBS (when they show an acute onset) or CIDP (when chronic and steroid-responsive) but their pathogenesis remain elusive and diagnostic labelling using know entities may be inaccurate. The ICI-PN patient here presented show some atypical findings, demonstrating mainly axonal damage and poor response to streroids. Cytokine and NfL pattern (in particular IL10, IFNgamma and CXCL10) are considerably higher than in GBS and CIDP patients [3], suggesting an involvement of T cells, in line with the proposed mechanisms of ICIs. [1]

Conclusions: PN-ICI demonstrates unique clinical and laboratory findings distinct from known dysimmune neuropathies such as GBS and CIDP, suggesting a different pathophysiology involving T cell-mediated mechanisms.

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## EFGARTIGIMOD IN REFRACTORY GENERALIZED MYASTHENIA GRAVIS. REAL-LIFE EXPERIENCE FROM A SINGLE CENTER


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Background and Objectives: Myasthenia gravis is a rare chronic autoimmune disease affecting the post-synaptic membrane of the muscle junction characterised by debilitating, and potentially fatal, muscle weakness. [1, 2]. Treatment options available for the management of generalized myasthenia gravis (GMG) are undergoing rapid expansion in recent years with the introduction of new drugs, especially for the 10-30% of MG patients who are refractory to conventional treatments [1]. Among the most recent, neonatal fc receptor (FcRn) blockers and complement factor C5a inhibitors have showed promising results [3]. The aim of our study was to collect real-life experience data on the use of efgartigimod alfa, a human IgG1antibody Fc-fragment engineered directed against FcRn to reduce pathogenic IgG autoantibody levels in GMG patients.

Materials and Methods: Efgartigimod alfa was administered by intravenous infusion at a dose of 10 mg/kg, once a week for 4 weeks (one therapeutic cycle) [2]. The primary outcome used to assess the efficacy of the drug was the evaluation of the patient's reported symptoms by using the MG-ADL scale. The scales were administered before the start of the cycle and at the end of the treatment cycle. The patients' baseline therapy remained unchanged during the entire course of treatment.

Results: A reduction in MG-ADL scores was observed at the end of the first treatment cycle compared to baseline with a mean change of

– 6,75 points (ranging from -12 to -3). None of these patients required IVIG infusion at the end of the cycle for symptom control.
Discussion: The decline in scores obtained testifies to the efficacy of treatment with Efgartigimod and the rapidity of its action onset. All patients undergoing treatment are classifiable as responders if they experienced a reduction in MG-ADL ≥ 2 points during the first cycle [2].

Conclusions: The implementation of this anti-FcRn treatment showed to be particularly effective to treat patients with refractory GMG and certainly represent a therapeutic frontier. Considering his tolerability, efficacy, rapid onset of action and manageability, efgartigimod could in the future eventually replace the use of traditional and more challenging immunosuppressive therapies in terms of side effects [1]. Further data and longer observations are needed to confirm our data.
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## ULTRASONOGRAPHIC AND ELECTRODIAGNOSTIC FOLLOW-UP IN COVID-19 VACCINE-INDUCED PARSONAGE-TURNER SYNDROME

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We present a case of a 61-years-old Caucasian man who developed Neuralgic Amyotrophy (NA) after the first dose of Pfizer-BioNTech COVID-19 vaccine injection, in December 2021. Few days later, sharp left shoulder pain began, nearby the injection site, followed by ipsilateral severe deltoid, supraspinatus, bicep brachii, thenar and flexor pollicis longus muscles weakness, joint to first three fingers hypoesthesia. The patient come to our attention in February 2022. Through Peripheral nerve high-resolution ultrasound (HRUS), we revealed an hourglass-like fascicular constriction in left median nerve at arm, in correspondence of motor conduction block detected at nerve conduction study (NCS). Moreover, both axillary and musculocutaneous nerves cMAP (compound muscle action potential) amplitudes were reduced, joint to denervation activity of deltoid at electromyography (EMG). NA was diagnosed. The patient undertook steroid therapy with prednisone 0,7 mg/kg/die for 15 days, Pregabalin daily and intensive rehabilitation physiotherapy for months. In June 2022, a second NCS/EMG and ultrasonographic evaluation showed appearance of denervation of left bicep at EMG, but improvement of fascicular constriction at HRUS. To date, patient shows a significant but slow improvement of strength and paraesthesia over time. NA, also called Parsonage Turner Syndrome (PTS) or idiopathic brachial plexopathy, is a multifocal inflammatory neuropathy characterized by unilateral sudden-onset shoulder pain, followed by neurological motor weakness and dysesthesia. Although the exact aetiology and pathophysiology of NA are unknown, it has been reported to occur after infections, vaccinations, but also trauma and surgery [1]. HRUS of the peripheral nerve is a rapid, non-invasive and cost-effective technique that allow to gain imaging in the early stages of NA, revealing pathognomonic abnormalities of involved nerves [2]. Compared to other diagnostic technique, as MRI, HRUS the most sensitive tool to detect focal nerve lesion, especially in upper limb nerve studies [3].
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## SUBACUTE SENSORY NEURONOPATHY OF DENNY BROWN ASSOCIATED WITH ANTI-HU/CV2 AUTOANTIBODIES: A CASE REPORT

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Introduction: Subacute Sensory Neuronopathy (SNN) was first described by Denny-Brown in 1948 [1]. This was associated with bronchial carcinoma and, in further studies, with autoantibodies specifically anti-HU. SSN usually presents a remarkable loss of proprioceptive sensibility resulting in pseudo-athetoid movements of the hands and severe instability on walking. Asymmetric pain and distal paresthesia are often observed. The most frequent neoplastic finding associated with SNN is small oat cell lung cancer, but recent studies have shown that it is also seen among patients with breast cancer, ovarian cancer and Hodgkin disease in 10-20% of cases [2-3].

Methods: Here we report a case of a 65 years old male patient hospitalized for subacute onset, in 15 days, of a severe alteration of the deep sensitivity of the limbs. His osteotendinous reflexes were ubiquitously abolished and a marked sensory ataxia, predominantly affecting the upper limbs at the distal level, was highlighted. The patient was no longer able to distinguish an object with his eyes closed in his hands. He did not complain of pain and cranial nerves were spared. A moderate diffuse atrophy and hypotonia were also revealed.
Results: He underwent an electroneurographic examination showing diffuse signs of sensory ganglionopathy. He also performed a CT scan of the body that did not revealed a lung cancer or other neoplasms typically correlated to sensory neuronopathies. As he had a history of intestinal polyposis he underwent also to a colonoscopy. The histological examination of an excised adenomatous polypoid lesion did not show a cancer. Onconeural autoantibodies research in serum and CSF was performed. Anti-HU and anti CV2 autoantibodies were found both in serum and CSF. The patient was treated with intravenous immunoglobulins and he obtained a partial recovery of his sensitivity disturbances over ten days.

Discussion: SNN is a very rare sensory neuronopathy almost always associated with the presence of a lung cancer discovered, in most cases, in the very early stage of the disease. Moreover, the detection of anti-HU autoantibodies in CSF and/or in serum strongly predicts the possibility of a lung cancer diagnosis over time. In our case we also detect in CSF anti CV2 autoantibodies which have been associated to small cell lung carcinoma as well. This evidence supports the need for a close

follow-up addressed primarily to a lung cancer detection. With this purpose a FDG-PET body scan can be of valid diagnostic aid.
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## A PROSPECTIVE OPEN-LABEL TRIAL WITH RITUXIMAB IN CIDP PATIENTS NOT RESPONSIVE TO CONVENTIONAL IMMUNE THERAPIES

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Aim of the Study: Chronic inflammatory demyelinating polyradiculoneuropathy is a chronic immune-mediated neuropathy often responding to steroids, intravenous immunoglobulins or plasma exchange. These therapies needs to be continued for a long period of time to avoid patient deterioration prompting the search for other immune therapies none of them proved to be effective in randomized trials. We evaluate the efficacy of rituximab in a prospective open-label study on patients with CIDP who had not improved to at least two conventional immune therapies.

Methods: We performed and open-label prospective study with intravenous rituximab (1 gram, day 1 and 15) on 20 patients with CIDP not responsive to at least two conventional immune therapies. The primary end-point was the proportion of patients improved by at least one point on the INCAT scale or two points on the MRC scale or four points on the RODs scale, 6 months after therapy with rituximab. Secondary endpoints included the proportion of patients who: improved 12 months after therapy; improved after 6 and 12 months in electrophysiological parameters; discontinued treatment with rituximab due to side effects or voluntary withdrew; improved the quality of life according to the SF-36 scale.

Results: Twenty patients were enrolled in the study including one who retired the consent before treatment and two screening failure. Thirteen of the 17 treated patients (76.5%) had improved at 6-month, 10 if we considered 4 MRC points improvement (58.8%). Of the 14 patients completing the 12-month follow-up (two lost to follow-up after being improved at month 8 and 10, and one deteriorated at 6 month), 13 had improved at 12 month (92.9%), 10 considering 4 MRC points (71.4%). When we included missing data, 15/17 had improved (88.2%; 12/17, 70.6% with 4 MRC). In 6/15 treated patients with available data (40.0%) nerve conduction parameters had improved by at least 20% in two nerves at 6-month and 7 of 13 (53.9%) at 12-month. Seven patients had moderate or mild adverse events including two that were possibly related to rituximab (cough and dysuria) but none of them retired from the study.

Discussion and Conclusion: Rituximab was a safe and effective therapy in patients with CIDP not responsive to conventional immune therapies.

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## TO BBE OR NOT TO BBE: THIS IS THE QUESTION

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Background: Bickerstaff brainstem encephalitis (BBE) is an immunologic disease characterized by the acute onset of external ophthalmoplegia, ataxia and consciousness disturbance. However, BBE may present with atypical phenotype overlapping with Guillain-Barré syndrome (GBS) variants. BBE is frequently (up to 70%) associated with IgG anti-GQ1b antibodies and more rarely with other anti-gangliosides antibodies. Herein we report a case of BBE overlapping with pharyngeal-cervical-brachial (PCB) variant of GBS.

Case-Report: A 75 years-old female was admitted with an acute onset of dysarthria. Moreover, relatives referred progressive 7-day history of agitation, irritability and unsteadiness. Her medical history was positive for rheumatoid arthritis and drug-treated hypothyroidism. Neurological examination revealed ataxic gait, bilateral dysmetria with intention tremor, slurred speech and absent deep tendon reflexes. Brain CT was unremarkable. Cerebrospinal fluid analysis (CSF) showed mild pleocytosis (10/mm3). CSF film-array PCR was negative. EEG revealed slow disorganized activity without paroxysmal features. The day after, she developed hypersomnolence, dysphagia and mild proximal weakness at the upper limbs, and psychiatric disturbances worsened with delirium. The patient underwent brain contrast-enhancement MRI and an extensive laboratory investigation including systemic inflammation, infection, tumor and metabolic markers that were normal. Electrophysiological study showed mild and asymmetric sensory neuropathy and H-reflex and of F-waves absent in lower limbs. Accordingly, BBE hypothesis was advanced and intravenous immunoglobulin (IVIG) was started with partial improvement. However, given the atypical clinical picture and unsatisfactory response to IVIG, intravenous methylprednisolone bolus was administered. Over few days, symptoms significantly improved. Serum anti-gangliosides analysis finally resulted positive for IgG anti-GD1a and anti-GT1b antibodies (IgG anti-GQ1b antibodies were negative).

Conclusions: Hypersomnolence and ataxia are consistent with the hypothesis of BBE. However, the atypical features of our case including the absence of ophthalmoplegia and the presence of oropharyngeal and brachial weakness, overlap with pharyngeal-cervical-brachial variant of GBS. This overlapping case provides further support that GBS variants and BBE are part of the same spectrum. The antibody profile influences the phenotype and IgG anti-GD1a and anti-GT1b antibodies may account for our atypical BBE phenotype overlapping with GBS variant. Corticosteroids are not recommended for the general management of GBS, however, their efficacy in GBS-variants might be useful.

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## A NOVEL EMILIN-1 VARIANT ASSOCIATED WITH NEURODEVELOPMENTAL DISORDER AND CHILDHOOD-ONSET POLYNEUROPATHY

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Background: Elastin microfibril interface located protein-1 (Emilin-1) is an extracellular matrix glycoprotein implicated in elastogenesis and cell proliferation. Variants in the Emilin-1 gene have been related to autosomal dominant connective tissue disease and distal neuropathy.

Case Report: We report the case of a 33 y/o man with a history of neurodevelopmental disorder, childhood-onset polyneuropathy, recurrent spontaneous pneumothorax, and HLA-B27-related syndrome with Crohn's disease and uveitis. Neurologic examination identified sensory impairment with spastic ataxic gait, limb dysmetria and acral hypo-paresthesia. Amyotrophy and hypostenia were limited to the lower extremities, with pedes cavi and absence of patellar, Achilles and plantar reflexes. Spastic dysarthria and palmomental reflex further characterized the clinical picture. Neuropsychological assessment detected attentional lability, alogia, executive dysfunction, and behavior disorder with apathy, obsessive thoughts and isolation. MRI showed FLAIR hyperintense bulbar and mesencephalic lesions with coexisting enlargement of lateral ventricles occipital horns, convexity subarachnoid space and cerebellar cisterns. Electromyography confirmed diffuse severe predominantly axonal sensorimotor polyneuropathy with a length-dependent pattern. Blood and cerebrospinal fluid tested negative for the main causes of acquired neuropathy. After negative first-level genetic analyses (PMP22, MPZ, GJB1, MFN2, FXN), Next Generation Sequencing on a panel of genes implicated in neuropathies and the subsequent segregation study revealed the heterozygous variant c.544_546delinsAAC (p.Glu182Asn) in the Emilin-1 gene. This variant maps in a coiled-coil domain of the protein involved in the supramolecular assembly and was predicted to be highly deleterious (PolyPhen-2 score: 0.943, CADD score: 25.50). Even if carrying the same variant, the proband's mother had a forme fruste, with mild signs of neuropathy and central nervous system (CNS) sparing.

Discussion: This is the first reported case of full-blown neurodevelopmental disorder and polyneuropathy, associated with a novel variant in the Emilin-1 gene. Although further research is needed, current data support a correlation with the phenotype. Neuropathy is consistent with the Emilin-1 putative function in intramuscular nerve bundles and peripheral vascular resistance. The neurodevelopmental disorder is instead in line with former studies showing central-peripheral degeneration overlap in neuropathies and suggesting a role of Emilin-1 in CNS development. Unknown genetic or environmental factors may justify the observed and previously reported phenotypic heterogeneity among relatives carrying the same variant.

Conclusion: Our findings contribute to expanding the phenotypic spectrum of Emilin-1-related pathology, corroborating its role in both central and peripheral nervous systems.

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## A NOVEL SPORADIC CASE OF MSTO1 GENE RELATED CONGENITAL MYOPATHY WITH SLOWLY PROGRESSIVE MUSCULAR INVOLVEMENT

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Objectives: To describe a novel patient affected by infantile onset myopathy and cerebellar involvement, harboring compound heterozygous variants in MSTO1 gene.

Materials: A 48-year-old woman has been followed since she was 3 years aged at our Neuromuscular Center, for delayed motor milestones, language and learning difficulty, muscle weakness. Her parents were non-consanguineous. She started walking at 3 years of age, when scoliosis, arched palate, triangular face were first noted. Subsequently, she manifested a mild progressive muscle and cerebellar involvement, with dysarthria.

Methods: Diagnostic assessment included blood tests, muscular enzymes determination, neurophysiological studies, Holter ECG 24-hour monitoring, echocardiography, respiratory function tests, brain and muscle MRI muscle biopsy, Next-Generation Sequencing (NGS) based molecular testing on leukocytes DNA performed along with fourth-years follow up.

Results: Creatine kinase (CK) was constantly elevated (min 218 - max 1750 UI/L), EMG resulted myopathic, nerve conduction and repetitive stimulation studies were normal. Whole body muscle MRI documented diffuse fatty degeneration, mostly in latissumus dorsi, anterior serratus, maximus gluteus, semitendinosus and sartorius muscles while STIR positivity occurred in some muscles. Brain MRI showed cerebellar hypotrophy; Holter ECG 24-hour, echocardiogram and respiratory testing have been regularly performed during follow up and were normal; muscle biopsy displayed chronic myopathic changes. The disease slowly progressed over 40 years of follow-up and the patient's deambulation is actually still independent; she complains running loss, difficulty in postural changes and gait, mild proximal weakness, dysphagia, dysarthria. Targeted enriched NGS panel for myopathies and congenital myasthenic syndromes was negative, while whole-exome sequencing (Illumina, TruSightONE) documented two variants (NM_018116:exon1:c.3_6del:p.Gly4Profs*68 and p.R279H) in MSTO1 predicted to be pathogenic. Her mother and the first brother

were heterozygous for one MSTO1 variant (p.R279H), the second brother for the other variant; her father died before the genetic test.

Discussion: MSTO1 is a cytoplasmic protein that regulates mitochondrial morphology and distribution. MSTO1 related myopathy is characterized by congenital/infantile onset, cerebellar and cognitive involvement, and pigmentary retinopathy, mostly recessive inherited. In our patient, we identified two likely pathogenic variants in MSTO1, one of which novel the other one previously reported. Her clinical presentation would fit with the phenotypic spectrum: slowly progressive gait disturbances, cerebellar and cognitive impairment, except for ophthalmologic involvement.

Conclusions: Our case enriches the genetic and clinical information of MSTO1 related myopathies and emphasizes the role of reverse phenotyping for addressing diagnosis of rare neurogenetic diseases assessed by NGS.

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## A CASE OF LATE-ONSET GENETIC LIPID STORAGE MYOPATHY IN A PATIENT WITH RHEUMATOID ARTHRITIS: A CASUAL ASSOCIATION?


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Objectives: Lipid storage myopathies (LSMs) are a heterogeneous group of genetic disorders characterized by abnormal deposition of lipid droplets in multiple body organs' muscle fibres. Most of the causative genes are still unknown. Adult onset LSMs usually present either with progressive muscle weakness or recurrent rabdomyolisis [1]. Here we describe the case of a patient with late-onset LSM and rheumatoid arthritis (RA).

Materials and Methods: A 71-year-old man with recent history of subacute progressive muscle weakness, exercise intolerance and rabdomyolisis underwent neurological and instrumental investigation, muscle biopsy and genetic sequencing.

Results: The patient was admitted to our emergency department complaining of gait disorder, weight loss and cramping pains of the limbs over the last three months. He struggled with climbing stairs and shaving. His past history was relevant for acute lymphoblastic leukemia (into remission) and RA, with his rheumatologist recently interrupting methotrexate for good balance. His parents were related. Neurological examination showed moderate muscle weakness (grade 4/5 for the proximal limbs) with inability to stand up from squatting. Blood tests revealed elevated muscle enzymes with Creatine Kinase 5714 U/L, Alanine Aminotransferase (ALT) 289 U/L and Aspartate Aminotransferase (AST) 605 U/L; he also had increased rheumatoid factor (422 U/mL). The EMG revealed chronic myopathy of proximal muscles [2]. Considering his oncological history, we hypothesized a paraneoplastic myopathy, but total-body PET was normal. Therefore, we thought of RA flare-up after methotrexate discontinuation and overlap syndrome with RA and polymyositis (PM), previously misdiagnosed. However, he tested negative to myositis-associated autoantibodies. He finally underwent muscle biopsy, which did not show typical pathologic findings consistent with PM but revealed numerous lipid vacuoles inside muscular fibres, especially type 1, with normal MAD activity; many fibres showed necrotic phenomena; glycogen content was normal. We thus performed genetic testing with sequencing of CPT2 (negative) and the exome sequencing (ongoing).

Discussion: Considering the biopsy results and his family history, we can conclude for a late-onset genetic LSM in a patient with RA. LSMs are usually associated with visceral involvement, especially heart and liver, so patients should also be evaluated by other specialists. To date treatment of two out of four LSMs may improve or reverse clinical symptoms, thus it is important considering LSMs as a cause of progressive weakness in adults [3].

Conclusions: To date there are no reports of an association between RA and exacerbation of LSMs, so further studies are needed to establish whether there could be a pathogenetic link.

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## PSYCHIATRIC SYMPTOMS IN MYASTHENIA GRAVIS


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Background: Myasthenia gravis (MG) is a neuromuscular disease, clinically characterized by fluctuating muscular weakness. MG have autoimmune background involving the neuromuscular transmission by the presence of specific antibodies targeting different postsynaptic components of the neuromuscular junction. The most frequently detected pathogenic autoantibodies are against acetylcholine receptors (AChRs), that can also target nicotinic AChRs present throughout the central nervous system, leading to cognitive and psychiatric symptoms in MG patients. In this case-control study, were evaluated the frequency of psychiatric symptoms in MG, as well as the clinical, immunological, and cognitive aspects.

Materials and Methods: A total of 51 MG patients matched with 48 controls, underwent anamnestic and clinical evaluation, serological testing, and behavioral/neuropsychological tests. To assess the presence and severity of depression and insomnia the Beck Depression Inventory (BDI) and the Insomnia Severity Index (ISI) was performed. The self-assessment of general psychic symptomatology was obtained by the SCL-90 scale, exploring 10 dimensions: somatization, obsessive-compulsive dimension, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, sleep disorders. The quality of life was evaluated by the Short Form 12 (SF-12)

scale, divided into Physical Component Summary (PCS) and Mental Component Summar (MCS). The frontal Assessment Battery (FAB) was used as a screening test for executive dysfunction.

Results: Somatization symptoms results significantly more represented in MG patient considering the SLC-90 subscores. Also, BDI-II score results significantly higher in MG patients respect controls. Confronting ocular and generalized MG we obtained a significant difference between the groups considering BDI-II and PCS scores. The univariate analysis showed an association between higher tilters of AChRs antibodies and higher BDI-II score. After multivariate analysis, MG patients with more generalized involvement have higher BDI-II score, while a trend toward a positive association between PCS, BDI-II and ISI score and arms/legs hyposthenia was found and a negative association between the Mestinon dosage and BDI-II score.

Discussion: The literature demonstrated an association between MG and psychiatric disorders, especially mood disorders. A cross-sectional study in Saudi Arabia reported that the odds of depression were twofold higher in MG patients. In two large meta-analyses long-term corticosteroid treatment in MG has also been linked to psychosis, depression and anxiety.

Conclusions: Depressive and anxiety symptoms usually develop as comorbidity during MG disease. This preliminary study showed the present of such psychiatric symptoms in MG. We need more studies to confirm these results with rather studies with larger number of patients.

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## FACIOSCAPULOHUMERAL DYSTROPHY: AN EPIDEMIOLOGICAL INVESTIGATION IN ABRUZZO


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Facioscapulohumeral muscular dystrophy (FSHD) is a skeletal muscle disorder characterized mainly by weakness in the facial muscles, scapula stabilizers and dorsiflexors of the foot caused by an autosomal dominant genetic defect consisting in a pathological decrease in the number of D4Z4 microsatellite repeats in the subtelomeric region of chromosome 4q35. FSHD is the third most common form of muscular dystrophy, after Duchenne dystrophy and myotonic dystrophy, with a prevalence between 1:15,000 and 1:20,000. In this survey we assessed the clinical, genetic, and epidemiological data of FSHD patients from Abruzzo followed in our Regional Centre for Neuromuscular Diseases in the last 20 years and compared with those currently available in literature in Italy and European countries (France and Netherlands). Our population consisted of 125 FSHD patients, from 68 families. Out of these, 93 patients from 48 families were from Abruzzo since almost one generation. Of these, 42.9% beginned with scapular involvement, 6.5% with facial weakness onset, 30.1% with lower limb involvement at onset, 1% experienced another onset, 19.5% were asymptomatic. Two had an allele size <15 Kb; 42 were in the 15-30 Kb subgroup and 49 had >30 Kb allele size. Regarding FSHD score 53.7% patients had 0-4 score, 27.0% a 5-9 score and 19.3% a 10-15 score. Comparing our population with the Italian data, the overall prevalence was higher (1,45/20000 vs 1,14/20000). We obtained the same result by comparing our results with those from the French FSHD registers (0.88/20'000) but a lower prevalence than in Netherlands (2.4/20'000). In addition, a further peculiar finding observed in our population was the high number of subjects with positive genetics with few or no symptoms. In conclusion we found a higher FSHD prevalence in the Abruzzo population compared with that in Italy and France but lower than Netherlands. We observed many cases of oligosymptomatic patients despite the presence of the genetic defect. These results can be attributed to the effort of the FSHD Italian network, and the deep and extensive genetic studies carried out both on patients with a suspected FSHD clinic and on their relatives, leading to a larger cohort of patients (symptomatic and asymptomatic) with a positive genetic result. Currently, more and more centre is collecting clinical and epidemiological data on these patients but further efforts are needed to better define the FSHD epidemiology and to identify patients to guarantee them early monitoring and treatment in a specialised neuromuscular diseases centre.

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## MANAGEMENT OF PRESYMPTOMATIC JUVENILE PATIENTS WITH LATE-ONSET POMPE DISEASE (LOPD)


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Objectives: To investigate the differences in disease progression and treatment response in juvenile patients with Late-Onset Pompe Disease (LOPD), compared to adult patients. To evaluate the proper timing to start Enzyme Replacement Therapy (ERT) in young presymptomatic patients.

Patients and Methods: We retrospectively collected clinical, morphological, biochemical, and molecular aspects in a cohort of 12 juvenile patients with LOPD. A longitudinal analysis of motor and respiratory functions assessed by MRC, 6MWT, GSGC, seated and supine FVC and muscle MRI findings was carried out.

Results: Mean actual age is 16.6 years. All patients were diagnosed for isolated hyperCKemia and mean age at diagnosis was 6.2 years (range 1-18). Median follow-up duration was 12 years (range 2-22). The commonest mutation was c.32-13T>G, found in compound heterozygosis in ten patients. Echocardiography was normal in all. Seven patients underwent muscle biopsy, which showed vacuolar myopathy with glycogen accumulation in four of them. Unspecific changes were detected in the other three cases. During the follow-up, five patients developed proximal muscle weakness, characterized by mild waddling gait and positive Gowers maneuver. One patient showed scapular winging. Symptoms onset occurred from 6 months to 6 years after the diagnosis. Muscle MRI revealed mild hypotrophy of the thighs before the development of symptoms in three cases. Four patients started alglucosidase alfa and one avalglucosidase alfa. Patients on ERT showed motor and respiratory stability over time.

Discussion: LOPD includes patients from 1 year of age to adulthood. The vast heterogeneity in clinical manifestations and disease progression is not fully explained, however a short disease duration and a young age seem predictors of good response to treatment. We have now sensitive diagnostic algorithms which allow an early diagnosis even in presymptomatic patients. In this subgroup, to intercept cellular pathological process, before organ damage and disease progression occur, and to choose the proper timing to start ERT is challenging. While a consistent biomarker of disease progression is still needed for LOPD, muscle MRI is a useful and sensitive tool to early detect muscle morphological alterations.

Conclusion: Juvenile patients represent an informative model for identifying prognostic factors and monitoring the disease progression under ERT. Early identification of clinical manifestations through a strict follow-up, including biannual clinical evaluation and annual muscle MRI is essential for a prompt treatment in young patients, which modifies the disease course.

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## A CASE OF RECURRENT PALSY OF THE ABDUCENS NERVE IN AN HBV-POSITIVE PATIENT


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Background: The sixth cranial nerve is prone to multiple types of damage. Its convoluted course and proximity to bone structures frequently lead to nerve compression in case of orbital traumatism or intracranial hypertension. Furthermore, this nerve is susceptible to metabolic insults, particularly related to diabetic ischemia or vitamin B1 deficiency. Sixth nerve palsy frequently exhibits a monophasic course, but recurrent impairment can also be observed, primarily as a manifestation of ocular myasthenia. We here report a rare case of recurrent palsy affecting the sixth cranial nerve, associated with an uncommon etiology.

Case Presentation: A 72-year-old man was referred to the Emergency Department due to the acute onset of binocular diplopia. The neurological and ophthalmological evaluations documented impaired left eye abduction, as confirmed by the Hess screen test. The fundus oculi examination spotted no abnormality, and a brain MRI scan excluded any orbital or cerebral abnormality. A blood workup did not support a diagnosis of diabetes, vasculitis, or thyroid pathology. Serum tests for myasthenia-related antibodies (anti-AchR, anti-MuSK) were negative. The patient's medical history only included HBV chronic infection. In the past fifteen years, the patient had experienced two similar episodes, affecting the same nerve and side. In the past episodes, the patient had undergone the same diagnostic workup, which resulted negative and was treated with oral steroid therapy that resolved the symptoms within a month. A subsequently implemented oral prednisone regimen proved effective in reducing the severity of diplopia.

Conclusions: The patient was diagnosed with recurrent sixth nerve palsy, likely due to HBV. Peripheral neuropathy is not an uncommon manifestation in patients with chronic hepatitis virus infection. However, cranial nerves are usually spared by HBV or may be involved in complex or atypical presentations.

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## CHECKPOINT INHIBITOR-INDUCED AUTOIMMUNE MYOSITIS WITH MYOCARDIAL INVOLVEMENT: THE IMPACT OF EARLY IDENTIFICATION AND SPECIFIC TREATMENT ON NEUROLOGICAL RECOVERY


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Objectives: Immune Checkpoint Inhibitor (ICI)-related autoimmune myositis is an example of toxicity occurring in 0.38% of patients treated with ICIs [1]. This condition has shown to have a poor prognosis, especially for cases with myocardial involvement [1], which occurs in 41% of cases of (ICI)-related autoimmune myositis [1]. Therefore, prompt identification and specific treatment are critical key points to determine a better outcome.

Materials and Methods: We present the case of a 73 years-old man with a metastatic G3 urothelial bladder carcinoma who developed ptosis in left eye, mild anisocoria, horizontal diplopia in binocular vision due to bilateral abduction deficit, hypophonia and parahyposthenia two weeks after a first administration of Pembrolizumab.

Results: Diagnosis of immune-mediated myositis was made by clinical findings, electromyography, and the evidence of anti-titin antibody positivity. A bicameral pacemaker was implanted and a coronary angiography with PTCA was carried out with the placing of a DES on the IVA due to the development of a III-degree atrioventricular block and cardiac troponin elevation. An intravenous corticosteroid cycle of Solumedrol 4 g was administered without benefit. A subsequent cycle of plasmapheresis (a total of 6 sessions) was performed, with full regression of signs and symptoms. Intravenous immunoglobulins were not administered due to the prothrombotic risk. After 22 months the patient still presented with no residual neurological deficits.

Discussion: The features of our case are in line with the literature, which showed that bulbar signs resulted to be independently associated to the development of myocardial involvement [1]. This condition turned out to be resistant to standard corticosteroid treatment, making necessary more aggressive strategies such as plasmapheresis, performed in 47% of ICI-related myositis with myocardial involvement [1]. However, our case adds important considerations about the outcome. Referring to the literature, death occurred in 53% of subjects affected by ICI-related myositis with myocarditis, despite the treatment, with 83% of cases directly caused by myositis [1]; instead, our

patient had a full recovery after a plasmapheresis cycle and no residual neurological deficit at 22 months.

Conclusions: ICI-related myositis is a rare but potentially fatal condition that can occur in patient treated with checkpoint-inhibitors immunotherapy. Myocarditis is a serious complication of ICI-related myositis, which can hesitate in treatment refractoriness and poor prognosis [1]. On the other hand, an early recognition and subsequent specific relatively aggressive treatment such as plasmapheresis can determine a better prognosis and even full neurological recovery.

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## BUILDING AN INTEGRATED MACHINE LEARNING-BASED PLATFORM TO STUDY FSHD: FROM DEEP PHENOTYPING TO PREDICTIVE BIOMARKERS

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Introduction: Facioscapolohumeral muscular dystrophy (FSHD) represents a complex disease with high clinical variability and an intricate genetic landscape. Diagnostic criteria are based on the detection of the molecular signature (contraction of D4Z4 repeat units at 4q35 and/or hypomethylation in presence of 4qA permissive allele); however, this paradigm does not completely fulfill the understanding of phenotypes and disease natural history and often complicates familial genetic counseling.

Aims: Many molecules are at study both in pre-clinical and clinical trials, further prompting the need for prognostic indicators and biomarkers describing disease progression. A diagnostic flow-chart based only on genetic signature may not highlight the differences among patients and possibly bias the interpretation of response to a certain treatment. On the other hand, the clinical complexity hides further molecular mechanisms to be investigated.

Methods: Starting from these considerations, we aim at using FSHD as a disease model and develop a dedicated digital platform that can comprehensively collect all the variables involved, enabling a deep phenotyping towards a personalized plan of diagnosis and care. This will be achieved through an integrated and multiparametric approach, converging on a single support cloud-based, GDPR-compliant platform.

Study proposal: The study will involve a multicenter collaboration between neurologists and IT-professionals. The platform will be developed starting from the structure of the Clinical Comprehensive Evaluation Form, a tool shared by the Italian Clinical Network for FSHD, and will comprise modules for phenotype and pedigree, genetics and MRI. A machine-learning approach will inform automatic algorithms for recognition of clinical, genetic and imaging patterns and provide clinicians with correlation analysis among variables.

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## HYPERKINETIC MOVEMENTS AND PARKINSONISM IN AXONAL SENSORY NEUROPATHY: ATYPICAL PATHS TO CANVAS

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Introduction: Cerebellar ataxia neuropathy vestibular areflexia syndrome (CANVAS) is a rare, inherited, late-onset, and slowly progressive disease, characterized by cerebellar ataxia, bilateral vestibular areflexia, and peripheral sensory neuropathy caused by the pathogenic biallelic pentanucleotide intronic repeat expansion in replication factor complex subunit 1 (RFC1) gene. [1]

Case report: A 64-years-old Caucasian woman with cerebellar ataxia and sensory neuropathy associated with hyperkinetic extrapyramidal syndrome came to our clinic in 2021. Her symptoms had started about seven years earlier with postural imbalance and dizziness. In addition, her past medical history included bronchial asthma, discopathies, arthropathies and mood tone deflection. The family history was unremarkable. Initial neurological examination revealed nystagmus, decreased reflexes and absent ankle reflexes, reduced vibration and joint position sense throughout with ataxic gait and positive Romberg sign, bradykinesia in the tapping test on the left with signs of plastic rigidity in the activation tests on the left upper and lower limbs, bilaterally rising movements of the hands. Laboratory tests were normal. Brain MRI showed cerebellar atrophy, with diffuse white matter hyperintensity and bilateral pallidal microdeposits. Nerve conduction studies showed sensory axonal polyneuropathy with normal motor action potentials. DAT-SPECT imaging was normal. Testing for acanthocytosis was negative. In the suspicion of parkinsonism, a therapeutic test was started with levodopa, without any significant improvement. Subsequent neurological evaluations highlighted: progressive worsening of the ataxia with the need of support for walking, the appearance of mild orthostatic and postural tremor and reduced vestibulo-ocular reflexes. These finding lead to suspicion of CANVAS syndrome with associated parkinsonism. An NGS panel for parkinsonism and hereditary ataxias was performed, which excluded common genetic ataxic syndromes and showed biallelic intronic AAGGG repeat expansion in RFC1 gene, thus confirming CANVAS. In addition, due to prominent hyperkinetic distal movements, a genetic testing in the HTT gene was performed, showing a number of CAG triplets in the lower bounds (two distinct alleles of 16 and 25 CAG repeat units).

Discussion: This case illustrates the phenotypic variability in patients with biallelic expansions in RFC1. Since the identification of the AAGGG expansion, the association between RFC1 gene and parkinsonism have been rarely reported [2]. Indeed, we may hypothesize that deafferentation of sensory stimuli from distal part of the body could favor hyperkinetic phenomena such as the "alien limb" phenomenon [3]. Furthermore, the CAG triplets expansion of the HTT gene in this patient, although not pathogenic, might have a clinical role in the pathophysiology of extrapyramidal symptoms.

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## LATE-ONSET MPZ-RELATED CMT: A TRANSLATIONAL COMPARISON OF P70S AND T124M MUTATIONS

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Background/Objectives: Neuropathies related to Myelin Protein Zero (MPZ, P0) mutations are very heterogenous and in Italy represent 10% of Charcot-Marie-Tooth disease (CMT) cases [1]. They are associated either with primary demyelinating CMT neuropathy with early onset (CMT1B) or with late onset predominantly axonal neuropathy (CMT2I/J) [2]. In this study we investigate two P0 mutations (P70S and T124M) associated with CMT2I and CMT2J, respectively.

Materials and Methods: By a translational approach, we have extensively characterized the clinical and neurophysiological phenotype of a large P70S-CMT2I population (n=29, with a likely founder effect in Northern Italy) and of eight T124M-CMT2J patients and studied axon-glial dysfunction mechanisms in cellular and animal models. We also evaluated a sural nerve and 12 skin biopsies from P70S-CMT2I patients by electron microscopy (EM) and immunohistochemistry (IHC), and three skin specimens from T124M-CMT2J subjects.

Results: P70S patients showed later onset and milder phenotype than T124M study participants (age of onset mean 52 vs 39 years, CMTES mean 9 vs 11/28). Upper limb motor nerve conduction velocities were in the CMT2 range in both patients' groups (42–60 m/s). Sensory impairment involved mainly vibration and pinprick sensation both in P70S and T124M subjects. 5/8 T124M patients had pupillary changes and 2/8 hearing loss. In vitro studies demonstrate that the P0-P70S mutant: reaches the cell membrane and does not co-localize with endoplasmic reticulum markers; maintains adhesion properties and is normally glycosylated whereas P0-T124M mutation prevents N-glycosylation and is likely responsible for extra modification not yet identified. Concerning the two authentic mouse models generated, T124M animals well recapitulate human disease [3]. P70S mice show only minimal evidence of axonal damage even at a late age but proteomic analysis will clarify the potential alteration of proteins involved in axonal transport. Finally, in EM the collected nerve and skin samples from P70S-CMTI patients reveal mostly normal nodes and very few abnormal paranodes. Preliminary results by IHC suggest a possible Schmidt-Lanterman incisures' involvement at least in T124M skin biopsies.

Discussion and Conclusions: How a mutation in a myelin protein causes an axonal neuropathy is still unclear but the role of P0 in Schwann cell/axon interactions appears crucial. With a translational approach we are starting to elucidate the role of the two variants in generating the CMT2I/J neuropathies.

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## A NOVEL MUTATION IN THE LRSAM1 GENE IN A FAMILY WITH AUTOSOMAL DOMINANT CHARCOT-MARIE-TOOTH TYPE 2P

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Objectives: Charcot-Marie-Tooth type 2P is a rare genetic axonal hereditary sensory-motor neuropathy disorder caused by mutations in the LRSAM1 gene.

Materials and Methods: We describe two siblings presenting with slowly progressive axonal sensory-motor polyneuropathy harboring a novel variant in LRSAM1 with autosomal dominant (AD) inheritance. Additionally, we conducted a review of the literature focusing on patients carrying a variant similar to the one reported herein.

Results: The proband, a 56-year-old woman, has been experiencing progressive distal lower-limb neuropathic pain and weakness since childhood. She started using foot-orthosis at the age of 25. Due to severe sensory ataxia and several accidental falls, she became wheelchair-bound at the age of 62. Neurological examination revealed moderate muscle weakness in ankle plantar/dorsal flexors, reduced pinprick and vibration sensations in the legs up to the knees, and absent deep tendon reflexes in lower limbs. Nerve conduction studies revealed sensory-motor axonal polyneuropathy in the lower limbs. Similarly, the proband's 48-year-old brother has been experiencing progressive symptoms since adulthood and began using unilateral assistance after a series of accidental falls. Clinical Exome Sequencing revealed a novel heterozygous variant, specifically c.2039_2043dup (p.Glu682AsnfsTer6), in the LRSAM1 gene. This variant resulted in a premature stop codon and loss of the RING motif, which is crucial for LRSAM1 activity.

Discussion: Our report presents clinical and genetic data from two patients belonging to the same family and carrying a novel heterozygous variant in the LRSAM1 gene. These patients exhibited phenotypes characterized by axonal polyneuropathy, with a predominant involvement of the sensory domain. This observation aligns with previous findings in Sardinian patients with AD CMT2P, who carried a closely related heterozygous mutation (p.Ala683ProfsX3). These findings confirm the variable age of onset, ranging from childhood to adulthood, and the slowly progressive disease course associated with CMT2P. Furthermore, we reported another closely related mutation (Glu680Asnfs*6) which has been reported in two patients with an early age of

onset (32 and 27) and initial sensory symptoms. Patients with a variant closely related to the one we reported, (p.Glu682_Ala683ins21), displayed impaired sensation of touch and disturbed proprioception.

Conclusions: This study expands the mutational spectrum of the LRSAM1 gene in CMT2P. Our data further validate the typical clinical hallmark of CMT2P as relatively mild and very slowly progressive axonal neuropathy, primarily affecting sensory domain. However, it is essential to recognize that, the sensory impairment associated with CMT2P can rarely impact functional independence, necessitating the use of unilateral assistance or wheelchair.

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## COGNITIVE ESTIMATION BUT NOT EMPATHY IS IMPAIRED IN PATIENTS WITH MYOTONIC DYSTROPHY TYPE 1. A VOXEL-BASED MORPHOMETRY STUDY


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Objective: Myotonic dystrophy type 1 (DM1) is the most common muscular dystrophy in adults that affects several organs including the brain [1-2]. High level cognitive dysfunctions have been reported including social cognition deficits [3]. Aim of the present study was to deepen social cognition deficits and their neural correlates with a special interest on cognitive estimation abilities and empathy in DM1 patients.

Methods: 10 DM1 patients and 12 Healthy Controls (HC) underwent an extensive cognitive assessment including the Cognitive Estimation Task (CET) and the Empathy Quotient- EQ. They also underwent 3T-MRI scanning to collect T1-weighted volumes for voxel-based morphometry analyses. One-way ANOVAs were used for between-group comparisons in neuropsychological data. A two-sample T-test model was used to compare groups in grey and white matter volumetrics (GM and WM). Finally, one-sample T-test models were used to assess potential associations between neuropsychological variables and GM volumes in all individuals.

Results: Compared to HC, DM1 patients showed lower performances in several tests of the administered cognitive evaluation including the CET and in the filler items of the EQ. DM1 patients compared to HC showed the expected pattern of GM (parahippocampal gyrus, frontal pole, medial frontal gyrus, inferior temporal and fusiform cortex) and WM (fimbria, longitudinal inferior fasciculus, fronto-occipital fasciculus) volumetric decreases. Moreover, DM1 patients showed an inverse association between error scores on CET and GM volumes in the fronto-temporal cortex and angular gyrus, and an inverse association between the filler items of EQ and GM volumes in the anterior cingulate cortex. Finally, HC showed inverse associations between error scores on CET and GM volumes in the cerebellum.

Conclusion: This study confirms the presence of social cognition deficits in DM1 patients highlighting the role played by the cognitive rather than empathetic aspects, the latter resulting preserved. VBM suggests a neurobiological substrate for these higher-level abnormalities that impact on everyday-life activities and success of DM1 patients.

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## A NOVEL DNM2 MUTATION IN A CASE OF A HEREDITARY PURE SENSORY AXONAL POLYNEUROPATHY


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Aims of the Study: Dynamin 2 (DNM2) belongs to a family of pleiotropic GTPases that mediate several cellular processes including endocytosis, actin assembly and centrosome cohesion. Mutations in DNM2 gene are associated with centronuclear myopathy, intermediate and axonal Charcot-Marie-Tooth (CMT) disease and lethal congenital contracture syndrome. The aim of this stydy is to report a new mutation in DNM2 gene associated to a hereditary pure sensory axonal polyneuropathy.

Material and Methods: We describe the case of a 59-year-old male who at the age of 30 presented an insidious onset of lower limbs numbness and burning pain that worsened in the last years leading to gait disturbances. His family history was positive for gait disorders. He, also, had been suffering for a long time from severe constipation and an abdominal X-ray revealed a giant faecaloma. Neurological and cognitive evaluation revealed bilateral pes cavus with hammer toes and visuo-spatial deficits associated to diffuse atrophy at Brain Magnetic Resonance Imaging scan. Nerve conduction study revealed a pure axonal sensory polyneuropathy. A genetic study was performed.

Results: The genetic and sequence analysis identified the heterozygous mutation NM_001005360.2:c.[383A>G]; NP_001005360.1:p.(His128Arg) in DNM2 gene (OMIM # 602378).

Discussion: We described clinical, instrumental and genetic aspects in a patient affected by pure sensory axonal polyneuropathy and carrying the novel p.Hys128Arg-DNM2 heterozygous mutation, which further expands the spectrum of DNM2 mutations and related phenotypes. Other interesting features are cognitive deficits and the stubborn constipation that we speculate is an expression of gastro-intestinal autonomic dysfunction, and we speculated that their association with DNM2 mutations could be not purely coincidental. However, additional series of DNM2 mutations carriers, adequately screened cognitive or for dysautonomic disorders, as well as further functional studies, will

be needed to verify this hypothesis and elucidate its possible underlying mechanisms.

Conclusions: This is the first description of a pure sensory axonal polyneuropathy associated with a novel p.Hys128Arg-DNM2 heterozygous mutation.

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## DEMOGRAPHICS, CLINICAL CHARACTERISTICS, AND RISK FACTORS IN PATIENTS WITH ISOLATED ACUTE-ONSET DIPLOPIA AND PTOSIS: A RETROSPECTIVE STUDY

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Objective: This retrospective study investigated demographics, clinical characteristics, and risk factors in patients admitted to the neurology unit with isolated acute-onset diplopia or ptosis.

Materials and Methods: A retrospective analysis of 5000+ medical records from 2016-2022 was conducted. Inclusion criteria: words "diplopia" or "ptosis" in medical history, presenting symptoms, or neurological examination, an extensive diagnostic work-up (brain magnetic resonance imaging, electromyography, lumbar puncture when required).

Exclusion criteria: Monocular diplopia, pre-existing ptosis, other neurological signs/symptoms beyond diplopia or ptosis, previous diagnosis of myasthenia gravis or multiple sclerosis, unclear discharge diagnosis. We assessed presence of diplopia/ptosis, cranial nerves involved, discharge diagnosis, and risk factors (hypertension, dyslipidemia, diabetes, stroke/myocardial infarction (MI) history). Differences in demographic and clinical characteristics between diagnosis groups were assessed through Kruskal-Wallis or Chi-squared as appropriates.

Results: Out of 126 selected patients (median age: 62; male-to-female ratio: 2.8:1), 85 (67%) had isolated diplopia, 4 (3%) had isolated ptosis, and 37 (30%) had both. Associated cranial nerve palsies included: abducens (36%), oculomotor (36%), trochlear (11%), two nerves involvement (6%), one patient had three nerves involved. Twelve cases lacked data about nerve involvement. Most common underlying mechanisms were: idiopathic mononeuropathy (IM) (50 patients), myasthenia gravis (MG) (28 patients), multiple sclerosis (MS) (19 patients) and ischemic strokes (IS) (15 patients). Younger age was associated with MS ($p<0.001$). Three out of 4 Isolated ptosis were diagnosed as MG. Among patients with Isolated diplopia: 15% was diagnosed as IS (13), 45% as IM (39), 18% as MS (16) while only 10% was diagnosed as MG. Almost half (16/37) of patients with diplopia-ptosis co-occurrence was diagnosed as MG ($\chi^2=29.7$, $p<0.001$). IV and VI cranial nerve palsy were associated with IM, while third nerve palsy was more common in MG. Co-occurrence of multiple cranial nerve palsies was similarly linked to MG and MS ($\chi^2=94.7$ $p<0.001$). Pre-existing stroke/MI and dyslipidemia were strongly associated with new-onset IS ($\chi^2=12.5$, $p<0.001$ and $\chi^2=22$, $p<0.001$ respectively). Hypertension was likewise associated with IS, MG, and IM ($\chi^2=24$, $p<0.001$). Diabetes prevalence was lower in MG than in IM, systemic polyneuropathy and IS groups ($\chi^2=15.8$, $p=0.001$).

Discussion and Conclusion: Our study provides insights into isolated acute-onset diplopia/ptosis based on a large sample and extensive time frame. Age, gender distribution, and cranial nerves involved align with previous research. Associations were found between risk factors and diagnoses: younger age with MS, III nerve palsy with MG, stroke/MI history and dyslipidemia with IS. Diabetes prevalence was lower in MG compared to other causes.

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## HOMOZYGOUS R596G VARIANT IN TRIM32 GENE RELATED TO LGMD IN A NON-HUTTERITE PATIENT

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Objectives: TRIM32 is a member of the Tripartite–Motif family of proteins characterized by a RING finger, a B-box motif, a coiled-coil region and six NHL-repeats [1]. TRIM32 has E3 ubiquitin ligase activity by participating in myofibrillar protein turnover. D487N mutation in the TRIM32 gene, has been associated with Limb Girdle Muscular Dystrophy Recessive type 8 (LGMDR8) in the inbred Hutterite population. We reported R596G homozygous missense variant in TRIM32 gene in a 54-year-old patient with LGMD from south Italy.

Material and Methods: Molecular analysis of the DYSF and FKRP genes was performed on the patient's DNA by direct sequencing. Subsequently the analysis was extended to 40 genes related with LGMD by NGS.

Results: We have identified in the patient a homozygous variant R596G in TRIM32 gene and the L276I heterozygous mutation in FKRP gene. The patient's parents were consanguineous.

Discussion and Conclusions: LGMDR8 was first described in Hutterites associated with the D487N mutation in the TRIM32 gene. To date, some missense, deletions, frameshifts variations in the same gene have been identified in European patients affected by LGMDR8. All variations fall into NLH domains of the TRIM32 gene. These domains are probably essential for the recognition of protein target that TRIM32 will have to ubiquinate [2]. We reported a patient with difficulty walking especially uphill already in the first decade of life. At about 22, he showed nocturnal calf cramps, hypotrophy and weakness of the shoulder girdle muscles, anterior tibialis and perineal deficits bilateral in the lower limbs, pes cavus, positive Gower, stepping gait, increased CPK and ventilatory failure. Immunohistological analysis of bioptic muscle tissue showed hypo/hyper atrophic fibers mainly rounded in shape, lipid accumulation, increase in

collagen and adipose tissue. Molecular analysis conducted by NGS for this patient showed the R596G homozygous missense variant in TRIM32 gene. This variant has been reported in the literature in a patient from southern Italy as probably pathological [3]. In silico analysis as Polyphen, MutPred2, Polyphen2, Panther, Sift, Mutation Taster also support a deleterious effect of the variant. Moreover, the patient showed the heterozygous Leu276Ile mutation in the FKRP gene which is the most frequent mutation responsible for LGMDR9. Both variants are likely responsible for the patient's phenotype with an additive effect. In fact, TRIM32 and FKRP proteins are part of the same pathway and they are essential for maintaining the integrity of the dystrophin glycoprotein complex.

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## A CASE OF ANTI-HU PARANEOPLASTIC BRAINSTEM ENCEPHALITIS AND SUBACUTE SENSORY NEUROPATHY IN A PATIENT WITH ADVANCED PROSTATE ADENOCARCINOMA

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Paraneoplastic neurological syndromes (PNS) are rare immune-mediated neurological disorders that commonly occur with certain malignancies; the most common is small cell lung cancer but prostate cancer is also related in 2.5%-6.3% of cases. Anti-Hu antibody associated syndrome is the most common form of PNS. A 75-year-old man with a history of metastatic prostate adenocarcinoma mildly responsive to radiotherapy and androgen-deprivation therapy came to our observation with a six-month history of progressive distal paresthesia and postural and gait instability. He then developed difficulty articulating speech and dysphagia. The neurological examination showed distal lower limb hypoesthesia and paresthesias, diffuse hypotrophy with sensory ataxia prevalent in the lower limbs with areflexia. Inability to maintain a sitting position due to retropulsion and gait ataxia. Brain MRI showed a mild medullo-pontine atrophy and a T2 and FLAIR hyper intense-appearing images of the posterior portion of the left thalamus with increased diffusivity. EMG revealed a sensory axonal neuropathy with mild upper motor neuron signs and sensory evoked potentials showed peripheral involvement. Cerebrospinal fluid analysis showed only mildly elevated protein levels (81 mg/dl) and no cancer cells. A whole-body contrast-enhanced CT scan showed no disease progression. Then we tested a panel of cancer-associated auto-antibodies with positive anti-Hu antibodies results. A diagnosis of paraneoplastic neuropathy and brainstem encephalitis was made. The patient was treated with high doses of steroids but no significant improvement was observed and severe dysphagia necessitated the placement of a PEG. Anti-Hu antibodies has been reported in a large number of patients with various neurological disturbances including subacute sensory neuropathy, limbic encephalitis, brainstem encephalitis, chronic gastrointestinal pseudo-obstruction and paraneoplastic cerebellar degeneration. The clinical symptoms may be confined to one part of the nervous system or, more frequently, involve multiple areas overtime. Anti-Hu associated brainstem encephalitis usually presents subacutely with preferential involvement of the medulla and represents the predominant syndrome in 11% of anti-Hu positive patients. Paraneoplastic syndromes arise infrequently in prostate cancer and when they occur, it is usually in the setting of small-cell carcinoma of the prostate or advanced, hormone-resistant disease. We report a case of anti-Hu brainstem encephalitis presenting with dysarthria and dysphagia, with concomitant sensory neuropathy leading to a progressive disabling ataxia associated with a prostate tumor. To the best of our knowledge, this is the first case of association of a subacute sensory neuropathy and brainstem encephalitis in a patient with advanced prostate adenocarcinoma.

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## CHARCOT MARIE TOOTH DISEASE ASSOCIATED WITH MME MUTATIONS: A CASE SERIES FROM FLORENCE, ITALY

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Objectives: Charcot Marie Tooth disease (CMTD) type 2T is an axonal motor and sensory neuropathy characterized by adult onset of slowly progressive distal muscle weakness and sensory impairment. CMTD2T patient harbour mutations of the gene for the membrane metalloendopeptidase (MME), also called neprilysin or CD10, a transmembrane protein with a wide spectrum of substrates and physiological functions. CMT2T is a recessive disease; however dominant MME variants with incomplete penetrance have also been reported. Here we describe a small case series of patients with neuropathy associated with biallelic and monoallelic MME mutations.

Material and Methods: All the cases diagnosed at AOU Careggi affected by polyneuropathy with a MME mutation were reviewed. Demographic, EMG, laboratory, and clinical data were examined. All the patients alive gave informed consent to the study.

Results: We included 8 patients (6 females) in 6 families, 4 with biallelic and 4 with monoallelic MME mutation. Two patients were siblings and two were related (mother and daughter); altogether we found 6 different MME mutations. The mean age at disease onset was 56.5 years, younger among patients with homozygous mutations (51) as compared with those with heterozygous mutations (62). In all the cases the EMG examination disclosed a length-dependent prevalently axonal polyneuropathy, though the conduction velocities were also markedly reduced in all but 1 case. Mean CMT neuropathy score at last examination was 13, without differences among the two groups. Seven patients

were also affected by one or multiple autoimmune conditions (multiple sclerosis, celiac disease, Sjogren syndrome, anti-GAD associated epilepsy, Hashimoto thyroiditis, etc) and two had an IgG monoclonal gammopathy. Three patients had been previously diagnosed with other disorders (motor neuron disease, inflammatory polyneuropathy, compressive radiculopathy).

Discussion: Our data confirm the older age at onset of CMT2T with heterozygous mutations; however, contrary to what observed by others, the severity of the disease did not differ between patients with heterozygous and homozygous mutations. Interestingly, all the patients were affected by autoimmune diseases and/or monoclonal gammopathy, which could result from a dysfunction of the immune system as the result of the MME/CD10 gene mutation. Further studies are needed, however, to clarify this hypothesis.

Conclusion: Our data contribute to the knowledge of hereditary neuropathies with late and very late onset. We hope to encourage a collaborative multicenter Italian study on MME mutations.

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## MELANOMA-ASSOCIATED CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: MORE THAN MEETS THE EYE

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Introduction: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare acquired immune-mediated peripheral neuropathy characterized by demyelination, generally responsive to immunosoppressive/immunomodulatory treatment. It can occur independently or in association with other diseases, including malignancies. We present an unusual case of a CIDP preceding a metastatic melanoma diagnosis.

Case report: A 54 years-old man presented with lower limbs paresthesias followed by bilateral weakness, to the point that he was unable to walk. Neurologic examination showed a moderate tetraparesis, diffuse paresthesias and unevokable deep tendon reflexes in the lower limbs. His medical history was unremarkable, except for a recent trip in the Philippines. A whole spine gadolinium-enhanced MRI showed cauda equina roots' hyperintensity, and EMG/ENG showed a sensorimotor demyelinating polyradicoloneuropathy; subsequently, a lumbar puncture was performed, with increased protein and normal glucose levels, 10 cells, a negative microbiological exam (including Borrelia, Flavivirus and Leptospira) and a damaged blood-brain barrier. Anti-MAG antibodies were positive, with a titer of 1:80, and so were anti-GD1A-IgG: anti-CASPR1, anti-contactin-1 and anti-neurofascin antibodies were negative. IVIG were administered for six days with unsatisfactory results. Methylprednisolone was then administered for five days, followed by five plasmapheresis procedures: a modest but temporary benefit was appreciated. Two chest-abdomen contrast-enhanced CT scans were performed in two months, the second of which showed an axillar lymphadenomegaly that revealed itself to be a melanoma metastasis. A dermatological examination found no lesion, while a global 18-FDG PET-scan showed a rectal and prostatic captation.

Discussion: When talking about paraneoplastic peripheral nervous system syndromes, there is a flourishing literature about hematological malignancies (mostly lymphomas), but fragmentary informations regarding solid tumors [1]. Melanoma-related CIDP has been described mainly in case reports, in contrast to the one associated with immunotherapy and immune-checkpoint inhibitors, the mainstay of this tumor treatment [2]. This case shows one of the possible diagnostic pitfalls in CIDP. The recent travel has initially led to speculations about a parainfectious etiopathogenesis, but a thorough investigation finally revealed the concomitant malignancy. Moreover, anti-MAG and anti-GD1A antibodies positivity, a potential confounding element, can be seen as a molecular mimicry phenomenon in an autoimmune arousal [3].

Conclusions: Although classically linked to other malignancies, melanoma must be considered in the CIDP diagnostic workup. Dermatological examination and stadiation with CT/PET scans are therefore required, especially when there is an unsatisfying response to IVIG and plasmapheresis. Unfortunately, there is insufficient evidence to determine whether this paraneoplastic syndrome correlates with a different prognosis or with peculiar electrophysiological and immunologic features.

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## CLINICAL AND ELECTROPHYSIOLOGICAL CHARACTERIZATION OF IGM-ASSOCIATED POLYNEUROPATHY, WITH OR WITHOUT ANTI-MAG ANTIBODIES: A CROSS-SECTIONAL STUDY

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Objectives: Clinical and instrumental assessment of a population with paraproteinemia-associated polyneuropathy, with or without serum reactivity to myelin-associated glycoprotein (MAG-Ab+/-).

Materials: We included 28 subjects (21 males, 7 females) with diverse haematologic diagnosis (MUGS: 18, Waldenstrom macroglobulinemia: 8, lymphoplasmacytic lymphoma: 1, non-Hodgkin B lymphoma: 1). Average age is 72.5 years (52-90). Average polyneuropathy duration is 9.3 years (1.2-22). Fifteen subjects received rituximab, one received cyclophosphamide, five received high-dose corticosteroids, one underwent periodic IvIg infusions for two years and two additional subjects were taking long-term oral corticosteroids because of concomitant rheumatological diseases.

Methods: Participants underwent MAG-Ab determination, clinical and disability evaluation (including mRS, ONLS, BERG, IRODS), extensive electrodiagnostic (EDX) testing including Terminal Latency Index (TLI) and modified F-ratio (mFR) determinations [1]. Additionaly, Quantitative Sensory Testing (QST) and, in a subset of 19 subjects, a force platform computerised balance assessment were performed.

Results: Twenty-eight subjects were MAG-Ab+. Clinically, polyneuropathy presented with distal symmetric reduced sensitivity (89%), paresthesia (61%), pain (21%), impaired gait/balance (57%), postural tremor (57%), muscle weakness (36%), cramps (57%). Eleven subjects (46%) reported some disability (mRS ≥2), 4 (14%) used walking aids and one (3,6%) was wheelchair-restricted. MAG-Ab+ subjects did not show significantly different disability than MAG-Ab- (mRS ≥2 in 50% vs. 40%; BERG score <45 in 33% vs. 30%; mean IRODS score 36,7 vs. 33,2, respectively). On EDX, eleven subjects had a predominantly axonal polyneuropathy (2 MAG-Ab+, 9 MAG-Ab-) and seventeen a predominantly demyelinating polyneuropathy (16 MAG-Ab+, 1 MAG-Ab-). All demyelinating polyneuropathies appeared symmetric, and nine showed a prominent distal involvement with at least one TLI <0.25 (including the MAG-Ab- case); TLI was not assessable due to severe impairment of different motor nerve responses (CMAP not elicitable) and/or median nerve entrapment at wrist in six patients. Two additional MAG-Ab+ cases showed an ulnar mFR >3.25, suggestive of proximal demyelination, together with TLI reduction. Spontaneous activity was recorded in distal muscles in eight cases (4 MAG-Ab+, 4 MAG-Ab-).

Discussion: Consistently with literature, MAG-Ab were associated with distal demyelinating and prominently sensory polyneuropathy. However, we found two MAG-Ab+ subjects with a primarily axonal neuropathy, and one IgM-associated distal symmetric demyelinating polyneuropathy without MAG-Ab. We also describe clinical and EDX evidence of relevant motor involvement. While half the patients showed some disability, only a few displayed severe mobility impairments.

Conclusions: The study outlines the heterogeneous peripheral nerve involvement in IgM paraproteinemia. QST, stabilometry and a twelve-months follow-up will provide additional insights.

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## NOT JUST A LAZY TEEN: A CASE OF A REVERSIBLE NEUROMUSCULAR CONDITION

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Objective: Highlight the importance of considering rare treatable neuromuscular conditions, such as lipid myopathies, among the differential diagnosis of weakness and fatigue.

Materials: Medical history, laboratory tests, imaging, muscle biopsy workout.

Methods: Review of the patient's history, clinical assessments, laboratory tests, and therapy.

Results: We report a case of a 17-year-old woman who accessed the ER for a 4-month progressive severe fatigability and myalgias, exacerbated by physical activity. Family and personal history were not relevant, apart from a long-standing refusal to practice sports, with a request for exemption from physical education at school and psychological support for depressive symptoms. No chronic medications were assumed. Previous cardiological assessments with echocardiography and ECG had resulted normal. All lab tests were normal, except for elevated CK (2769 UI/L). At neurological examination proximal girdle weakness, lumbar hyperlordosis, and waddling gait were observed. Thyroid tests, immune-rheumatological screening, neuromuscular junction antibodies, myositis-specific and myositis-associated antibodies tested negative; a lower limbs muscle MRI showed hyperintensities in STIR and T1 sequences in the thighs, significant for edematous areas and initial fibro-fatty substitution. After 21 days, a quadriceps muscle biopsy excluded an inflammatory myopathy, showing a diffuse, marked lipid accumulation in myofibers. The acylcarnitine profile on DBS confirmed an increase of the C8-C18 chains and the organic acid profile was altered (organic aciduria). Even though a genetic diagnosis was not available yet, the clinical signs and the laboratory findings suggested a diagnosis of Multiple Acyl-CoA Dehydrogenase Deficiency. The patient, therefore, started supplementary therapy with riboflavin, carnitine, and ubidecarenone with significant benefits to her condition. At neurological re-evaluation, after 3 months, neither myalgias nor fatigue were reported, and a clear improvement in proximal strength was observed.

Discussion: Lipid myopathies are characterized by a spectrum of clinical manifestations varying from severe infantile forms to paucisymptomatic adult-onset conditions, due to defects of mitochondrial fatty acid transport or metabolism [1]. In milder forms, hyperckemia and/or limitation in physical activity may be the only signs, whose timely detection may reduce the diagnostic delay and allow a prompt effective therapy.

Conclusions: Common non-specific symptoms such as fatigue and myalgias in teenagers might hide underestimated conditions. Although rare disorders, the presence of neuromuscular red flags should prompt further investigations. In this case, the patient recovered after a rapid laboratory and histological diagnosis and appropriate treatment [2,3]. Muscle biopsy may represent a faster tool for investigating neuromuscular treatable conditions than genetic assays, especially in differential diagnosis of seronegative inflammatory myopathies.

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## DIAGNOSTIC COMPLEXITIES IN TWO FAMILIES WITH DESMINOPATHY

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Introduction: Mutations in the desmin gene (DES) produce a variety of myopathic phenotypes including myofibrillar myopathy and limb-girdle muscular dystrophy, cardiomyopathy, ventricular arrhythmia and/or cardiac conduction disease including atrioventricular blocks. Desminopathies are often characterized by the presence of intracellular accumulation of desmin aggregates and their inheritance is typically autosomal dominant. We describe two families of desminopathy carriers presenting different clinical features. Family 1: A 54 y.o. man came to our attention for a history of myalgias and weakness in lower limbs. Notably, his brother and mother were followed by the Neurology Unit

of our hospital for a diagnosis of distal myopathy associated to the c.1280A>T variant in DES gene, predicted to be pathogenic through a splicing alteration. His muscle MRI showed slight oedema of right posterior leg. At muscle biopsy we observed several subsarcolemmal basophilic aggregates and the ultrastructural examination confirmed a pattern consistent with a myopathy likely to be classified as a myofibrillar myopathy. Surprisingly, a first genetic testing with NGS study of DES gene failed to identify any variant. Immunohistochemical analysis for desmin is currently underway to better characterize the pathological findings. We are planning to repeat the desmin genetic analysis in the patient and possibly proceed with an exome sequencing. Family 2: A 47 y.o. woman presented with a 3 years history of progressive limb-girdle weakness and hyperCKemia. Her 18 y.o. son was affected by a distal myopathy with dilatative cardiomyopathy (heart transplant at 11 years of age) and myofibrillary features at the muscle biopsy. He underwent genetic analysis by NGS panel that revealed a VUS in TTN gene, also detected in the asymptomatic father. Her muscle MRI showed fatty infiltration of legs bilaterally, vastii medialis and intermedius of left quadriceps, and fatty substitution of the glutei bilaterally. Myocardial MRI revealed diffused pattern of sub-epicardial and transmural fibrosis. She needed an ICD implant in January 2022. Reanalysis in trios in the SolveRD framework unraveled a mutation in DES gene.

Conclusions: These cases highlight the challenges faced in diagnosing myopathies with a particular variability of clinical and genetic features. A comprehensive approach combining clinical, histopathological, and genetic investigations is essential for accurate diagnosis, appropriate management, and genetic counseling in affected individuals and their families.

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## A CASE OF DROPPED HEAD SYNDROME CAUSED BY TREATMENT WITH AN IMMUNE CHECKPOINT INHIBITOR

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Introduction: Immune checkpoint inhibitors (ICI) are monoclonal antibodies increasingly used in cancer immunotherapy. By blocking down-regulators of the immune system, ICI could trigger neurological adverse events [1]. Only few cases of myositis and/or myasthenia gravis have been presented with Atezolizumab, an ICI targeting the protein programmed cell death-ligand 1 (PD-L1) [2].

Material and Methods: We present an 82-year-old Italian male with recurrence of multifocal hepatocarcinoma treated with hepatectomy and radiotherapy one year before, and then started on Atezolizumab plus Bevacizumab (inhibiting vascular endothelial growth factor A). After 3 cycles of the PD-L1 inhibitor, he suddenly developed shoulders and neck pain with mild proximal symmetrical limb weakness and, after few days, severe head-drop, cingular myalgia and mild dysphagia. Blood tests showed elevated serum creatine kinase levels without myositis, acetylcholine receptor and muscle-specific kinase antibodies. Electromyography and repetitive nerve stimulation test showed acute myopathic suffering of the cranial and cingular district. Myocardial involvement was excluded.

Results: We concluded for immune-related myositis involving neck and upper cinguli muscles. At first he was treated with high-dose intravenous steroids for 3 days with benefit limited to myalgia and, then, with intravenous immunoglobulins with almost complete resolution of the muscle deficits, at that time the CK level normalised. On follow-up, a month later, he reported a minimal weakness of the head extension in orthostatic position. Unfortunately, the abdominal follow-up showed disease progression and no further anticancer therapy was started. To prevent any muscle worsening, we restarted a low dose oral steroid, as maintenance therapy.

Discussion: Neurologic Toxicity of ICI includes weakness of proximal limbs, ptosis, dropping head and cervical extensor muscle weakness. Few cases of proximal weakness and dysphagia are described with Atezolizumab [2;3]. A systematic review of 18 RCTs showed an incidence of 0.38% for myositis in patients treated with ICI. Most patients received glucocorticoids, half of them IVIG and some received immunosuppressants with recovery of myositis in 68% of patients [2]. Our patient had ameliorated with IVIG, but low dose oral steroids were used as maintenance treatment. He recovered from his muscular condition that was severely affecting his quality of life.

Conclusions: We herein report a case of dropping head syndrome associated to Atezolizumab. This is an atypical presentation of an uncommon immune-related adverse event of PD-L1 inhibitors. Early recognition and proper treatment of muscle involvement could improve quality of life. Although there is no defined therapeutic protocol, our case mostly responded to IVIG.

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## SERUM NEUROFILAMENT LIGHT CHAIN AS A BIOMARKER IN INFLAMMATORY DEMYELINATING POLYNEUROPATHIES: A SINGLE CENTER STUDY

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Introduction: As axonal damage leads to the release of neurofilament light chain (NfL) into the cerebrospinal fluid (CSF) and plasma, NfL has recently been recognized as a diagnostic and prognostic biomarker of different central and peripheral neurodegenerative disease such as Alzheimer disease and amyotrophic lateral sclerosis. In the last years, different studies investigated the role of serum NfL (sNfL) as a biomarker of peripheral inflammatory neurological disease, such as chronic inflammatory demyelinating polyneuropathies (CIDP).

Methods: We collected the serum samples of adult patients with a probable or definite CIDP diagnosis and we measured the NfL concentration with ELLA system. Demographic, clinical and therapeutic data were available in electronic medical records. To evaluate the disability rate, we used modified Rankin Scale (mRS) and Overall Neuropathy Limitations Scale (ONLS) in its total, leg and arm sections.

Results: A total of 32 patients with CIDP were included in this study and most of them were on treatment at the time of sample collection. In our cohort, sNfL tended to be non-significative higher in patients with relapsing-remitting course (6/32) compared to chronic progressive course (26/32). Even if median sNfL levels resulted higher in patients with severe disability (mRS 4-5) than no, mild or moderate disability (mRS 0-3), no significant difference emerged. Similarly, no correlation was demonstrated between sNfL levels and ONLS score.

Conclusion: With this single-center retrospective study, we did not demonstrate any association between sNfL concentration and disability level or disease course in CIDP patients. Considering the limitations of this study (the small number of participants, the lack of treatment-naïve patients and the absence of subsequent sNfL dosage after the baseline), we can assume that these results are compatible with the efficacy of ongoing therapies and the lower entity of axonal damage characterizing inflammatory demyelinating diseases compared to neurodegenerative disorders.

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## IMMUNE-MEDIATED SENSORY POLYRADICULONEUROPATHY AND ATYPICAL CORTICOSTEROID RESPONSE

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Objectives: Immune-mediated purely sensory polyradiculoneuropathy is recognized as a variant of CIDP. Caution should be exercised treating it with high doses of steroids as an adverse outcome is possible.

Materials and Methods: A 56-year-old female was admitted to our Department because of 18-month history of progressively worsening numbness and paresthesia in hands and feet and impaired balance. Neurological examination revealed decreased pin-prick and touch sensation in stocking-glove distribution, reduced vibration and joint position sense and areflexia. Muscle strength and cranial nerves were normal. The gait was wide-based and Romberg's sign positive.

Results: Electroneurography (ENoG) showed normal motor nerve parameters and reduced amplitude of all sensory nerve action potentials (SNAPs). Cerebrospinal fluid (CSF) examination showed an increased protein level (1,88 g/L) and a normal number of white blood cells supporting a albumino-cytologic dissociation. CSF polymerase chain reaction (PCR) for viruses and microscopic and coltural exams for bacteria, fungi and BK yielded a negative result. All blood exams (thyroid function tests, protein electrophoresis and immunofixation, vitamin B12, Treponema, Borrelia, HIV, autoimmune and paraneoplastic screening) were negative. No anti-ganglioside, anti neurofascin, anti contactin-1, anti caspr-1, anti sulfatide and anti MAG antibodies were detected. Chest and abdomen computed tomography scans showed a focal portal vein thrombosis. Magnetic resonance imaging (MRI) of the lumbar spine showed enlargement and enhancement of lumbar nerve roots.

Discussion: Considering the immune-mediate genesis, we primarily discarded plasmapheresis and intravenous immunoglobulins because of venous thrombosis; a bolus methylprednisolone (1 g/day for 5 days) was started. Since the fourth infusion, the patient began to present a drastic worsening of the pre-existing symptoms and a drammatic muscle weakness, including the cranial district. The EnoG now showed absence of all SAPs and of F-waves and diffuse reduction of motor conduction velocities nerve suggesting a demyelinating sensori-motor neuropathy. The patient was treated with plasmapheresis, which was not tolerated because of an abrupt hypotensive drop. We started intravenous immunoglobulins (IVIG – 0,4 g/kg/day for 5 days) with a gradual recovery. After discharge, she performed a nerve biopsy which confirmed CIDP diagnosis.

Conclusions: According to the criteria of the European Federation of Neurological Societies/Peripheral Nerve Society our case should be considered as atypical CIDP. In most cases, pure sensory neuropathy is a condition considered idiopathic. As the pure motor CIDP, an unfavorable response to steroid treatment in some cases of sensory CIDP is possible, suggesting to exercise caution when treating these cases with high dose steroids.

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## ATYPICAL PRESENTATION OF HEREDITARY TRANSTHYRETIN AMYLOIDOSIS

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Objectives: Hereditary Transthyretin Amyloidosis (hATTR) is a rare and progressive disease caused by a mutation in TTR gene. The peripheral nervous system involvement in late onset hATTR is characterized by disabling axonal sensory-motor length-dependent neuropathy, whereas cardiac involvement is characterized by hypertrophic cardiomyopathy with preserved ejection fraction. However, hATTR amyloidosis represents a diagnostic challenge for neurologists considering the great variability in clinical presentation. Here we report a hATTR case with atypical cardiological presentation.

Materials: A 68-year-old male patient suffering from dilatative cardiomyopathy (ejection fraction <28%, interventricular septum =9 mm) was referred to our Neurophysiology Unit for a one-year history of tingling at feet.

Method: Neurological examination revealed reduced tactile and pinprick at lower limbs and reduced distal deep tendon reflexes in the upper limbs and absent in the lower limbs. Nerve conduction study showed a sensory-motor multi-neuropathy and extensive laboratory workout was carried out to exclude more common acquired conditions of sensory-motor neuropathy. Meanwhile, he had undergone bone scintigraphy for a suspected foot stress fracture that unexpectedly demonstrated diffusely increased tracer uptake in the heart (Perugini score 3).

Results: Therefore, TTR genetic analysis was performed and Val-30Met mutation was detected. Therefore, he started treatment with Tafamidis 61 mg.

Discussion: Early diagnosis of hATTR is already challenging but becomes even more when hATTR presents with atypical phenotypes. In such case cardiac amyloidosis incidentally was detected by bone scintigraphy as dilated cardiomyopathy was certainly misleading. Also, he initially showed a multi-neuropathy pattern although it later evolved into a poly-neuropathic pattern, as emerged from the follow-ups.

Conclusions: However, though cardiac phenotype of hATTR usually presents as a restrictive or hypertrophic cardiomyopathy, rarely dilated cardiomyopathy has been described as well. In addition, a large variability of the electrophysiological tests is possible.

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## NEURO-ONCOLOGY

### ELECTRO-CLINICAL, NEUROIMAGING FEATURES AND NEUROPATHOLOGICAL CHARACTERIZATION OF POLYMORPHOUS LOW-GRADE NEUROEPITHELIAL TUMOR OF THE YOUNG (PLNTY)

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Introduction: Polymorphous low-grade neuroepithelial tumor of the young (PLNTY) as classified by 2021 WHO Central nervous system classification. It is an epileptogenic tumor, affecting young age, with peculiar radiological, and pathomolecular features [1, 2]. Only 52 cases of PLNTY have been described up to now. Besides typical morphological features, molecular profiling showed the evidence of BRAFV600E mutation and fusions involving FGFR2 and FGFR3 [2]. Herein, we describe 13 patients in an extensive approach.

Material and Methods: We selected patients affected by PLNTY based on data extraction from the FONDAZIONE IRCCS ISTITUTO NEUROLOGICO CARLO BESTA (FINCB) Cancer Registry (Apr 2017-Apr 2022) and on the histological review of 87 epileptic tumors (2017-2022). For the 13 identified PLNTY, we retrospectively collected history, electro-clinical (EEG and VEEG), neuroimaging and histo-molecular data. and high-resolution (1.5 or 3 T) IDH1/2, BRAF (V600E) sequencing, Kiaa1549::BRAF, FGFR3::TACC3, FGFR2::KIAA1598 and FGFR2::CTNNA3 fusion analyses was performed.

Results: We describe 13 patients, aged around 20.6 years (12.3-46.4). Most patients suffered from different degrees of epilepsy, mostly focal and some drug-resistant before surgery. Most of the patients showed any type of memory/executive impairment. The main feature of seizures was a difficult localization and even lateralization. Post-surgical seizure control was excellent. The tumors (n=11/13 temporal) presented as solid or solid-cystic cortical mass; calcifications were present in 4, and cyst in 6 cases. Microscopically the tumors showed infiltrative growth pattern, oligodendroglial-like cells. Malformation of cortical development was associated to the PLNTY in 2 cases. BRAF V600E mutation was detected in n=3 out of 7 cases, and FGFR3 fusion in n=5 out of 11 analyzed cases.

Conclusions: This study significantly extends the number of reported PLNTY. The electro-clinical data of our patients were characterized by bilateral interictal epileptiform discharges (IEDs) and difficult to lateralize seizures, both from the clinical and the electroencephalographic point of view. MRI features of the lesions were not homogeneous. PLNTY may present focal cortical dysplasia (n=2) and exhibit a tendency to develop extended epileptic networks. PLNTY, despite its name, occurs also in adult, and electro-clinical and radiological diagnosis can be challenging. As recently described, PLNTY can show the MAPK pathway activating alterations. The role of these mutations in the evolution of the disease need to clarify further.

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### INTRACRANIAL HYPERTENSION MANAGEMENT IN FULMINANT CEREBRAL EDEMA AFTER CAR T-CELL THERAPY: NOT ALL IS LOST!

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Immune effector cell-associated neurotoxicity syndrome (ICANS) is a well-known complication after CAR-T therapy that may range from mild encephalopathy to coma or death due to fulminant diffuse cerebral edema (FCE). FCE is the most extreme neurological complication after CAR T-cell therapy: it occurs with a rapid neurological deterioration which typically lead to brain death within 24 hours. Hereby, we describe a case of CAR-T related FCE successfully treated with intensive neuro-intensive support in addition to immunosuppressive therapy. The patient is a 55-year-old woman suffering from follicular non-Hodgkin lymphoma infused with axicabtagene-ciloleucel. Prophylaxis with levetiracetam was administered. After CAR T-cells infusion, she developed a grade I Cytokine Release Syndrome (CRS) treated with tocilizumab (day+2) and steroids (methylprednisolone MPS, 1 mg/kg/q12h; day+4). Twenty hours later (day+5), she acutely developed headache and vomiting,

becoming comatose within few hours. Despite a normal brain-CT, FCE was suspected and high-dose-MPS (1000 mg/q12h), Anakinra (100 mg/q12h) and Siltuximab (11 mg/kg, single-dose) was promptly started. Intraparenchymal pressure monitor showed an initial ICP value of 45 mmHg. A stepwise management of ICP was started including hyperventilation, 30°elevation, hypertonic solution, and sedation with propofol and midazolam, and then thiopental because of refractoriness. Brain-CT performed the next day showed a diffuse brain edema. Anesthetic treatment was progressively tapered targeting on ICP. At anesthetic withdraw (day+9), the patient presented with non-convulsive status epilepticus treated with phenytoin and propofol. Based on cEEG, anesthetic was gradually withdrawn and stopped again (day+13). The patient presents a full recovery without neurological impairment at discharge (day+35). Fewer than ten FCEs related to CAR-T therapy have been reported: all but one has met an inauspicious end. Diagnosis of FCE needs to be initially based on clinical suspicion only, to avoid any delay of the neurointensive approach. Management of ICP elevation should begin at initial presentation and escalated based on ICP value, which represent an important biomarker of immunological therapy response in the early days too. Reaching rapidly normal ICP value is central in management of FCE to prevent secondary brain injury, allowing time for the immunosuppressive therapy to shut down the cytokine-storm. Since no prospective studies are available, an empiric immunosuppressive strategy toward multiple molecular targets (IL-6, IL-1, steroids) was justified by the severity of clinical features. In patients treated with CAR-T therapy, signs of cerebral hypertension should alert clinician to a prompt neurointensive management in addition to immunosuppressive therapy, because they may let the poor prognosis of FCE completely reversible.

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## INSIDIOUS ONSET HEMIDYSTONIA DUE TO GLIONEURONAL TUMOR OF THE RIGHT PUTAMINAL-CAPSULAR REGION, IN A 9-YEARS-OLD-MALE: A CASE-REPORT


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Background: Central nervous system (CNS) tumours are the most common pediatric solid cancers and a leading cause of cancer death in children aged 0 -14 years. Glioneuronal tumours represent over 30% of pediatric CNS neoplasms.

Methods: A 9-year-old boy presented for a 2 years clinical history characterized by prolonged and painful involuntary muscle contractions of the left lower limb, exacerbated by voluntary movement, resulting in unstable gait, and gradually extending to the ipsilateral upper limb with a slowly progressive evolution.

Results: Neurological examination showed left brachio-crural choreo-dystonic movements, worsened by motor tasks and relieved by antagonistic gestures. Routine blood tests, serum ceruloplasmin, 24-hour urinary copper excretion and cupremia were normal, as were genetic tests, and microscopic examination of the peripheral blood smear showed no acanthocytes. Brain MRI showed an ovoid lesion in the right putaminal-capsular region, surrounded by mild vasogenic oedema. Signal was isointense to grey matter on T1-weighted and markedly hypointense with a small central hyperintensity on T2-weighted images. DWI showed no signal restriction except for a thin peripheral border. Due to slight inhomogeneous hyperintensity on SWI, the patient underwent CT scan which excluded the occurrence of calcifications. Spectroscopy demonstrated a moderate increase in Cho/Naa ratio. After gadolinium injection, an intense and homogeneous enhancement was observed in absence of other similar formations in both brain and spine. DSC perfusion MRI showed a 2 relative cerebral blood volume (rCBV) value compared to unaffected contralateral side.

Discussion: On MRI evidence, the patient underwent frameless stereotactic neuronavigation biopsy using Stealth autoguide® robotic arm through right precoronal hole with trajectory avoiding left cortico-spinal tract on the basis of three-dimensional diffuse tensor imaging (DTI) tractography. Histology showed glial and neuronal cells. Immunohistochemistry showed GFAP+, Olig 2+/-, chromogranin -, NeuN-, Map2a +/-, synaptophysin -/+, CD34- , H3.3K27me (conserved), Ki-67 3%, plurifocally expressed P53, concluding for glioneuronal tumour diagnosis. Finally, the patient was transferred to the MRI suite, (Philips 1.5 Tesla) and under thermographic sequence three consecutive thermal ablation points with laser interstitial thermal therapy (LITT) were performed, which covered 90% of tumour volume.

Conclusion: Approaching diagnosis and treatment of childhood chorea-dystonia is a challenging condition. For timely therapeutic intervention, it is important to exclude potentially treatable causes. Advanced Brain Neuroimaging is crucial to guide the histological diagnosis of CNS lesions and to perform less invasive surgical procedure.

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## INCRESED BRAIN TOXICITY AFTER RADIOTHERAPY IN MULTIPLE SCLEROSIS


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Radiotherapy could promote exacerbations of Multiple Sclerosis (MS) as described in literature, but it seems not to be responsible for its onset. MS lesions can look like metastases or radionecrosis, therefore differential diagnosis will be fundamental. Here we discuss how the presence of MS MRI pattern could represent a confounding factor for the correct diagnosis of post attinic brain damages and possibly induce its onset. We describe the case of a 26-year-old woman treated with proton therapy for

a great condrosarcoma of Petrous rock. Several lesions consistent with MS were occasionally discovered during MRI for the diagnosis of condrosarcoma. The diagnosis of MS was made according to McDonald's criteria and relation to the lesion load, preventive treatment with beta 1A Interferon was carried out. The condrosarcoma was inoperable and underwent diagnostic biopsy only. She received proton therapy 70 Gy in 35 daily fractions. The patient well tolerated the course of the radiation, without unexpected side effects and did not develop any neurological manifestations during the treatment. Only one month after proton radiation, she presented right facio-brachio-crural pyramidal hemisyndrome with ataxia, diplopia and dizziness. The MRI revealed lesions in the brainstem, posterior arm of the right external capsule, thalamus and hypothalamus suggestive for radionecrosis. She was treated with steroid ev without particular benefit. In the following weeks she was treated with bevacizumab 5 mg/kg/ev every 21 days for 6 cycles with clinical and radiological improvement. This case is atypical due to the early onset of radiotherapy complications and for the aggressiveness of the radionecrotic lesions. In fact, one month after the end of radiotherapy represents an extremely early onset time for brain radionecrosis. Pathophysiology of radiation-induced brain injury is well known. The radiation damage involves cellular elements in the inflammatory microclimate and leads to modifications such as increase permeability of blood-brain barrier (BBB), cellular swelling and vacuolization. Damage to these structures leads to hypoxia and increase of VEGF. Recent hypotheses indicate a damage of BBB in the pathogenesis of MS. Consequently we think that in our case MS and radiotherapy could have acted synergistically in anticipating and enhancing post-actinic complications. We advise that MS patients undergoing radiotherapy should be subjected to earlier post-radiotherapy radiological checks. We also believe that the site of any demyelinating lesions should be considered before planning treatment. Perhaps patients with MS could represent ideal models to understand what predisposing conditions for radiation toxicity.

## LIQUID BIOPSY OF MYD88L265P MUTATION FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL): A PROSPECTIVE, OBSERVATIONAL STUDY

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Background: Primary Central Nervous System Lymphomas (PCNSLs) harbour MYD88L265P mutations in up to 60-70% of cases. Whether detection of MYD88L265P by liquid biopsy may be accurate for the diagnosis and disease monitoring of PCNSL patients is an emerging issue. In this study we aimed to assess the feasibility of MYD88L265P detection in the cerebrospinal fluid (CSF) and blood of patients with PCNSL and validate its use as a potential marker for diagnosis.

Patients and Methods: We prospectively collected data of patients who presented at our Institution with suspected PCNSL. CSF was obtained by lumbar puncture to analyse cytology, B cells immunophenotype, and MYD88L265P mutation status. MYD88L265P mutation was analysed by droplet digital PCR (ddPCR). Chi-square test and COX regression were used for statistics correlations.

Results: From May 2016 to March 2023, 29 patients were included. Median age was 71.0 years. 11 patients (37.9%) had multifocal lesions. 13 patients (44.8%) had a positive brain FDG-PET. All patients underwent lumbar puncture at diagnosis. CSF cytology was informative in 8 patients (27.6%), and CSF immunophenotype in 11 (37.9%). 18 patients (61.1%) underwent biopsy, whereas the remaining ones did not due to elevated surgical risks. Overall, MYD88L265P mutation was detected in the CSF and blood in 18 (62.1%) and 10 (34.5%) cases, respectively. In patients undergoing biopsy, MYD88L265 mutation was assessed on tumour tissue in 14/18 (77.8%) cases and found in 13/14 (92.8%). Among 13 patients with confirmed MYD88L265P mutation on tumour tissue, 8 (61.5%) and 6 (46.1%) harboured the mutation also in the CSF and blood MYD88, respectively. The only patient with no evidence of MYD88L265P mutation on tumour tissue had also CSF and blood negative results. Interestingly, in 4/11 patients (36.4%) who did not undergo biopsy and with negative CSF cytology and immunophenotype, the presence of the MYD88 L265P mutation on the CSF allowed to confirm the diagnosis of PCNSL. The presence of multifocal lesions, FDG-PET positivity and CSF positive cytology did not correlate with CSF/blood MYD88L265P positivity. Patients with CSF MYD88L265P mutation tended to have positive CSF immunophenotype as compared to MYD88L265P-intact (50.0% vs 18.0%, $p = 0.087$). The presence of MYD88L265P mutation did not correlate with progression-free survival or overall survival.

Conclusions: In our series, the presence of the MYD88L265P mutation was found in the majority of PCNSL patients who underwent biopsy (92.8%) and was confirmed in the CSF in most positive cases (61.5%). This suggests that liquid biopsy of CSF may be helpful for PCNSL at diagnosis and – potentially – for disease monitoring during treatments. Further correlations with clinical and radiological features, outcome, and potential therapeutic implications should be investigated in next prospective studies.

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## SEIZURE OUTCOME ACROSS DISEASE TRAJECTORY IN IDH-MUTANT GRADE 2 GLIOMAS: WHICH IS THE IMPACT OF STANDARD ANTINEOPLASTIC TREATMENTS?

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Introduction: Most patients with IDH-mutant grade 2 gliomas suffer from seizures. Recently, the INDIGO trial showed that vorasidenib prolonged progression-free-survival (PFS) and time-to-next-intervention in IDH-mutant grade 2 glioma patients after surgery. We aimed to

identify which factors influence seizure-control in patients with similar characteristics of those of the INDIGO trial.

Patients and Methods: We retrospectively collected data of non-enhancing IDH-mutant grade 2 glioma patients (as per WHO-2021) who presented with seizures and evaluated seizure-freedom at 2 months after surgery, 6 months from starting either observation or adjuvant treatments, at recurrence, and 6 months after treatment of recurrence.

Results: Ninety-five patients were included. Oligodendrogliomas IDH-mutant/1p19q-codeleted grade 2 were 69 (72.6%), astrocytomas IDH-mutant grade 2 were 26 (27.4%). Thirty-five (36.8%) received gross-total resection (GTR). After surgery, 49 (51.6%) achieved seizure-freedom, more frequently after GTR vs non-GTR (57.9% vs 35.1%, p=0.048). Sixty-eight (71.6%) low-risk patients underwent observation, while 27 (28.4%) high-risk patients received adjuvant radiotherapy (RT) and/or chemotherapy (CT). Among the latter, 17/27 (63.0%) had persistent seizures before treatment initiation and, after 6 months, all of them displayed seizure-reduction, with 2/17 (7.4%) achieving seizure-freedom. In a multivariable analysis on PFS, ≥50% seizure-reduction (vs < 50%) after 6 months of adjuvant treatment reduced the risk of progression (HR 0.048, 0.004-0.585, p=0.017). Eighty-six (90.5%) patients recurred, and 51/86 (59.3%) displayed seizures. After 6 months of treatment of recurrence, 50/51 (98.0%) achieved seizure-reduction, with 10/51 (19.6%) reaching seizure-freedom. In a multivariable analysis, either CT or RT increased the probability of seizure-freedom at 6 months after recurrence (HR 5.316, 1.582-17.869, p=0.007).

Conclusion: We defined the entity of seizure-control after standard treatments throughout the disease course. Two findings are noteworthy: the prognostic importance of seizure-reduction after adjuvant treatments; the possibility to achieve seizure-control also with treatment of recurrence. This study could serve as a benchmark for a future evaluation of seizure-control after IDH inhibitors.

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## USE OF VISMODEGIB IN ADULT PATIENTS WITH NEOPLASTIC MENINGITIS FROM SONIC HEDGEHOG (SHH)-ACTIVATED MEDULLOBLASTOMAS: A CASE REPORT


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Background: Vismodegib is a SHH-inhibitor that proved to be effective in locally-recurrent SHH-activated medulloblastoma. However, whether vismodegib is effective in case of neoplastic meningitis (NM) as well has not been assessed so far. Here, we present a case of a patient with NM from SHH-activated medulloblastoma who showed a dramatic response to vismodegib.

Case Report: A 34-year-old patient was diagnosed with a SHH-activated cerebellar medulloblastoma in 2015. He underwent gross-total resection, cranio-spinal radiotherapy (RT) and 5 cycles of lomustine, vincristine and cisplatin. Then, he remained disease-free until October 2021, when the MRI showed a new single contrast-enhanced nodule in the spine (T10), which was treated with stereotactic RT. However, the following MRI showed a diffuse leptomeningeal involvement, with new multiple linear and nodular lesions. The CSF cytology confirmed the presence of neoplastic cells. Therefore, in April 2022 vismodegib (150 mg daily) was started. The treatment was well tolerated, except for increased creatine phosphokinase (CTCAE v3.0 grade 1). After only 2 months of therapy, a reduction of the meningeal enhancement was seen on MRI, and after 4 months all nodular and linear lesions disappeared. Similarly, CSF cytology became negative after 4 months of treatment. However, after 8 months of treatment (December 2022), the MRI of the spine showed the new appearance of meningeal contrast-enhanced lesions, and CSF cytology confirmed the presence of neoplastic cells. Therefore, vismodegib was dismissed. In few days, the patient (who did not have any symptoms so far) developed severe meningeal symptoms, and palliative care was started, until his death in February 2023.

Conclusions: To our knowledge, this is the first report of an adult patient with NM from SHH-activated medulloblastoma achieving a complete response with vismodegib, even if temporary. Data from larger series are needed to confirm the effectiveness and safety of vismodegib in case of leptomeningeal spread.

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## A RARE CASE OF HYPOSMIA


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Introduction: Esthesioneuroblastoma (or ENB), or olfactory neuroblastoma, is a rare malignant neoplasm of ectodermal origin originating from the olfactory neuroepithelium with neuroblastic differentiation and involving the sinonasal tract. It constitutes about 2% of all sinonasal neoplasm and presents and incidence of 0.4 per million population. A mild female predominance has been found in various studies. A bimodal age distribution has been described, with two peaks of age (30-50 years the first one, the seventh decade the second one). Three staging systems have been proposed: Hyams, Kadish, Dulguerov. The prognosis of EBN is both stage- and grade-dependent. 1700 cases in the world have been reported. We report the case of a 81 years –old Caucasian woman with mild neurological symptoms who was diagnosed with esthesioneuroblastoma.

Materials and Methods: She was evaluated due to persistent diplopia in primary position associated with stuffy nose and hyposmia gradually worsened in the previous sixth months. She denied recent viral infection, epistaxis, facial pain, excessive lacrimation or headache and her medical history was unremarkable. Neurological examination resulted normal (in particular ocular movements) despite diplopia in primary position. No cervical lymphadenopathy was seen.

Results: She performed brain computer tomography and brain magnetic resonance imaging showing a tumor of anterior cranial fossa hypointense to gray matter on T1-weighted images and hyperintense on T2-weighted sequences with diameter of 2.4 cm x1 cm x 1.8 cm, associated with fronto-orbital vasogenic edema, focal erosion of lamina papyracea and calcifications. Fronto-ethmoidal extracranial component involved presented diameters of 2 cm x 1.8 cm x 1.4 cm. Cervical magnetic resonance imaging resulted negative for metastases. She was sent to another center for surgical evaluation.

Discussion: We reported a case of esthesioneuroblastoma in an old Caucasian woman in good health, thus expanding existing literature.

Conclusions: In every patient, presenting with unilateral nasal obstruction with or without orbital and intracranial symptoms and signs, the diagnosis of esthesioneuroblastoma should be considered and prompt clinical and radiological evaluation should be performed.

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## PARKINSONISM DUE TO MIDLINE GLIOMA: DIFFERENTIAL DIAGNOSIS AND ROLE OF DRUG THERAPY

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Objectives: Parkinsonism is an umbrella term that refers to brain conditions that cause slowed movements (bradykinesia), rigidity and tremors. The most common form of parkinsonism is Parkinson disease (PD), a chronic, progressive disorder caused by degenerative loss of dopaminergic neurons in the brain. Differential diagnoses of PD should always be considered. A wide variety of conditions can cause secondary parkinsonism. Structural causes include: normal pressure hydrocephalus, chronic subdural hematoma, tumors involving striatonigral circuits, head trauma. Movement disorders caused by brain tumors are rare. The purpose of this case report is to emphasize the importance of differential diagnosis in parkinsonism.

Materials and Methods: 58 y/o male patient presented ictal fine rest tremor in left hand and hyposthenia/rigidity of left hemisoma. Initially interpreted as an onset of PD he underwent a MRI that showed a diffuse T2/FLAIR alteration on right side of midbrain and pons with patchy and incomplete contrast enhancement. A stereotactic biopsy was performed and diagnosis of "diffuse midline high-grade glioma H3-wildtype and IDH-wildtype (P53 and GFAP negative)" was confirmed. Radiotherapy was started, and during follow-up the patient developed a worsening of clinic in term of tremor, bradykinesia and rigidity in the left limbs. Diagnosis of parkinsonism was made and Levodopa challenge test was performed.

Result: At the time point of parkinsonism's diagnosis, our patient had at MDS - Parkinson's Disease Rating Scale motor part three (MDS-UPDRS III) 30 points. He had no non motor symptoms related to PD. A initial dose of Levodopa was started without benefit. So he underwent a maintenance dose of Levodopa (400 mg daily) and antiedeman therapy (dexamethasone 6 mg daily), patient presented clinical improvement of tremor and bradykinesia with MDS-UPDRS III of 23.

Discussion: Diagnostic process for PD is complex and includes several features; presence of observable response to high-dose levodopa is an significant criteria. In this case report PD's clinical features are typical (asymmetrical parkinsonism) and he present a partial clinical improvement secondary to levodopa; but there are also two significant red flegs: ictal clinical onset and antiedema steroid therapy response. Our patient appears to have secondary parkinsonism due to diffuse midline high-grade glioma. Follow-up will be necessary to evaluate the clinical role of radiotherapy and the clinical response.

Conclusion: We emphasize the importance of neuroimaging in the onset of movement disorders, because in some cases it significantly improves prognosis and it allow to make differential diagnosis.

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## ASSOCIATION BETWEEN BRAIN METABOLISM AND COGNITIVE IMPAIRMENT IN GLIOMA: A PRELIMINARY STUDY

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Objectives: Brain gliomas show an altered cellular metabolism characterized by abnormally elevated glucose metabolism. The utilization of glucose can be examined in vivo through Positron Emission Tomography (PET) using fluorodeoxyglucose (18F-FDG). 18F-FDG PET imaging technique is used to characterize the tumor extent or tissue and detect the tumor recurrence/progression [1]. The link between metabolism and cognitive performance has been studied just in relation to radiotherapy [2]. The aim of this study was to investigate the relationship between regional glucose metabolism and cognitive functions in glioma.

Materials: 49 patients with glioma underwent a 60 min 18F-FDG PET imaging and, in the same session, a comprehensive neuropsychological assessment (verbal and visual memory, language, visual attention, working memory, executive functions).

Methods: Standardized glucose uptake value ratio (SUVR) was calculated, using the ipsilateral cerebellum white matter as reference, in 200 cortical parcels organized in 17 functional networks (Schaefer Atlas) and 12 subcortical and cerebellar parcels (HammersSmith Atlas). First, a Principal Component Analysis (PCA) was performed on the cognitive scores to reduce the dimensionality of the data. Then, we conducted a bivariate Spearman correlation analysis between the selected components and parcel-wise SUVR values.

Results: The PCA analysis revealed two main components explaining 57% of the total behavioral variance: PC1 loaded positively with scores reflecting overall 'cognitive performance'; PC2 loaded differentially on right (i.e., visuo-spatial attention, visuo-spatial span and working memory) vs. left hemisphere functions (i.e., verbal span and long-term memory, naming, verbal fluency). Metabolically, PC1 correlated significantly with SUVR with nearly all parcels of the left hemisphere

(r: 0.41±0,04 (mean±SD); p<0.05, FDR corrected). Specifically, PC1 correlated with parcels of the left temporo-parietal network (100% of the parcels), left central visual network (83%) and left dorsal attention network (83%). In contrast, PC2 showed a negative correlation with SUVR of right hemisphere networks (r: -0,44±0,06; p<0.05, FDR corrected), including somato-motor, control, default mode and temporo-parietal networks.

Discussion: These results reveal a well delineated pattern of correlation between cognitive performance and metabolism in glioma, which underlies a lateralization of function. Overall cognitive performance appears to positively correlate with metabolism of left-lateralized networks, while verbal memory and language functions are negatively linked to right-lateralized networks.

Conclusions: This study highlights, for the first time in literature, the role of alterations in metabolism in determining cognitive impairment in glioma patients.

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## DIFFUSE MIDLINE GLIOMAS WITH H3K27M MUTATION: MONO INSTITUTIONAL EXPERIENCE

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Introduction: Diffuse midline gliomas (classified as a grade IV CNS tumor according to WHO) represent poor prognosis brain tumors that arise mainly in pediatric age, peaking between 5 and 10 years of age. However, although rarely they are also reported in adulthood, with a prognosis that remains severe even in this age group. These tumors are characterized for more than 90%, by mutations in the H3K27M protein. Due to the lack of adequate literature, the classification, epidemiologic, radiographic and clinical features still remain debated, especially in adults. Most cases are managed with surgery, radiotherapy and drugs. However, due to localization, the role of surgery is mainly for diagnosis.

Methods: We present a case report of adult diffuse midline gliomas (age >18 years at diagnosis) operated and treated at our institution since 2016 with description of tumor and radiologic, clinical characteristics and with description of treatments performed, together with PFS and OS of the group under review.

Results and Conclusions: From January 2016 to June 2023, 15 adult patients, 8 males and 7 females aged 20-68 years (median 42 years) were operated on at our institute with histological diagnosis of diffuse midline glioma. In 6/15 cases, the lesion was located at the thalamic level, in 5/15 cases at the midbrain bulb ponto level, in three/15 cases at the level of the basal nuclei, and in one case at the dorsal intra medullary level. Fourteen/15 patients underwent brain biopsy of the lesion, only one patient underwent partial exeresis of the lesion. The post diagnostic treatment of choice was radiation treatment with combination of temozolomide either concomitant or adjuvant. The prognosis of these tumors remains severe with median OS less than one year.

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## PERAMPANEL IN BRAIN TUMOR-RELATED EPILEPSY: A SYSTEMATIC REVIEW

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Aims of the study: Brain tumor-related epilepsy (BTRE) is a common comorbidity in patients with brain neoplasms and it may be either the first symptom or develop after the tumor diagnosis. Increasing evidence suggests that brain tumors and BTRE share common pathophysiological mechanisms. Glutamatergic mechanisms can play a central role in promoting both primary brain tumor growth and epileptogenesis. Perampanel (PER), which acts as a selective antagonist of glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, may play a role both in the reduction in tumor growth and the control of epileptiform activity. This systematic review aimed to summarize the pre-clinical and clinical evidence about the antitumor properties, antiseizure effects and tolerability of PER in BTRE.

Materials and Method: We performed a systematic literature search using MEDLINE (accessed by Pubmed), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and the US National Institutes of Health Clinical Trials Registry, from inception to week one of October 2022 (update on week one of February 2023). The search strategy included keywords in different combinations using Boolean operators. Duplicates, reviews, and articles in languages other than English were excluded. The risk of bias in any included clinical trial was assessed using the RoB 2 tool. This systematic review is reported according to the recommendations of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.

Results: Eight pre-clinical and eight clinical studies were identified. Discussion: The currently available evidence suggests that PER can be an effective and generally well-tolerated therapeutic option in patients with BTRE. In vitro studies demonstrated promising antitumor activity of PER, while no role in slowing tumor progression has been demonstrated in rat models; clinical data on the potential antitumor activity of PER are scarce.

Conclusions: Additional studies are needed to explore further the effects of PER on tumor progression and fully characterize its potentialities in patients with BTRE.

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## PREDICTIVE SOCIAL FACTORS ASSOCIATED TO PLACE OF DEATH IN MALIGNANT GLIOMAS

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Background: Malignant gliomas (MG) are tumors affecting central nervous system (CNS) with a poor prognosis. Fast neurological decline (motor, cognitive and behavioural) causes high burden for patients and caregivers and requires specific setting of care (especially palliative care) helping patients to preserve their autonomy and assuring, in the end-of-life phase, the best care represented by dying at home with dignity that is considered in the literature an indicator of good quality of care in cancer patients.

Methods: The home care program for MG utilized in our Institution is aimed to offer palliative and supportive care during all the trajectory of disease and to facilitate death at home. To identify possible factors related with place of death, we've retrospectively investigated social and health data to discover possible factors associated with dying at home in MG patients. Every patient and caregiver/family were analyzed for many factors including sex, work, family relation, presence or absence of caregiver/family, presence of children.

Results: From January 2016 to December 2020, we've assisted at home 263 MG patients and collected complete data in 257 patients (6 patients was lost in follow-up). 174 (68%) of them were affected by Glioblastoma Multiforme (GBM) and 83 (32%) were affected by grade 3 anaplastic gliomas; 155 patients (61%) were male and 102 (39%) female. 137 patients (54%) died at home, 88 patients (34%) died in hospice and 32 patients (12%) died in hospital. Male caregivers assisted 178 MG patients of which 141 was male patients (79%); female caregivers assisted 79 MG patients of which 65 was female patients (82%) ($p<0.001$); presence of social network (family or other type) influenced positively place of death: MG patients who has social network died frequently at home respect on MG patients who didn't have social network that died frequently in hospital or hospice ($p<0.001$). No differences were found between age, sex (patient and caregiver), presence of minor children, education level, work, marital status and place of death.

Discussion: In this cohort of MG patients followed with a palliative home care service, place of death and dying with dignity is influenced by presence of social network and reliable caregiver. The evaluation social data in addition to clinical data is an important factor in order to plan timely the end-of-life phase and the decisions about possible place of death.

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## RACTAC TRIAL: PHASE II MULTICENTRIC ITALIAN TRIAL ON REPOSITIONING OF THE ANTIPSYCHOTIC DRUG CHLORPROMAZINE AND ITS COMBINATION WITH TEMOZOLOMIDE IN MGMT UNMETHYLATED GLIOBLASTOMA PATIENTS

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The poor prognosis of patients affected by glioblastoma (GBM) prompts the search for new and more effective therapies, particularly for GBMs with unmethylated MGMT. In this regard, drug repurposing, can represent a safe and inexpensive way to bring novel pharmacological approaches from bench to bedside. Chlorpromazine, a medication in use since six decades for the therapy of psychiatric disorders, shows in vitro features that make it eligible for repositioning in GBM therapy. In our experimentation on six GBM cell lines, chlorpromazine inhibited cell viability in an apoptosis-independent way, induced polyploidy, reduced cloning efficiency as well as neurosphere formation and downregulated the expression of stemness genes. Notably, we found that chlorpromazine synergized with temozolomide, in reducing cell viability and strongly cooperated in reducing cloning efficiency and inducing cell death in vitro for all the GBM cell lines assayed. With these assumptions, we started a multicentric Phase II clinical trial on newly diagnosed GBM patients with unmethylated MGMT by adding chlorpromazine to temozolomide in the adjuvant phase of the standard first-line therapeutic protocol. The experimental procedure involves the combination of CPZ with standard treatment with TMZ in the adjuvant phase of the Stupp protocol. CPZ was administered orally at a dose of 50 mg/day – GG 1-28 – of every cycle of the adjuvant treatment with TMZ. Efficacy outcomes were evaluated using Kaplan–Meier methodology. OS was measured from diagnosis to death; PFS was determined from radiotherapy to the first sign of PD or death due to any cause. The trial was closed on December 2022. 53 patients have been enrolled, 39 male, 14 female. 21 patients completed 6 cycles of treatment, without relevant toxicity. The results shows a median PFS of 7 months (St. Dev. 5,7) and a median OS of 15 months (St.Dev. 6,9). 23 patients are still alive (43%). The addition of Chlorpromazine to the standard adjuvant chemotherapy with temozolomide was well tolerated in newly diagnosed Glioblastoma unmethylated patients, with promising impact on outcome measures. On the basis of the RACTAC trial results, a phase II multicentric trial evaluating Chlorpromazine added to standard treatment (RT+TMZ+adj TMZx 6 cycles plus CPZ) in newly diagnosed Glioblastoma patients is in preparation.

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## INSIGHTS INTO HEALTHCARE PROFESSIONALS' PERCEPTIONS AND ATTITUDES TOWARD NANOTECHNOLOGICAL DEVICES APPLICATION: WHICH IS THE CURRENT SITUATION IN GLIOBLASTOMA RESEARCH?

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Aims: Neuro-oncology might be a promising field for the application of nanotechnologies, especially for malignant brain tumors with a low survival rate as glioblastoma. As a contribution to a broader perspective of the current state of research, we attempt to give an overview of healthcare practitioners' perceptions and intentions to use nanotechnology, with a focus on neuro-oncology.

Materials: A preliminary literature search did not identify any study focused on clinicians' perspectives towards nanotechnology in neuro-oncology. Therefore, we considered extending the search to nanomedicine to (i) spot any possible piece of knowledge within glioblastoma and (ii) evaluate whether potential useful information from other research fields could be transferred within glioblastoma research.

Methods: Studies had been identified by conducting a systematic search of electronic databases using keywords related to "nanotechnology", "perception" and "healthcare professionals". Studies were included if clinicians' knowledge (i.e. factual information) and/or opinions (i.e. judgment not necessarily based on facts) toward nanomedicine had been explored, regardless of the field of application.

Results: Seven studies published from 2011 to 2021 conducted in five countries were considered eligible. Cross-sectional study designs were used to assess students, medical residents, and clinicians' opinions toward nanomedicine. Participants' attitudes were positive, although accurate knowledge of nanotechnology was poor. Inadequate access to information on nanotechnology was reported, with education gaps in nanomedicine and the need to update university curricula claimed by students, medical residents, and clinicians equally.

Discussion: Current models of risk assessment suggest that time-saving cognitive and affective shortcuts support both laypeople and experts in the decision-making process under uncertainty, whereas they might be a source of error. Whether the knowledge is poor, heuristics are more likely to interfere with decision-making. Knowledge about current and future research in nanomedicine should be improved to (i) provide reliable sources of information, (ii) enable proper decision-making of upcoming healthcare workers, and (iii) minimize the influence of subjective variables.

Conclusions: Given the multi-professional nature of neuro-oncological care, internal shared knowledge and perspective are advisable, especially if international consensus on treatment strategy is unclear. A dedicated survey directed to all specialists involved in the diagnosis and treatment of gliomas exploring the possible impact of intention to use nanotechnology in glioblastoma is currently ongoing. Therefore, future search might be helpful to improve the knowledge of clinicians' perspectives in this field.

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## TUMOR CELL LINES-RELEASED MICROVESICLES AND EXPRESSION OF ADHESION MOLECULES IN AN IN VITRO MODEL OF BLOOD BRAIN BARRIER FOR THE STUDY OF METASTATIC BRAIN DISEASE

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Aim: We aimed at assessing the effects of microvesicles released by different human cancer cell lines and of adhesion molecules expression on transmigration of cells through an in vitro model of blood-brain barrier and on endothelial cell apoptosis.

Materials and Methods: Human lung and breast cancer cell lines - A549, H460 (human lung cancer cells), MDAMB 231, MDAMB 453, SKBR3 and MCF7 (breast cancer cell lines) were all obtained from ATCC and were characterized for adhesion molecule expression and used to evaluate their migration ability in an in vitro model, consisting of rat astrocytes and either human umbilical cord endothelial cells or cerebral microvascular endothelial cells grown on the opposite sides of a porous polycarbonate, collagen-IV-coated membrane. Conditioned culture media and isolated EVs, characterized by super resolution and electron microscopy, were tested to evaluate their pro-apoptotic properties on human umbilical vein endothelial cells and human cerebral microvascular endothelial cells (HCMEC/D3) by annexin V binding assay.

Results: Our data showed a direct correlation between expression of ICAM1, ICAM2, β3-integrin and α2-integrin and the ability to firmly adhere to the blood–brain barrier (BBB) model, whereas the same molecules were down-regulated at a later step. Extracellular vesicles released by tumor cell lines were shown to be able to induce apoptosis in HUVEC while brain endothelial cells showed to be more resistant.

Conclusions: Down-regulation of adhesion molecules at a step immediately following transmigration might be one of the mechanisms implied in the temporary dormancy state of microscopic metastatic foci in the brain.

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## QUANTITATIVE MGMT PROMOTER METHYLATION AND GLIOBLASTOMA LOCALIZATION: A VOXEL-WISE STUDY

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Objectives: The O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status is one of the most important prognostic factors in glioblastoma (GBM) patients [1]. GBMs mainly arise in temporal, frontal and parietal lobes, however, tumour location does not directly impact patient prognosis, unless it influences the extent of surgical resection. Several studies assessed the relationships between MGMT methylation status and GBM location, yet no consistently significant association was reported [2,3]. Nonetheless, there is currently no published data regarding the association between GBM localization and the extent of quantitative MGMT methylation. The aim of the present study was to investigate the relationships between both qualitative and quantitative MGMT promoter methylation status and GBM topological characteristics.

Materials: Patient inclusion criteria were: histopathological diagnosis of GBM (WHO 2021); available presurgical routine MRI acquisitions including T2W, FLAIR, pre- and post-contrast T1W sequences; surgical operation in the departments of Neurosurgery of the "Azienda Ospedaliera Universitaria di Padova"; known MGMT methylation status.

Methods: Quantitative methylation assessment was obtained through pyrosequencing. GBM lesions were segmented into 4 tissues: necrosis, contrast-enhancing and non-contrast-enhancing tumor, that altogether were considered as "core", and "edema". The three resulting masks (core, edema and global) were normalized to a standard space (MNI). We investigated volume differences between MGMT-methylated and unmethylated GBMs through t-tests and performed Pearson's correlations between quantitative MGMT methylation status and mask volumes. Subsequently, two-sample t-tests assessing voxel-wise differences in mask location between MGMT-methylated and unmethylated tumors were performed with the FSL general linear model software and the "randomise" function (5000 random permutations). Furthermore, we both investigated linear relationships between quantitative MGMT methylation status and mask location and assessed location differences between highly- and lowly-methylated patients. The analyses were also repeated correcting for core, edema and global volumes, separately. Results underwent voxel-wise family-wise error correction; significance level was set to 0.05.

Results: 93 patients were included (66 males; mean age: 62.3±11.3 years), 41 were MGMT-methylated. The mean methylation level was 33.9±18.3%. GBMs were mainly located within frontal, temporal and, to a lesser extent, parietal lobes. No difference in GBM volume and location was found between MGMT-methylated and unmethylated patients. Moreover, we found no relationship between GBM topology and quantitative MGMT status.

Discussion and Conclusions: The present study not only confirms that MGMT methylation status is unrelated to specific anatomical localizations of GBMs, but also suggests that GBM topology, among MGMT-methylated tumors, does not depend on the level of MGMT promoter methylation.

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## LONGITUDINAL NEUROCOGNITIVE AND NEURORADIOLOGICAL CHANGES IN MALIGNANT GLIOMA PATIENTS

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Background and Aim: Current treatment options have increased overall survival in brain tumor patients, especially in low grade ones, reaching a 10-year rate of 60-80% according to tumor grade [1]. For this reason, cognitive and radiological long-term treatment effects have become relevant issues in clinical and research field. The few previous reports on this topic highlight progressive decline of attentional [2], mnesic and executive functions, associated with radiological abnormalities [3]. The aim of this study was a longitudinal evaluation of the correlation between radiological features and neurocognitive status malignant glioma patients with disease control.

Materials and Method: Malignant glioma patients were retrospectively selected from the database of the Regina Elena neuro-oncology unit. All of them underwent basal neuropsychological assessment and 3 follow-up evaluations (mean:21 months), tapping short and long-term memory, executive functions, attention and visuo-constructional abilities. They also underwent longitudinal neuroradiological examinations. Neurocognitive performances were corrected according to italian normative standard, while neuroradiological data (volumetry, cortical thickness and leucoencephalopathy) were compared with control subjects.

Results: 20 malignant glioma patients with neurocognitive and neuroradiological longitudinal data (12 male, mean age: 45 y; mean edu.: 12 y) were selected in a database of 1200 neurocognitive evaluations. All of them presented with stable disease and underwent longitudinal MRI scans. Histology was mostly oligodendroglioma (n.=7) and astrocytoma (n.= 8), while only 3 patients were diagnosed with glioblastoma. Patients underwent post-surgical and pre-radiotherapy cognitive assessment and 3 follow-ups. At baseline neurocognitive assessment 50% of patients presented with at least 1 cognitive

deficit, mainly affecting executive and mnesic functions. At follow-up 8 patients showed a stable and preserved cognitive status and in 5 patients a neuropsychological improvement was found. Among them, 2 patients presented with no deficit. 2 patients worsened neurocognitive performance and 7 showed longitudinal fluctuations. At the last follow-up, significant correlations emerged between cognitive deficits and leucoencephalopaty (p= 0,03), total grey-matter volume (p=0,03) and educational level (p=0,01). Patients with greater leucoencephalopaty and grey-matter reduction showed worse cognitive performances, while patients with higher education suffered less deficits.

Discussion: Although in a small sample size, our results confirm the role leucoencephalopaty and cortical volume play on neurocognitive status. Furthermore, data evidence the key importance of cognitive reserve to promote neurocognitive functioning in patients with disease stability. Overall, these results highlight the necessity of monitoring neurocognitive status in glioma patients even in case of stable disease.

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## WHAT IS THE ROLE OF THE SECOND SURGERY TO RECURRENCE IN GLIOBLASTOMA: REAL LIFE EXPERIECE OF NEUROSURGERY

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Background: The majority of patients with Glioblastoma will experience disease progression. At recurrence, treatment options have limited efficacy. Many studies report a limited response rate and when present, it is of short duration. Surgery is an option for some patients, and surgical debulking can alleviate mass effect and symptoms. Some evidence showed that greater extent of resection at recurrence is associated with improved survival; however, other studies have not found an absolute benefit in terms of survival. The purpose of this study is to evaluate what is the impact of neurosurgery at recurrence in Glioblastoma patients.

Materials and Methods: We have included patients undergoing to surgery for recurrence of GBM with age >65 years. All patients were followed at the Neurosurgery Unit of National Cancer Institute Regina Elena and we considered patient not underwent to surgery.
Result: From neuroncology database of Regina Elena we extracted 138 patients underwent to second surgery (Sample 1) and 422 patients underwent to other treatments (sample 2). The median age in the sample 1 was 56 and 61 in the sample 2. The median number of cycle of temozolomide was 8 in the sample 1 and 6 in the sample 2. For the sample 1 the median time of second surgery was 13 months and in 49% previous 12 months, 51% after 12 months. At multivariate analysis we observed that on overall survival the second surgery have an impact after 12 months from first surgery, MGMT methylated, age at diagnosis. The factors that influence progression free survival was time to second surgery after 12 months and number of temozolomide.

Conclusions: This data is according with literature data. The role of second surgery may be at important role in selected patients in terms of progression and survival. The study has a large case study. The limitation of the study is that it is retrospective.

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## VOLUMETRIC HIPPOCAMPAL CHANGES IN GLIOBLASTOMA: A BIOMARKER FOR NEUROPLASTICITY?

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Purpose: The pleiotropic effect of gliomas on the development of cognitive disorders and structural brain changes has garnered increasing interest in recent years [1] While it is widely accepted that multimodal therapies for brain cancer can foster cognitive impairment, the direct effect of gliomas on critical cognitive areas before anti-tumor therapies is still controversial [2]. In this study, we focused on the effect of IDH1 wild-type glioblastoma on the human hippocampus volume.

Methods: We carried out a case-control study using voxel-based morphometry assessment, analyzed with the Computational Anatomy Toolbox software. Glioblastoma diagnosis was performed according to the latest 2021 WHO classification [3]. Due to stringent inclusion criteria, 15 patients affected by IDH1 wild type glioblastoma were included and compared to 19 age-matched controls.
Results: We observed a statistically significant increase in the absolute mean hippocampal volume ($p = 0.017$), as well as in the ipsilateral (compared to the lesion, $p = 0.027$) and the contralateral hippocampal volumes ($p = 0.014$) in the group of patients. When the data were normalized per total intracranial volume, we confirmed a statistically significant increase only in the contralateral hippocampal volume ($p = 0.042$).

Discussion: We theorize that the presence of the GBM, with both its local and widespread detrimental effects, may induce a compensatory response within the hippocampus, one of the few sites having a neurogenesis capability in the adult brain. Brain tumors may thus represent an additional provocative factor for hippocampal plasticity. The higher proximity of the brain tumor may justify the volumetric differences observed between ipsi and contralateral mesial temporal areas, with ipsilateral limbic areas being more affected by the local cytotoxic effect exerted by the tumor, disrupting local brain networks. Moreover, the finding of substantial integrity and resilience in the mesial temporal areas before to the start of the multimodal therapies, suggests that the prominent memory deficits emerging during the course of the disease may be related to the radio- chemotherapy treatments, rather than being a direct consequence of the glioma.

Conclusions: To the best of our knowledge, this is the first study to explore hippocampal volumetric changes in a cohort of adult patients affected by IDH1 wild-type glioblastoma, according to the latest WHO classification. We demonstrated an adaptive volumetric response of the hippocampus, which was more pronounced on the side contralateral to the lesion, suggesting substantial integrity and resilience of the medial temporal structures before the initiation of multimodal treatments.

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## PAIN

### NEUROIMAGING, NEUROPHYSIOLOGICAL AND PSYCHOPHYSIOLOGICAL ANALYSIS OF CONCOMITANT CONTINUOUS PAIN IN TRIGEMINAL NEURALGIA

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Aim: A distinctive phenotype of Trigeminal Neuralgia (TN) is characterized by the presence of an additional type of pain, continuous and burning, besides the characteristic electric shock-like paroxysmal pain. Since this continuous pain tends to respond less to available treatments, it may be due to a different pathogenetic mechanism. The aim of the present study is to identify the neuroimaging, neurophysiological and psychophysiological characteristics that distinguish patients with concomitant continuous pain from patient with purely paroxysmal pain.

Materials and Methods: Patients with a definite diagnosis of Primary Trigeminal Neuralgia were subclassified according to the presence of concomitant continuous pain through a detailed clinical interview. Both groups underwent high-resolution 3T MRI with a volumetric study of the trigeminal nerve, laser-evoked potentials (LEP), and quantitative sensory testing (QST) according to the DFNS protocol.

Results: A total of 73 TN patients were enrolled, of which 28 reported concomitant continuous pain (38%). Patients with concomitant continuous pain showed a more severe trigeminal root atrophy ($p<0.001$), an attenuation of the LEP elicited by stimulation of C fibres ($p<0.005$) and of the Cold Detection Threshold as assessed by QST ($p<0.05$). The volume of the affected nerve showed a correlation with Wind-Up Ratio ($p<0.05$).

Discussion and Conclusions: Our multimodal findings converged in showing that concomitant continuous pain is characterized by axonal loss and impairment of the small trigeminal fibres. The correlation of the volume of affected nerve with Wind-Up Ratio suggests that the axonal loss may trigger hyperexcitability in the second order neuron. This abnormal activity could underlie the development of concomitant continuous pain.

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### SMALL FIBER NEUROPATHY IN SYSTEMIC LUPUS ERYTHEMATOSUS. A CLINICAL, NEUROPHYSIOLOGICAL, AND HISTOPATHOLOGICAL STUDY

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Aim: Patients with Systemic Lupus Erythematosus (SLE) commonly complain of painful and autonomic disturbances. The impact of small fiber neuropathy (SFN) on these symptoms has been fragmentarily investigated, as well as its relationship with disease activity and immunologic variables. As a result of limited knowledge, SFN is still an underrecognized SLE complication. In this prospective study we aimed at assessing small fiber related diagnostic test findings in patients with SLE and painful disturbances, and at evaluating the association between SFN, immunologic disease variables, and clinical symptoms.

Materials and Methods: We enrolled 50 patients with SLE and painful disturbances and performed a comprehensive clinical and neurophysiological evaluation through Nerve Conduction Study (NCS) and Quantitative Sensory Testing (QST), a complete laboratory assessment of the main disease immunologic variables, and an extensive skin biopsy analysis, with somatic and autonomic innervation assessment and the detection of complement and inflammatory cells infiltrate.

Results: 38% of patients had diagnostic findings compatible with SFN, mostly with a non-length dependent distribution. 14% of patients had a mixed neuropathy (MFN) with both large and small fiber involvement. Patients with MFN were older respect to those with SFN ($p=0.0143$); large fibers mediated variables, i.e., sural nerve action potential amplitude and QST vibration detection threshold, showed a negative correlation with age ($p=0.0002$, $r=-0.502$; $p=0.0010$; $r=-0.471$) and disease duration ($p=0.0064$; $r=-0.392$; $p=0.0057$, $r=-0.420$), whereas small fibre related variables did not. Patients with SFN had more frequently presented hypocomplementemia in their clinical history ($p=0.0058$) and had more frequently been treated with cyclosporine A ($p= 0.0114$) respect to patients without neuropathy. No differences were found in painful and autonomic symptoms between patients with and without SFN.

Discussion and Conclusions: Our study shows that SFN with a non-length dependent distribution is a highly prevalent complication in patients with SLE and is an early manifestation of SLE related neuropathy. SFN is associated to hypocomplementemia, thus showing a relation with disease immunologic activity, and may also be related to disease modifying therapy. However, its role in conditioning painful and autonomic symptoms in SLE patients remains elusive.

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## PREVALENCE OF HEADACHE IN A COHORT OF PATIENTS WITH PARKINSON'S DISEASE

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Objective: Our aim was to assess the lifetime and last year prevalence and the phenomenology of the headache in a cohort of PD patients in comparison with control subjects (Ctrl).

Methods: We recruited 80 patients (36 F; 44 M) and 76 Ctrl (37 F; 39 M) selected among spouses and not consanguineous caregivers, comparable for age, sex and education. All participants underwent Beck Depression Inventory scale and a questionnaire assessing the presence of a history of headache and days with headache during the last year, describing characteristics of pain as well. Only patients were clinically evaluated by the motor section of Unified PD Rating Scale (UPDRS-III) and Hoehn and Yahr (HY) scale.

Results: Forty-seven patients (57%; 24 M/23 F) and 46 Ctrl (60%; 24 M/22 F; p=0.871) presented headache during the whole lifetime, whereas 28 patients (35%; 12 M/16 F) and 34 Ctrl (45%; 18 M/16 F; p=0.514) had suffered in the last year. No significant difference was observed in the overall prevalence of lifetime migraine among PD patients (30%; 5 M/9 F; p=0.387) compared to Ctrl (39%; 6 M/12 F; p=0.178), as well as the prevalence of tension-type headache (TTH) was comparable between the two groups (70% vs 61%; p=0.619). Migraine prevalence was significantly higher among women in both groups (11% M vs 25% F; p=0.067; 15% M vs 32% F; Ctrl: p=0.016). We found higher occurrence of headache family history (40% vs 13%; p=0.004), more common headache remission with age (p<0.001), particularly after the onset of motor symptoms (23%; p=0.037), among PD subjects rather than Ctrl. Furthermore, patients reported more common gradual onset of the pain (6% vs 16% p=0.068), less frequent visual aura (46% vs 64% p<0.001), and shorter attack duration than Ctrl (2% vs 13%; p=0.058).

Conclusions: The prevalence of migraine and TTH did not differ between PD subjects and controls. PD does not seem to act as a risk factor in the development of headache, but the dopaminergic pathway degeneration and progressive loss of DA activation on the trigeminal-vascular system might affect the severity and duration of the attacks and favor the improvement and remission of the headache in these patients.

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## SEX DIFFERENCES IN TRIGEMINAL NEURALGIA

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It is well established that trigeminal neuralgia is more prevalent in females that in males. Neurovascular compression with morphological changes of the trigeminal root represents the most recognized etiological factor. However, other factors may play a role in the framework of a multi-hit model. The primary aim of this study was to investigate sex differences in radiological and clinical characteristics of trigeminal neuralgia to better understand the multifactorial origin of this peculiar neuropathic pain condition. In this cross-sectional study patients with a definite diagnosis of primary trigeminal neuralgia were consecutively enrolled. Each patient underwent 3T MRI with sequences dedicated to the study of neurovascular compression. Major morphological changes of the trigeminal root were quantitatively assessed. Clinical characteristics were sistematically collected through a dedicated questionnaire. A logistic regression model was implemented to predict radiological and clinical characteristics based on sex. 114 patients with classical (87) or idiopathic trigeminal neuralgia (27) were enrolled. Female sex was predictive for Idiopathic trigeminal neuralgia. Male sex was predictive, among the comorbidities and clinical characteristics, for hypertension, the involvement of the left side and the second trigeminal division, alone or with the ophthalmic division. The preponderance of TN in the female sex and the association between idiopathic TN and the female sex suggest the role of additional etiological factors in the framework of a multi-hit model. The identification of clinical variables predicted by sex suggests the possibility that distinct phenotypes, with peculiar pathophysiological and therapeutic aspects, may occur females and males.

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## AN OPEN STUDY OF BOTULINUM-A TOXIN TREATMENT FOR 1 YEAR OF CHRONIC NEUROPATHIC PAIN

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Introduction: Neuropathic pain is one of the most difficult pain syndromes to manage. In fact, current medical therapy often remains unsatisfactory. Recent evidence suggests that botulinum toxin type A (BoNT/A) may also modulate the firing of afferent sensory fibers, thereby relieving chronic peripheral and central neuropathic pain [1].

Methods: An open-label pilot study of intradermal BoNT/A for neuropathic pain in patients with chronic peripheral or central neuropathic pain was conducted to evaluate its efficacy. We administered three targeted intradermal treatments with BoNT/A (50-300 Units), each performed every 4 months. The outcome measures were: reduction in visual analog scale (VAS) pain score and reduction in pain frequency compared with baseline values, and duration of benefit after each treatment.

Results: We recruited 31 patients with chronic neuropathic pain (18 females,13 males; mean age 58± 27). Divided as follows: trigeminal neuralgia group (32%), post-herpetic neuralgia group (10%), mixed peripheral neuropathic pain group (42%), central neuropathic pain group (16%). In trigeminal neuralgia group we find a significant reduction in VAS of pain of 56%( by 9.5 ± 1.5 at baseline to 4.2 ± 2.4 at 12 months) and 47% in the frequency of pain paroxysms, with an average duration of benefit of about 2.5 months; in post-herpetic neuralgia group we observed an average reduction of VAS pain of 44%( by 8.3 ± 0.5 at baseline to 4.6 ± 0.5 at 12 months), with an average duration of benefit of about 2 months; in peripheral neuropathic pain group we find a reduction of VAS pain of 47% ( by 8.3 ± 0.9 at baseline to 4.8 ± 1.3 at 12 months) and 58.33% reduction in pain frequency, with an average duration of benefit of 3 months; in central neuropathic pain group there was a reduction of VAS pain of 39%( by 8.6 ± 1.3 at baseline to 5.8 ± 2.2 at 12 months), with an average duration of benefit of 2.5 months. No serious adverse events were reported in all patients.

Conclusions: This open-label study demonstrates that targeted intradermal injections of BoNT/A for chronic neuropathic pain are safe and effective, suggesting that in patients with intractable neuropathic pain they could be a useful therapeutic strategy.

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## SLEEP

### LONG-TERM MAINTENANCE OF EFFICACY AND SAFETY OF PITOLISANT IN THE TREATMENT OF RESIDUAL SLEEPINESS IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

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Objective: In people with obstructive sleep apnea (OSA) excessive daytime sleepiness (EDS) is a prominent symptom and it can persist, despite adherence to continuous positive airway pressure (CPAP). Pitolisant was effective in reducing EDS in two randomised controlled trials (RCTs), one in patients adherent to CPAP (HAROSA 1) and another in patients refusing or not tolerating CPAP (HAROSA 2). Being OSAS a chronic condition and since EDS might require prolonged treatment, we would verify whether the efficacy and safety profile which pitolisant showed in the short term is confirmed in the long-term.

Materials and Methods: Following the 12 weeks double-blind phase, to all adults included in the HAROSA RCTs, both the ones randomized in the pitolisant and in the placebo arms, an open label treatment, from week 13 to week 52 with pitolisant up to 20 mg/day, was proposed. The primary efficacy endpoint was the change in the Epworth Sleepiness Score (ESS) between baseline and week 52. Safety endpoints were: treatment-emergent adverse event(s) (TEAE), serious TEAE (TESAE) and special interest TEAE (TEAESI).

Results: 376 out of 512 adults included in the RCTs completed the 1-year follow-up. The mean baseline ESS were respectively 15.2±3.2 in the placebo group and 15.3±3.0 in the pitolisant arm. Any significant difference between studies were found for baseline ESS (p=0.538), age (p=0.06) and gender (p=0.09. The pooled mean difference in ESS from baseline to one year for the Intention to Treat sample was -8.0 [-8.3, -7.5]. Secondary endpoints, such as OSLER, EuroQol-5D, Clinical Global Impression, Patient's Global Opinion and PFS, showed significant improvements from baseline until the end of the year of follow up. The overall proportions of TEAE, TESAE and TEAESI were 35.1%, 2.0% and 11.1%, respectively, without any significant difference between the patients treated with pitolisant or placebo in the double blind phase. No cardiovascular safety issues were reported and systolic and diastolic blood pressure and heart rate didn't show clinically or statistically significant changes.

Discussion: Pitolisant was effective in reducing daytime sleepiness over one year in adults with OSA, with or without CPAP treatment and showed a good general and cardiovascular safety profile.

Conclusion: The outcomes of the present one year follow up open label study showed that pitolisant is suitable for the long term pharmacological management of OSAS's EDS.

### CIRCADIAN PHASE AND CLINICAL PHENOTYPE IN INSOMNIACS: PRELIMINARY RESULTS OF AN IN-HOME SALIVARY MELATONIN TEST IN 71 ADULT PATIENTS

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Objective: Although insomnia and circadian rhythm disorders are distinctive diseases, extreme chronotypes and desynchronised circadian phase may contribute to insomnia pathophysiology. In particular extreme chronotypes and a desynchronised circadian phase may influence insomnia phenotype. The present study aimed to investigate the relationship between circadian phase and insomnia phenotype in both drug-free and treated patients affected by chronic insomnia disorder.

Materials: Seventy-one primary chronic insomniacs (M/F: 34/37; median age 51 years) and 20 healthy controls (HC; M/F: 13/7; median age 44 years) were enrolled. According to the timing of sleep

difficulties, patients were divided into subgroups: sleep-onset insomnia (SOI, 15 patients), early morning awakening insomnia (EMA, 27 patients), sleep-maintenance insomnia (SMI, 17 patients) and mixed insomnia (MI, 12 patients).

Methods: Patients were investigated for insomnia phenotype and subjective sleep quality by using clinical sleep scales and a sleep diary. Circadian phase was determined through Dim Light Melatonin Onset (DLMO) by means of a five-point in-home evening melatonin salivary test and phase angles were then calculated based on the sleep timing reported in the diary.

Results: The mean value of DLMO clocks did not differ between insomniacs and controls (p=0.54). However, the 26% of the insomniacs, 49% of whom were taking gaba receptor agonists as sleep aids, used to go to bed at a wrong circadian phase (BTWCP). This behaviour proved to be more frequent in patients with a late circadian phase. In fact, in insomnia group phase angles showed to correlate negatively with DLMO (Spearman's correlation index: -0.63 (95% CI -0.75 to -0.46). Furthermore, insomniacs show a significant lower percentage of long phase angles (longer than 2 h) than controls (p=0.02).

Discussion: Our data indicated that a late circadian phase was more frequent in SOL and SMI than in the EMA insomnia. These findings concur to indicate that circadian phase timing is likely to modulate clinical phenotypic insomnia subtype. In insomniacs' group phase angles showed to correlate negatively with DLMO, with patients having later circadian phases showing shorter phase angles. The distribution of this wrong behaviour was also different according to the clinical phenotypic insomnia subtype.

Conclusion: Our data confirm that circadian components of sleep regulation is likely to contribute to primary chronic insomnia phenotype in real life condition, in both untreated and treated patients. Investigating these components may help to expand our knowledge of the ultimate complex pathophysiology of chronic insomnia and to optimize the insomnia treatment.

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## LONGITUDINAL ANALYSIS OF MUSCLE ACTIVITY IN SLEEP IN PATIENTS WITH ISOLATED REM SLEEP BEHAVIOUR DISORDER


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Objective: To analyze the motor activity in all sleep phases in patients with isolated REM sleep behaviour disorder (iRBD), a well-recognized prodromal state of an underlying α-synucleinopathy [1], and to compare this activity with healthy controls and longitudinally at a certain follow-up, using a recently validated automatic method together with the manual score of motor events.

Materials: Sleep was studied with video polysomnography (vPSG) and scored using American Academy of Sleep Medicine diagnostic criteria. A total of 30 vPSG were analyzed; the electromyographic activity (chin, upper and lower limbs) was analyzed both manually and automatically through the Distribution of Normalized EMG values (DNE) method [2].

Methods: We enrolled 10 patients referred to our centre with a diagnosis of iRBD and 10 healthy controls: firstly, we compared motor activity during sleep between these two groups; then, between patients' first vPSG (baseline) and a follow-up performed after 2,78 ± 2,41 years.

Results: Patients had 66,20 ± 7,29 years (80% males) with a disease duration of 8,19 ± 5,30 years at baseline; controls had 66,09 ± 7,31 years (90% males) and showed no significative differences in age (p=0,974) and sex (p=0,531) with patients. We found that patients presented more hypnic jerks compared with controls at baseline (p=0,029) and the number increased at follow-up (p=0,016). DNE method showed greater motor activity during REM sleep in patients than in controls, while there were no significative differences in sleep motor activity between baseline and follow-up groups analyzed with DNE.

Discussions: Our results showed that overall motor activity of patients with iRBD did not differ from controls during sleep period (except for REM phase) and did not change over time; however, we interstingly found an increased number of hypnic jerks as difference with both controls and baseline patients. Furthermore, DNE automatic method, already used for comparing motor activity in patients with synucleinopathies [3], was used for the first time in patients with iRBD and showed increased EMG activity in REM sleep in patients than in controls.

Conclusions: Although mostly stable over time, motor activity in sleep showed there are some motor phenomena (such as hypnic jerks) that should be considered in futher studies about pathophysiological aspects of iRBD and synucleinopathies and their role as possible disease biomarkers in iRBD patients. In addition, our pilot study suggested the automatic DNE method may have a role as a future diagnostic and monitoring method in these patients.

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## WHY AND HOW OSA PATIENTS REFER TO CENTERS: THE OSAREDS STUDY DATA


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Introduction: Several data suggest that obstructive sleep apnea (OSA) is underdiagnosed in many Countries, including Italy. Defining the journey of OSA patients may help in easing the referral, even educating the public on disease's symptoms. Objective: analysis on why and how patients included in the OSAREDS (OSA-related Residual EDS prevalence in Italian patients) study were referred to the Sleep Centers.

Methods: The reason for referring to Centers and the way the referral happened, besides characteristics, symptoms, comorbidities and CPAP variables, were retrospectively collected from medical records of OSA patients followed up by 7 Italian sleep Centers, and descriptively analyzed.

Results: The whole cohort included 2727 patients with a pre-CPAP visit (males: 77.3%, mean age±SD: 55.7±9.4 yrs, BMI: 31.2±4.7 kg/m2). For the majority of patients (69.9%), symptoms in general were the main reason for a first referral to Centers, more frequently requested by general practitioner (GP) (30.1%), than by specialist's prescription (26.2%) or spontaneous access (26.7%). In females, the GP's prescription prevailed (41.9%), while for males the spontaneous access was the more frequent way of refer to Centers (29.2%). The OSA symptoms that more often drove patients to Centers were: snoring (63.2%), EDS (20.2%) and breath pauses during sleep (10.0%). There were sex-related differences in symptoms driving the first referral: snoring was more frequent in males (M: 65.3% vs F: 56.1%) while EDS (Epworth Sleepiness Scale [ESS] score >10) was more frequent in females (M: 18.9% vs F: 24.8%). First referral to specialist was more often to neurologists (45.4%), pulmonologists (28.8%) and ear, nose an throat specialists (12.7%). Males more frequently referred to neurologists (M: 46.9% vs F: 39.9%) than to pulmonologists (M: 26.3% vs F: 38.1%). Occurrence of EDS seems related to the choice because, comparing patients that referred first to neurologists with the ones that consulted pulmonologists, both mean ESS score (10.1±5.4 vs 8.2±4.5) and frequency of EDS were higher (54.2% vs 23.8%).

Conclusions: In the OSAREDS study, symptoms, and in particular snoring more often than EDS, were the main reasons for referral to OSA Centers. Neurologists were more frequently the first specialist consulted in general, but gender and presence of EDS influenced the choice.

## CPAP THERAPY IMPROVED SLEEP AND EPILEPSY DISORDER IN A YOUNG, OBESE EPILEPTIC AND OSA WOMAN

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Introduction: Sleep disorders and epilepsy are both common diseases in the general population. Comorbidity between Obstructive Sleep Apnea Syndrome (OSA) and epilepsy varies from 8% to 76% [1], with a recent meta-analysis reporting a 33.4% prevalence of mild-to-severe OSA in epileptic patients, which proved to be more susceptible to OSA than healthy controls [2].

Case report: We report a case of a 39 y.o. woman, non-smoker, suffering from temporal lobe epilepsy; she was diagnosed in 2018 upon experiencing her first nocturnal tonic-clonic seizure. She also suffers from hyperinsulinism, obesity (BMI: 36.3) and Von Willebrand Syndrome. In 2020, she came to our Sleep clinic because of excessive daytime sleepiness (EDS). She was taking Lacosamide (LAC) 150 mg twice daily with partial control of seizures, she had interictal bi-temporal epileptiform discharges (IEDs) during both wake and sleep more evident over the left hemisphere. She completed the following self-administered questionnaires: Epworth Sleepiness Scale (ESS; 13, n.v.<10); Pittsburgh Sleep Quality Index (PSQI; 14, n.v.≤5), Hamilton Anxiety Rating Scale (HAM-A; 23, n.v.≤17), Beck Depression Inventory (BDI; 22, n.v.≤10). An ambulatory cardiorespiratory monitoring showed AHI 28.9 (n.v. <5), with mean oxygen saturation of 93%. We suggested a CPAP treatment and she is currently sleeping with a CPAP device at 9 cmH2O with complete disappearance of EDS (ESS: 3). Very recently, the 2022 check-up showed withdraw of IEDs during sleep, and LAC has been reduced to 100 mg twice a day. At last check-up in May 2023, she reported improved sleep and life quality with no more EDS nor seizures. LAC has been also further reduced to 50 mg twice a day. Her CPAP compliance is excellent, with a median nocturnal use of 5 h 26 min and AHI of 0.5. The EEG background is within normal limits.

Conclusions: This is a case of a young, obese epileptic woman with persistent seizures despite antiseizure medication. Interestingly, the only CPAP treatment let to seizures and EEG abnormalities disappearance suggesting the potential role of CPAP in stabilizing sleep and epilepsy.

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## IDENTIFICATION OF RISK FACTORS FOR OBSTRUCTIVE SLEEP APNEA IN PUBLIC TRANSPORT WORKERS

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Objective: Sleep Obstructive sleep Apnea (OSA) is more frequent in professional drivers than general population, leading to an increased risk daytime sleepiness and traffic accidents. Our multicenter study, conducted in collaboration between University of Cagliari and University of Milan aims to evaluate risk factors associated to OSA in a population of public transport companies workers.

Materials: We recruited 623 people (483 in Cagliari, 140 in Milan) who underwent yearly clinical evaluation with the occupational physician in the two centres. After signing informed consent, workers filled in different sleep questionnaires: Epworth sleepiness scale (ESS) for daytime sleepiness, Berlin Questionnaire (BQ) for risk of OSA, Morningness Eveningness Questionnaire (MEq) for chronotype, Pittsburgh Sleep Quality index (PSQI) for Sleep quality. Moreover we collected clinical and anthropometric data such as age, gender, BMI, smoke and alcohol consumption, blood pressure (BP), presence of comorbidities, neck circumference and Mallampati score.

Method: We considered as Suspected OSA patients those with a positive Berlin questionnaire, documented apnea episodes and at

least three of the following characteristics: history of hypertension or BP>140/90, BMI >35, persistent daily snoring for at least 6 months, Mallampati IV, neck circumference >41cm. To identify predictive risk factors for OSA we analyzed 20 clinically relevant characteristic for OSA association. We used a combination of univariate analysis therefore we used logistic regression in order to evaluate the combined effect of factors.

Results: We recruited 623 workers of public transport companies in Sardinia and Lombardy: 611 were man (98%) and 12 women (2%). Of those 623, 463 (68%) were drivers, others were maintenance workers. 112 (18%) workers were considered OSA patients. Univariate analysis showed a significant association between OSA and Mallampati IV, elevated diastolic BP, presence of metabolic comorbidities (metabolic syndrome, diabetes, hypothyroidism) elevated ESS score. Multiple regression confirmed all of the before mentioned as significant predictive factors for OSA except diastolic BP.

Discussion: Massive instrumental screening for sleep OSA in professional drivers would be the gold standard but is not feasible because of limited resources and reluctance from drivers to undergo polysomnography exam. Our study allowed the identification of predictive risk factors for OSA in a population of professional public transport workers. Identification of these factor is fundamental for the occupational physician in order to identify those patients at risk and refer them for further evaluation.

Conclusion: Screening for OSA in professional drivers is fundamental for the reduction of risk of traffic accidents and screening for risk factors helps the occupational physician to identify subjects to address to second level examinations.

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## EXPLORING THE IMPACT OF OBSTRUCTIVE SLEEP APNEA IN NEUROLOGY INPATIENTS: INSIGHTS FROM STROKE AND TIA CASES


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Objective: Obstructive sleep apnea syndrome (OSAS) is characterized by the presence of apneas and/or hypopneas, desaturations, frequent arousals, and sleep fragmentation. This study aimed to assess the prevalence of sleep breathing disorders among patients admitted to our neurology department and to examine their specific characteristics.

Material and Methods: The study enrolled 166 patients (95 males, M:F 1,33, mean age 68,56 ± 16,04 years, mean BMI 26,35 ± 4,66); 94 received a recent diagnosis of stroke or TIA, 72 were hospitalized for other neurological conditions. The patients with stroke or TIA underwent an immediate polysomnography (PSG), while among the remaining patients only those with ESS>8 and high risk BerlinQ performed the PSG. We investigated smoking, hypertension, hypercholesterolemia, diabetes, and atrial fibrillation (AF) as risk factors.

Results: A total of 65 patients underwent polysomnography: 38 had stroke/tia (77,55%), 32 hypertension (65,30%), 24 hypercholesterolemia (48,97%), 11 AF (22,4%), 8 diabetes (16,32%), 8 previous stroke/TIA (16,32%) and 10 were smokers (20,4%). A diagnosis of OSAS was made in 49 individuals (M:F = 1,72, mean age 73,28 ± 11,4, mean BMI 27,83 ± 3,51) in which we performed a stratification: mild OSAS (30,61%), moderate OSAS 20,40%, moderate-severe OSAS (4,08%) and severe OSAS (44,89%); among the patients with severe OSAS, 68,18% of them were admitted for stroke/TIA. In the patients where OSAS was excluded we found that 12 were admitted for stroke/TIA (75%), 3 individuals with a ESS > 8, and 9 individuals with a High Risk BerlinQ. Among those 9 patients, 7 (77,78%) were admitted for stroke/TIA.

Discussion and Conclusion: OSAS emerges as a significant and independent risk factor for cerebrovascular events. Therefore, it should receive comparable attention and investigation as other established cerebrovascular risk factors. Given that polysomnography can be conducted both in hospital settings and at patients' homes, it should be considered an essential examination for individuals with a history of stroke and TIA. Moreover, it is imperative to highlight the importance of systematically studying patients with neurological access through the use of questionnaires and polysomnography. In eligible patients, the implementation of continuous positive airway pressure (CPAP) therapy should be contemplated and actively promoted, in conjunction with addressing the primary risk factor.

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## SLEEP DISORDERS IN ACROMEGALIC PATIENTS: THE EXPERIENCE OF OUR SLEEP CENTER


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Introduction: Sleep disorders are frequent in acromegaly, an endocrinologic disorder characterized by disproportionate skeletal, tissue, and organ growth due to GH and IGF-1 overproduction.

Objectives: To evaluate the prevalence of sleep disorders, comorbidities and their possible causes and consequences on quality of life in an acromegalic population.

Materials and Methods: Thirty-eight consecutive acromegalic patients (19 M) from Sicily and Calabria (ages 25-81 years) were evaluated through a structured sleep interview. The Epworth Sleepiness Scale (ESS n.v. <10) questionnaire was administered to those reporting excessive diurnal sleepiness (EDS), and the International Restless Leg Syndrome Rating Scale (IRLS-RS) to those suffering from RLS. The Pittsburgh Sleep Quality Index (PSQI), Hamilton Anxiety Rating Scale (HAM-A), and Beck Depression Inventory (BDI) were administered to all patients. Furthermore, they underwent ambulatory cardiorespiratory monitoring to evaluate the presence of sleep apnea (OSA).

Results: Our cohort presented the following comorbidities: cardiopathy (55%), diabetes (39%), hypertension (68%), steatosis (34%), thyroidopathy (23%), and psychiatric disorders (18%). EDS was reported in 94.9% (36 patients) of the sample. RLS was diagnosed in 38.5% (14) of acromegalic patients, insomnia in 73.7% (28), and snoring in 74.4% (28). OSA was diagnosed in 55.3% (21) of patients, with 41%

(15) employing CPAP or AutoBiPAP treatment. After six months of treatment, ESS and the other scores improved with the disappearance of diurnal somnolence and reduced anxiety and depression.
Discussion: RLS and OSA were frequent in our sample, as corroborated by the literature. A correlation between OSA and hypertension was observed, with a high risk of cerebrovascular outcomes. All thyroidectomized patients that were taking L-thyroxine suffered from RLS. Eight patients had both RLS and moderate-severe OSA. Insomnia was frequent in RLS patients, whereas EDS was prevalent in OSA patients.

Conclusions: OSA and RLS treatment could ameliorate sleep and improve the quality of life of these patients. Therefore, sleep studies should be considered in all patients diagnosed with acromegaly.
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## SLEEP QUALITY IN MIGRAINE PATIENTS TREATED WITH ANTI-CGRP MONOCLONAL ANTIBODIES – A REAL-LIFE STUDY


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Aims: Our aims were to assess sleep quality in patients with high frequency or chronic migraine: i) before and after 3 months of treatment with anti-calcitonin gene related peptide (CGRP) (galcanezumab, fremanezumab) or anti-CGRP-receptor (R) (erenumab) monoclonal antibodies (mAbs); ii) comparing responders to non-responders, defining a response to anti-CGRP(R) mAbs as a reduction on monthly migraine days (MMD) of at least 50%.

Materials and Methods: In this monocentric observational study, 50 consecutive migraine patients resistant to conventional oral prophylaxis started treatment with anti-CGRP(R) mAbs. Patients were evaluated at baseline and after three months of therapy, considering changes in MMD, and in sleep quality by means of the Pittsburgh Sleep Quality Index (PSQI) questionnaire.

Results: Median age was 48 (41-59), with 35 (70%) female patients. At baseline patients had a median of 21 (14-30) MMD. Twenty patients started erenumab, 22 galcanezumab and 8 fremanezumab. At baseline, sleep quality was poor (PSQI median score 6 (5-10) in the whole group, and 20 patients (40%) were regularly taking hypnotic drugs. After 3 months of treatment, we observed a median significative reduction of 15 MMD (MMD at 3 months of 6 (2-14), p <0,001), and PSQI median scores to 5 (4,7), p 0,001. Thirty-three patients (66%) were at least 50% responders. Besides, number of patients taking hypnotic drugs did not change. Comparing responders (R) to non-responders (NR), we found no significant differences evaluating sleep quality, neither at baseline (PSQI R 6 (5-9) vs PSQI NR 8 (5-10), p 0,360) or after treatment (PSQI R 5 (4-8) vs PSQI NR 6 (5-7), p 0,481). Nevertheless, sleep quality significantly improved after treatment, both in responders (PSQI t0 6 (5-9) vs t1 5 (4-8) p 0,002) and in non-responders (PSQI t0 8 (5-10) vs t1 6 (5-7), p 0,013). The rate of poor sleepers among non-responders is the same after treatment (14 vs 14 patients), whereas they decrease among responders (28 vs 22patients, p 0,070).

Discussion and Conclusion: After three months of treatment with anti-CGRP(R) mAbs, a significant improvement in sleep quality occurred in migraine patients - who were overall poor sleepers-, although it was not enough to define a good sleep quality. Improvement seems to occur both in responders and non-responder patients, even if the rate of poor sleepers decreases only in responders. More longitudinal studies including objective sleep measures are needed to assess the impact of anti-CGRP(R) mAbs on sleep quality.
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## TELEMEDICINE FOR INNOVATIVE MULTIDISCIPLINARY CARE OF PEOPLE WITH NARCOLEPSY, THE TELEMEDICINE FOR NARCOLEPSY (TENAR) RANDOMIZED CONTROLLED TRIAL


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Objectives: Narcolepsy is a rare central disorder of hypersomnolence associated with metabolic, endocrine and psychosocial problems, requiring a multidisciplinary approach. Sleep centers with adequate skills and experience to manage disease complexity are sparse at a national level, thus forcing patients to undergo long and expensive journeys, further increasing the disease-related burden. We report the main results from a non-inferiority randomized controlled trial of televisit vs in-office management of people with narcolepsy, funded by the Italian Ministry of Health (RF-2016-02364742).

Materials: People with narcolepsy aged > 14 years were eligible for inclusion in a randomized controlled trial that compared multidisciplinary management (neurological, endocrinological, and psychosocial care) performed via televisit versus in-office visit for one year. Primary outcome was control of sleepiness (according to the Epworth Sleepiness Scale, ESS) at 12 months, with a non-inferiority margin of 1.5 points. Secondary outcomes were control of other symptoms, treatment compliance, metabolic control, quality of life, patient satisfaction with care, safety, and disease-related costs.

Results: 208 patients (106 female, 102 male; mean age 34 yrs; 13 teenagers) were randomized and 202 completed the study at 12 months (101 televisit arm; 101 in-office arm). At baseline, clinical and outcome variables were well balanced in the two groups. At 1 year follow-up, ESS score improved by 1.4 mean points in both groups; the adjusted

mean difference between groups was 0.44 (95% confidence interval -0.48 and 1.35). Cataplexy, Narcolepsy Severity Scale, Global Impression Scale, and Beck Depression Inventory did not differ at 12 months between groups. Among the metabolic outcomes, daily caloric intake, daily physical activity, body mass index, weight, and glucose improved in both groups, without difference between groups. Among psychosocial outcomes, patients that lost workdays due to narcolepsy were less in the telemedicine group (36% vs 64%).

Discussion: The multidisciplinary care of patients with narcolepsy through televisit was non-inferior to that provided with in-office visit, in terms of management of sleepiness and other symptoms. Overall, the multidisciplinary approach, including metabolic assessment, produced an improvement also in body mass index and adherence to physical activity, without differences between the two approaches. Instead, televisit allowed a lower impact on lost workdays compared with in-office visit.

Conclusions: Our data indicate the viability in terms of effectiveness and safety of multidisciplinary telemedicine care procedures for narcolepsy in adults and teenagers, paving the way to applying it in clinical practice and to other rare diseases.

## OVERLAPPING PHENOTYPE ASSOCIATED WITH A NOVEL DNMT1 VARIANT: THROUGH THE DEFINITION OF A COMPLEX DISORDER

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Aim: To describe a patient carrying a rare heterozygous DNMT-1 (DNA methyltransferase 1) variant who developed an overlapping clinical phenotype between hereditary sensory neuropathy with dementia and hearing loss (HSN1E) and cerebellar ataxia with deafness and narcolepsy (ADCA-DN).

Patient and Methods: The proband is a 45 yo male who presented with anxiety and depressive symptoms since age 18, with later occurrence of postural and intention tremor, slurred speech, hypersomnia and involuntary limb movements during sleep. Over the years he was diagnosed with bilateral symmetrical sensorineural hearing loss and mild cognitive impairment, performed negative genetic analysis for MERRF, PTEN, ATX1, CGH array, NPC1-2 mutations. For further clinical worsening coupled with episodes of sudden loss of muscle tone, frequently causing falls, he was admitted to our Neurology department.

Results: Neurological examination at the admission showed ataxic gait, postural tremor, moderate dysarthria, severe hearing loss, hyperreflexia, positive bilateral Hoffman's sign, lower-limb hypopallesthesia, dysmetria and telekinetic tremor. A polysomnography was performed, which showed reduced sleep efficiency with a severe periodic limb movement disorder, and a Multiple-Sleep-Latency-Test recording a mean sleep latency of 3.4 minutes and two sleep onset rapid-eye-movement (SOREM) episodes. A diagnosis of narcolepsy type 1 was made and treatment with sodium oxybate 2.25 g BID was started, with referred clinical benefit on daytime sleepiness. The patient underwent an MRI that reported thinning of corpus callosum, ventricular dilation with reduced midbrain, cerebellar vermis and peduncles volume, and a fluorodeoxyglucose PET, not showing significant hypometabolism. A lumbar puncture was performed, with the evidence of normal CSF chemical analysis and biomarkers of neurodegeneration (total and phosphorylated tau, amyloid-β42). Electroneurography documented an axonal sensory-motor polyneuropathy. Under the hypothesis of DNMT1-related disorder, genetic studies were performed using next-generation sequencing: the heterozygous missense variants c.1619A>G, p.Tyr540Cys and c.2552T>C, p.lle851Thr were identified. Testing for HLA-DQB1 haplotype*06:02 was negative. The patient's parents and sibling underwent genetic counseling, with negative results.

Discussion and Conclusion: The mutation p.lle851Thr is described as a variant of unknown significance, while p.Tyr540Cys is reported as potentially pathogenic, with limited related literature. Our patient presented with clinical features outlining both phenotypes of DNMT-1 mutations. Overlapping symptoms and signs have already been described between the two entities, namely sensory neuropathy, cognitive decline, hearing loss [1] and narcolepsy [2], suggesting the definition of these diseases as a continuum. Further studies are needed to confirm the pathogenicity of the p.Tyr540Cys variant and to foresee different clinical presentations of DNMT1-complex disorder.

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## PINEAL GLAND DYSFUNCTION: RELATIONSHIP WITH SEVERE SLEEP DISTURBANCE AND MULTIORGAN PATHOLOGIES

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Introduction: The pineal gland is a small and unique organ which is localized in the geometric center on the brain. Description of this gland date back to antiquity but its functions are only partially known. We describe a case of a woman with severe sleep disturbance and a multiorgan and multi-functional pathologies caused by a voluminous cyst of the pineal gland with displacement to the left of its axis.

Material and Methods: In this study we describe the case of a woman who at the age of 41 yrs began to develop a series of multiorgan and multifunctional pathologies associated to a severe sleep disturbances. She was taken care of by numerous specialists for paroxysmal tachycardia and recurrent thrombophlebitis (cardiologist), environmental neurotoxic immune syndrome (psychiatrist), thyroiditis and adrenal adenoma and reduced function of CYP4502D6 (endocrinologist), endometriosis (gynecologist), deficit IgG3 e NK (immunologist) and lower eyelid basalioma (oncologist).

Result: Sleep disturbance (severe insomnia) was associated with stress due to a numerous and severe pathologies which on the other hand, had never been associated with a common cause. After three years she performed a neurological examination and a brain MRI which revealed a voluminous cyst of the pineal gland with displacement to the left of its axis.

Discussion: The pineal gland has a primary role in controlling sleep cycles by secreting melatonin and in neuroendocrine control. Anti-oxidant, anti-aging and anti-tumoral properties have also been attributed to it. Several cardiovascular effects are due to melatonin such as antihypertensive properties, regulation of heart race and vascular resistance. Melatonin is an important player in the regulation of immunogenecity, energy metabolism and glucose homeostasis. The pineal gland may influence the psychic function with a sophisticated immunoneuroendocrine network. The disrupted afferent and efferent pathways and the alteration / slowing of the secretion of neurohormones and neurotransmitters could be at the basis of pathological processes.

Conclusion: This case highlights "in vivo" the multiple but still partly unknown functions of the pineal gland. Unfortunately, the study of the pineal gland is currently very fragmented and sectoral by every specialist, which diagnoses and cures the effect but does not seek the cause. For this reason, this important organ and its complex functions should be investigated with new enthusiasm and interest in the future and a multispecialistic approach.

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## TELEVISIT AS DIAGNOSTIC TRIAGE FOR PEOPLE WITH SUSPECTED NARCOLEPSY: THE TELEMEDICINE FOR NARCOLEPSY (TENAR) RELIABILITY AND DIAGNOSTIC ACCURACY STUDY

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Objectives: Narcolepsy is a rare central disorder of hypersomnolence. Onset occurs at a young age, but patients experience an extended diagnostic delay. Sleep centers organized for narcolepsy work up are few and sparse at a national level, thus forcing patients to expensive journeys. Diagnostic reliability and accuracy of televisit compared with in-office visit was assessed in patients with suspected narcolepsy in the Telemedicine for NARcolepsy (TENAR) project, funded by the Italian Ministry of Health (RF-2016-02364742).

Materials: 220 patients (101 M, 119 F, mean age 35.3 years) were included. Forty-eight percent of the patients were from Emilia-Romagna, 25% from other region in the north of Italy, 17% from the center, and 10% from the south or islands.

Methods: We carried out a cross-sectional study with prospective recruitment of patients of any age with suspected narcolepsy referred to the Bologna outpatient Clinic for Narcolepsy. Reliability of the diagnostic judgment made after interview through televisit and after usual in-office visit was assessed with Kappa statistic. Diagnostic accuracy of the same judgment made after televisit was calculated compared with the final diagnosis (reference standard = ICSD3). The televisit was conducted via tablet for the patient, and via equipped pc in another room for the physician. The two visits (televisit or in-office) were conducted by two different physicians using a semi standardized clinical interview, and whenever a physician suspected narcolepsy the diagnostic work-up was offered to the patient.

Results: The raw agreement of diagnostic judgment between the two modalities (i.e., televisit and in-office) was 77%, corresponding to Kappa 0.65 ("substantial agreement"). At the end of the diagnostic process, 33% of patients were diagnosed with narcolepsy (51 type 1, 14 type 2). Televisit showed a sensitivity of 100% and a specificity of 45%. These results were comparable to those of the in-office visit (sensitivity 100%, specificity 41%).

Discussion: In people with suspected narcolepsy, diagnostic conclusions reached through televisit agree with those reached through the in-office visit. Diagnostic accuracy was almost identical between the two interview modalities.

Conclusions: Televisit with a semi standardized clinical interview could be considered as a diagnostic triage procedure, as it is accurate in excluding people without narcolepsy from advanced diagnostic procedures without losing any patients with actual narcolepsy. This approach should be implemented to reduce patients' mobility (e.g. people living far from sleep centers; health emergencies).

## HIV-ASSOCIATED NEUROCOGNITIVE DISORDER (HAND) MIMICKING NARCOLEPSY: A CASE REPORT

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Introduction: Classical presentation of HIV-associated neurocognitive disorder (HAND) comprises difficulties in concentration, impairment in memory and executive functions and psychomotor slowing [1,2]. We describe a patient with HAND presenting with excessive daytime sleepiness mimicking narcolepsy.

Case: A 48-year-old previously healthy man presented with a five-month history of excessive daytime sleepiness and visual hallucinations. After a few months he developed cognitive decline and he experienced some falls without loss of consciousness. Neurological examination showed mild cerebellar ataxia. Epworth Sleepiness Scale (ESS) score was 22/24 (n.v. < 9). Neuropsychological tests revealed moderate multi-domain neurocognitive disorder. In the hypothesis of narcolepsy, we performed a multiple sleep latency test (MSLT) and brain MRI. MSLT evidenced hypersomnolence but was negative for sleep onset rapid eye movements periods (SOREMPs). Brain MRI revealed multiple lesions with T2-hyperintense signal in deep white matter and basal ganglia, in particular in hypothalamic-subthalamic region, without contrast enhancement. Hematologic examination revealed a borderline leucopenia (3.100 cells/ mm3) with lymphopenia (660 cells/ mm3). A HIV-1 antibody test was positive with a serum viral load of 500.000 copies/ml; CD4-cell count was 20 cell/ mm3. CSF analysis showed lymphocytic pleocytosis (52 cells/mm3), increased albumin count (3470 mg/dl) and normal glucose level. CSF orexin levels were not analyzed. We then performed a broad screening for infectious diseases, with syphilis and HBV test positivity. TPHA, VDRL, JCV-DNA test, Toxoplasma Gondii-DNA test, CMV-DNA test, HHV6 and HHV8-DNA test on CSF were negative; EBV-DNA test and HIV1-RNA test on CSF were positive. HAART and penicillin therapy was started. After two months there was a great improvement of daytime sleepiness (ESS score of 11), neurocognitive disorder and brain-MRI abnormalities.

Discussion: It is well known that narcolepsy is caused by hypothalamic dysfunction [3]. In our patient, the clinical picture was dominated by excessive daytime sleepiness and hallucinations, but criteria for narcolepsy were not met due to the absence of SOREMPs. These narcolepsy-like symptoms could be explained by brain lesions involving the hypothalamic-subthalamic region. Our report expands the phenotypic spectrum of HAND clinical manifestations.

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## VEGETATIVE NERVOUS SYSTEM

### ACUTE UNILATERAL MYDRIASIS: ONLY BAD NEWS?

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Introduction: Acute unilateral mydriasis alerts neurologist, as it can potentially be related to serious neurological conditions, including cerebral aneurysm, stroke, intracranial haemorrhages, meningitis, and optic neuritis. However, this condition may sometimes be associated with less severe conditions, including migraine, trauma or drug exposure. Benign episodic mydriasis (BEM) has also been described.

Case Report: We present the case of a 28-year-old female with no significant medical history except for a personal and family history of migraine headaches. She came to emergency department for the sudden occurrence of an acute visual disturbance associated with unilateral pupil abnormalities. She reported prism-like vision, zigzag lines in the periphery of the left visual field, intense photophobia, and subsequent visual field deficit. At the evaluation, she exhibited impaired monocular visual acuity, blurry vision, and a dilated, sluggishly reactive left pupil. The patient did not report any other neurological symptoms, including headache. The neurologic evaluation did not reveal any significant findings, except for a persistent unilateral dilated sluggishly reactive pupil. A brain MRI with contrast and angiography resulted normal, as well as blood tests, including virological screening. An ophthalmic examination also resulted negative: she showed full visual fields on Computerized Visual Field testing, and normal intraocular pressures in both eyes. The patient was treated with FANS and the visual disturbance resolved completely in the following 14 hours, with two brief recurrences lasting less than an hour in the days after.

Discussion: Benign episodic mydriasis is a rare cause of acute anisocoria, predominantly affecting females with a history of migraine. It is a harmless condition that resolves spontaneously and does not cause permanent damage to the eye involved or to the visual system. The underlying pathophysiology of this condition remains poorly understood, however a hyperactivity of the sympathetic nervous system or a hypoactivity of the parasympathetic nervous system are likely involved. Patients with BEM may present with an isolated anisocoria or may experience additional symptoms like blurry vision, photophobia, orbital pain, nausea, eye redness, diplopia, or headache. Prompt and comprehensive evaluation is crucial to rule out the above-mentioned severe causes of visual disturbances and pupils abnomalities.

Conclusion: In our case, the patient was diagnosed with unilateral BEM. This diagnosis could be challenging for the Neurologist especially at the first presentation. BEM must be kept in mind in patients with episodic pupils abnormalities and normal imaging and laboratoristic findings, especially in female with a history of migraine.

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### EVIDENCE OF CARDIOVASCULAR AUTONOMIC DYSFUNCTION IN A PATIENT WITH ACERULOPLASMINEMIA

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Background: Aceruloplasminemia is a rare autosomal recessive disease classified among "neurodegeneration with brain iron accumulation" (NBIA), secondary to reduced activity of ceruloplasmin, a ferroxidase involved in the export of iron from cells. Clinical hallmarks include dementia, retinal degeneration and diabetes. The spectrum of neurological manifestations is remarkably broad including cerebellar symptoms, hyperkinetic movement disorders and, more rarely, hypokinetic movements. We describe here the main features of the autonomic nervous system involvement.

Clinical Case: A 62-year-old woman referred to our Institute with a history of about 13 years of progressive cognitive impairment, chorea, dysphagia and dysarthria. The non-motor signs and symptoms were microcytic anemia, constipation, urgent urinary incontinence and orthostatic hypotension. Before evaluation at our Institute was made early diagnosis for positive family history with evidence of microcytic anemia and elevated liver enzymes. The patient was treated, before the onset of neurological symptoms, first with deferiprone and later, due to the progression of the disease, with deferoxamine. Finally was proposed therapy with ferrochelant and fresh frozen plasma with high levels of ceruloplasmin, refused by the patient. Brain MRI showed iron deposition in basal ganglia nuclei, thalami, midbrain, dentate nuclei and white matter of the semioval centers associated with cerebral, cerebellar atrophy and diffuse cortical siderosis. DAT-scan assessed the integrity of presynaptic dopamine transporters in basal ganglia. Plasma epinephrine levels were reduced in both clinostatism 13 pg/ml (20 - 190) and orthostatism 11 pg/ml (20 - 190) while norepinephrine levels were normal both in clinostatism 249 pg/ml (70 - 480) and orthostatism 212 pg/ml (70 - 480), showing a slight reduction in orthostatism. 123I-mIBG scan showed a reduced density of the adrenergic cardiac sympathetic nerve endings. Cardiovascular autonomic reflexes showed presence of baroreflex failure, with delayed orthostatic hypotension at head up tilting test and impaired adrenergic sympathetic function at the Valsalva manouvre.

Discussion and Conclusion: Our patient showed reduced plasma levels of epinephrine, slight decrease in epinephrine and norepinephrine plasma levels in orthostatism. Myocardial scintigraphy proved impairment of post-ganglionic sympathetic cardiac innervation. Finally with cardiovascular autonomic test we found baroreflex failure and confirmed the dysfunction of the sympathetic system. Autonomic nervous system studies may provide interesting data to increase the awareness regard this rare condition and to extend the clinical spectrum of aceruloplasminemia.

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## CARDIOVASCULAR AUTONOMIC FUNCTION IN GBA-ASSOCIATED PARKINSON'S DISEASE

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Objectives: Data retrieved from questionnaires suggested that patients with Parkinson's disease carrying GBA variants (GBA-PD) have an increased risk of dysautonomia, compared to patients with idiopathic Parkinson's disease (i-PD). Recent laboratory evidence also supported these findings, but a comprehensive electrodiagnostic assessment of the autonomic nervous system in GBA-PD is lacking. This case-control study provides a laboratory-based assessment of cardiovascular autonomic function in GBA-PD compared to i-PD with the aim to describe the prevalence, characteristics, and severity of cardiovascular dysautonomia in the two groups.

Materials and Methods: All patients underwent an autonomic battery including head-up tilt test, Valsalva maneuver, and deep breathing. The sympathetic noradrenergic system was assessed by measuring heart rate and blood pressure response to the head-up tilt and blood pressure response to the Valsalva maneuver. Parasympathetic function was assessed by measuring the Valsalva Ratio and the respiratory sinus arrhythmia. The severity of dysautonomia was graded with the Composite Autonomic Severity Score cardiovascular subscore (cv-CASS). The late heart-to-mediastinum ratio of 123I-MIBG uptake was calculated. Symptoms related to autonomic dysfunction were collected in each patient by means of the SCOPA-AUT questionnaire. The association of cv-CASS score and sympathetic and parasympathetic subscores with other clinical variables was explored using linear regression analysis. All calculations were performed with the Stata 15 program, considering significant a $p < 0.05$.

Results: A total of 34 GBA-PD and of 33 i-PD patients participated in the study. Age at disease onset was younger in the GBA-PD group. The main between-group differences were a greater supine and orthostatic heart rate in GBA-PD. This was coupled with evidence of higher parasympathetic cv-CASS subscores and higher SCOPA-AUT scores. There was no inter-group difference in the H/M ratio. Demographic and clinical features did not correlate with the severity of cardiovascular dysautonomia.

Discussion: We found a prominent dysfunction in parasympathetic parameters in the GBA-PD group, while sympathetic parameters were similar. It is arguable that cardiovagal dysfunction occurs earlier in the disease history than sympathetic dysfunction. The early parasympathetic dysfunction in GBA-PD may arise from an ascending pathology during the disease course, with a gut-to-brain spreading of alpha-synuclein aggregates through the vagus nerve, as proposed in the body-first subtype of PD.

Conclusions: We suggest a selective parasympathetic dysfunction in GBA-PD. This is the first study that performed a complete battery of cardiovascular autonomic tests in GBA-PD. Our data should be confirmed pathologically or with imaging studies to assess parasympathetic innervation.

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## THE INVOLVEMENT OF THE SENSORY AND AUTONOMIC PERIPHERAL NERVOUS SYSTEM IN HYPERMOBILITY SPECTRUM DISORDER: MORPHOLOGICAL AND FUNCTIONAL STUDY

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Objectives: Patients affected by Hypermobile Ehlers Danlos and Hypermobile Spectrum Disorder (HSD) often have a long history of sensory and autonomic symptoms complains. The aim of this study is to assess the peripheral involvement of sensory and autonomic nervous system in HSD.

Methods and Materials:14 patients with HSD (3 male, 11 female, 38±12 years) and 16 patients with idiopathic SFN (6 male, 10 female, 50±11 years) were recruited. Both patient groups underwent clinical evaluation and assessment of sensory and autonomic dysfunction trough the "Small Fiber Neuropathy Symptoms Inventory Questionnaire" (SFN-SIQ), the "Composite Autonomic Symptoms Score" (COMPASS-31), Quantitative Sensory Testing (QST), cardiovascular reflexes (Ewing's battery test), sympathetic skin response (SSR) and the Dynamic Sweat Test (DST). Cutaneous sensory and autonomic innervation was analyzed on punch skin biopsies from leg, thigh and fingertip applying indirect Immunofluerescence procedures.

Results: HSD patients were younger, with earlier onset of symptoms and longer disease duration then SFN patients ($p<0.05$). They also frequently suffered of migraine-type headache, dysimmune diseases, food and drug allergies and urticaria. They complained of pain with a generalized distribution and involvement of the perineal region in a third of the cases. Abnormal QST for each sensory modality was observed without significant differences in between patient groups. Autonomic symptoms involving the cardiovascular, gastrointestinal and sudomotor domains were significantly ($p<0.05$) more frequent in HSD than in SFN patients. Moreover, impairment of autonomic cardiovascular function with evidence of Postural Orthostatic Tachycardia Syndrome (PoTS) was observed in 7 HSD patients while it was absent in SFN

group (p<0.05). DST showed that in HSD compared with SFN patients a non-length-dependent reduction of sweat output per individual gland was present (3.56±2.73 nl/min vs. 8,97±7,49 nl/min). The morphological analysis of cutaneous nerves revealed a more severe loss of pilomotor and sudomotor nerve fibers, with a mild non-length dependent loss of epidermal nerve fibers (ENF) in HSD compared to SFN patients.

Conclusion: Small fiber involvement in HSD compared to SFN patients, presents with a distinctive pattern of generalized pain, often including perineal region and autonomic symptoms mostly involving cardiovascular and gastrointestinal domains. The morphological picture underlying this condition is a more severe loss of autonomic nerves and a mild non length-dependent loss of ENF.

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## AUTONOMIC DYSFUNCTION IS ASSOCIATED WITH DISEASE PROGRESSION AND SURVIVAL IN AMYOTROPHIC LATERAL SCLEROSIS: A PROSPECTIVE LONGITUDINAL COHORT STUDY


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Background: Among non-motor symptoms, autonomic disturbances have been described in Amyotrophic Lateral Sclerosis (ALS) and reported as mild to moderate in up to 75% of patients [1, 2]. To date, no study has systematically investigated autonomic symptoms as prognostic factors in Amyotrophic Lateral Sclerosis (ALS). Main aim of this longitudinal study was to examine the association of autonomic dysfunction with disease progression and survival in ALS.

Methods: We enrolled newly diagnosed ALS patients and a healthy control group (HC). Time from disease onset to disease milestone (King's stage 4) and death were calculated to assess disease progression and survival. Autonomic symptoms were assessed by a dedicated questionnaire. Longitudinal evaluation of parasympathetic cardiovascular activity was performed by the heart rate variability (HRV). Multivariable Cox proportional hazards regression models on the risk of the disease milestone and death were used. A mixed-effect linear regression model was used to compare autonomic dysfunction with a HC group as well as its impairment over time.

Results: A total of 102 patients and 41 HC were studied. Autonomic symptoms occurred in 69 (68%) patients at diagnosis and progressed over time (post6: p= 0.015 and post12: p<0.001), especially in bulbar patients (p<0.001). A higher autonomic symptom burden was an independent marker of faster development of King's stage 4 (HR: 1.05; 95% CI 1.00 to 1.11; p= 0.022), whereas urinary complaints were independent factors of a shorter survival (HR: 3.12; 95% CI 1.22 to 7.97; p= 0.018). Lastly, ALS patients, compared with HC, complained more autonomic symptoms, and displayed a significant reduction of HRV (p=0.018); patients also showed a significant decrease of HRV at follow-up (p=0.009).

Conclusions: Autonomic symptoms at diagnosis were associated with a more rapid development of disease milestones and shorter survival in patients with ALS.

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## ISOLATED CENTRAL DYSAUTONOMIA AS A LONG-STANDING PRODROME TO MULTISYSTEM ATROPHY: A CASE REPORT AND LITERATURE REVIEW


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Objectives: To describe the clinical features of a young-onset isolated central dysautonomia evolving into a clinically probable multisystem atrophy, and to review the relevant literature on the dysautonomic onset of this disease.

Case Report: A 38-year-old man presented with progressive dysautonomic symptoms. His past medical history included a previous hospitalization due to pulmonary embolism, linked to coagulation factors IX, XI, and XII deficiency, requiring chronic anticoagulant therapy. The patient exhibited a five-year history of hypotonic bladder dysfunction as the initial symptom, followed by constipation and erectile dysfunction after two years; he recently developed orthostatic hypotension. No other significant neurological symptoms were reported; the patient didn't complain of hyposmia or RBD symptoms. Upon admission, the neurological examination revealed only a mild left finger-to-nose dysmetria. Routine blood tests were normal. Cerebrospinal fluid analysis, including the search for oligoclonal bands, onconeural and neuronal cell surface antibodies (including anti-ganglionic acetylcholine receptor antibody), as well as neurodegeneration markers, were normal. Brain and spinal magnetic resonance imaging revealed small ischemic lesions in the bifrontal white matter and right cerebellar hemisphere, prompting a complete cerebrovascular screening that yielded negative results, except for the known coagulation factor deficits. SPECT with DaTSCAN and cardiac scintigraphy with MIBG showed normal results. Electromyography, electroencephalography, and motor and sensory evoked potentials were within normal limits. Autonomic nervous system testing revealed severe cardiovascular dysautonomia with cardiac and vascular sympathetic dysfunction, resulting in syncope at the fifth minute of the tilt test. Supine and orthostatic plasma norepinephrine levels were normal. Dynamic sweat test was normal, while sympathetic skin responses to endogenous stimuli were abnormal, indicating intact postganglionic sudomotor function. Ambulatory blood pressure monitoring documented a non-dipper blood pressure profile. Genetic testing for familial amyloidosis due to transthyretin gene mutation was negative. The patient was discharged with a diagnosis of central dysautonomia in the absence of prominent parkinsonian or cerebellar motor symptoms. At the two-month follow-up visit, the neurological examination revealed mild rigidity, bradykinesia and a rest tremor in

the left upper limb, ultimately meeting the 2022 criteria of clinically probable multisystem atrophy.

Conclusions: We presented a case of a young-onset, progressive, and long-standing isolated central dysautonomia, with the development of a mild parkinsonism 5 years after onset. The differential diagnosis between central or peripheral dysautonomic disorders (such as pure autonomic failure) is crucial in determining the clinical course and prognosis. The clinical follow-up of these patients, particularly from a motor perspective, is essential to better define the diagnosis.

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## A CASE OF SEVERE MULTI-DOMAIN AUTONOMIC DYSFUNCTION

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Objectives: Cases of multi-domain autonomic dysfunction may be challenging for clinicians for diagnosis and treatment.

Materials: We report a case of a 70 year-old male patient, with negative history, who started 10 years ago presenting loss of sweating in the right side. After 3-4 years symptomatology evolved in generalized loss of sweating, heat and exercise intolerance and frequent lipothymic episodes. Since 5 years he suffered from orthostatic intolerance, fatigue, dry skin, photophobia, weak urinary flow, urgent urination, absent ejaculation, erectile dysfunction, nocturnal dyspnea, constipation and burning pain. At physical examination anisocoria, tonic pupil in the left eye and weak light reflex in the left eye, absent in the right, were found. No motor function impairment was detected.

Methods: The patient underwent extensive neuroradiologic and neurophysiologic assessment. Moreover autonomic testing exploring cardiovascular and sudomotor function, quantitative sensory testing and cutaneous innervation analysis trough skin biopsy were performed.

Results: Brain and spine MRI and electroneurography were normal. Cardiac scintigraphy showed a global reduced 123 I-MIBG uptake. Cardiovascular reflexes revealed severe failure of parasympathetic and sympathetic function with evidence of orthostatic hypotension. Thermoregulatory sweat test showed generalized anhidrosis and a peripheral postganglionic damage was detected by the dynamic sweat test that showed a severe hypohidrosis after pilocarpine stimulation. Sympathetic skin response was absent and sensory thresholds were increased. Skin biopsy revealed a moderate loss of epidermal nerve fibers and Meissner corpuscles and a severe loss of autonomic cutaneous nerves. An extensive screening for causes including the search for TTR gene mutation and ganglionic AChR antibodies was negative. We performed a further analysis of cutaneous innervation observing intraneural deposits of phosphorylated a-synuclein.

Discussion: Based on symptoms, signs and functional and autonomic evaluation our patient had a picture of severe autonomic ganglionopathy. Since 50% of autoimmune autonomic ganglionopathy remain seronegative we could not exclude this diagnostic hypothesis, although the long course of the disease. Detection of deposits of phosphorylated a-synuclein orientated for the diagnosis of pure autonomic failure (PAF). A 3 year follow up demonstrated a lack of progression overtime with no appearance of motor involvement.

Conclusions: The search for cutaneous deposits of phosphorylated a-synuclein may help clinician in differentiating seronegative autoimmune autonomic ganglionopathy from PAF, avoiding unnecessary immunomodulatory treatment. Such patients may improve with symptomatic nonpharmacologic and pharmacologic strategies, but they need to be monitored overtime to early identify possible phenoconversion.

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## SUCCESSFUL TREATMENT OF RETROGRADE CRICOPHARYNGEUS DYSFUNCTION WITH LOW DOSE BOTULINUM TOXIN. THE FIRST CASE REPORT FROM ITALY

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Objective: The Retrograde Cricopharyngeus Dysfunction (R-CPD), identified for the first time in 2019, refers to a range of signs and symptoms such as gurgling noises from the chest and lower neck, excessive abdominal bloating, flatulence, painful hiccups, emetophobia and inability to belch. Since a systematic literature on this topic is still lacking, here we describe the first case report from Italy successfully treated with low dose botulinum toxin.

Materials and Methods (case description): A 28-year-old female patient suffered from abdominal swelling, gurgling noises, painful hiccups, nausea, flatulence and abelchia since she was a child. Over the years she underwent numerous specialists and was diagnosed with different kinds of diseases, including celiac disease and somatoform disorder, without any benefit from related therapies. When she was admitted to our department, she underwent a multidisciplinary assessment, which consisted of a Fiberoptic Endoscopic Evaluation of Swallowing, neurological and neurophysiologic examinations. An electrokinesigraphic and electromyographic evaluation of the laringo-pharyngeal district was performed, with normal findings. The patient was diagnosed with R-CPD based on clinical pictures and treated by the off-label injection of 10 units of onabotulinum toxin-A. In the subsequent days all her symptoms including pain and abdominal swelling began to improve.

At the time of this writing (3 months after treatment) the improvement persists and no significant adverse events has been reported.

Results: Since any other possible cause of the symptoms was ruled out, R-CPD was diagnosed based on patient's anamnesis, clinical symptoms, normal findings at instrumental investigation, and the clinical improvement following the low dose botulinum injection.

Discussion: The Retrograde Cricopharyngeus Dysfunction (R-CPD) is still largely unknown and often misdiagnosed as a gastrointestinal pathology. Since the injection with botulinum toxin served for both diagnosis and treatment, in this report we present the first case of R-CPD diagnosed in Italy, successfully treated with unilateral, anesthesia-free injection of 10 units of onabotulinum toxin-A into the cricopharyngeus muscle, representing the lowest dose reported to date.

Conclusions: Although pathophysiological mechanism are not clearly understood, the Retrograde Cricopharyngeus Dysfunction, once diagnosed, represents a treatable condition with a high rate of response, even at low doses of botulinum toxin injection treatment.

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## THERMAL QUANTITATIVE SENSORY TESTING IN THE ITALIAN POPULATION USING THE Q-SENSE DEVICE: REFERENCE VALUES ACCORDING TO AGE, GENDER AND BODY SITES


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Objective: Our purpose is to provide reference values of thermal Quantitative Sensory Testing in the Italian population according to age, gender and different body sites using the new device Medoc 'Q-sense'.

Materials: 84 Italian healthy volunteers were recruited and divided into three age groups (18-39, 40-59 and 60-80 years). The test was performed by using an air-cooled heat probe connected to the Q-sense Conditioned Pain Modulation (CPM) device.

Methods: Temperature thresholds (Warm Detection Thresholds – WDT, and Cold Detection Thresholds – CDT) and Heat Pain Thresholds (HPT) were measured in all participants on the thenar eminence of the right hand, the right supraorbital frontal region and the dorsum of the right foot. To test the WDT and CDT, both the method of limits (MLI) and method of levels (MLE) were applied at each body site. The MLI was used to measure the HPT.

Results: Non-parametric reference limits (2.5th–97.5th) were calculated according to age, gender and tested site. WDT, CDT and HPT were affected by age, since subjects over 40 years old presented higher WDT and HTP values and lower CDT values. In the extra-trigeminal body sites, females showed lower WDT and higher CDT, while males had higher HPT. Worse sensory discriminative abilities and increased HPT values were found in people aged over 40 on the foot. Age-related differences were more evident with the reaction time-dependent MLI vs. MLE paradigm.

Discussion: This study is the first study to assess normative values of thermal QST in the Italian population, and the first study to report gender- and age-specific reference values in healthy subjects using the Q-sense device. Our study confirms that thermal QST values not only change with age, but body site- and gender-specific reference values are needed. Since we observed age related differences on the foot dorsum for both MLI and MLE paradigm, we assumed that a physiological reduction of small nerve fiber density with a length-dependent pattern might occur with age. About gender differences, our results showed that females have better sensory discriminative abilities than males.

Conclusions: Our findings show that demographic factors (e.g., age and gender) and the tested body site greatly affect thermal QST measures. These differences must be considered when QST is performed in patients with suspected small fibre neuropathy or different chronic pain syndromes.

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