ABSTRACTS

CONSIGLIO DIRETTIVO SISC

PRESIDENTE

Paolo Calabresi

PRESIDENTE ELETTO

Franco Granella

PAST PRESIDENT

Pierangelo Geppetti

SEGRETARIO

Gianluca Coppola

TESORIERE

Innocenzo Rainero

CONSIGLIERI

Anna Ambrosini
Domenico Cassano
Edoardo Mampreso
Vincenzo Raieli
Grazie Sances
Vittorio Sciruicchio

PRESIDENTI ONORARI

Marcello Fanciullacci
Vincenzo Guidetti
Giuseppe Nappi
Lorenzo Pinessi
Luigi Alberto Pini
Giorgio Zanchin

COMITATO SCIENTIFICO

Anna Ambrosini, *Pozzilli (IS)*
Gianluca Coppola, *Latina*
Edoardo Mampreso, *Padova*
Vincenzo Raieli, *Palermo*
Innocenzo Rainero, *Torino*
Antonio Russo, *Napoli*
Simona Sacco, *L'Aquila*
Paola Sarchielli, *Perugia*
Grazia Sances, *Pavia*
Vittorio Scirucchio, *Bari*
Cristina Tassorelli, *Pavia*

Whole brain surface-based morphometry study in subtypes of migraine with aura patients

C. Abagnale[1], A. Di Renzo[2], G. Sebastianelli[1], E. Tinelli[3], B. Petolicchio[3], M. Serrao[1], V. Parisi[2], M. Fiorelli[3], F. Caramia[3], V. Di Piero[3], G. Coppola[1]

[1]Sapienza University of Rome Polo Pontino, Department of Medico-Surgical Sciences and Biotechnologies, Latina, Italy; [2]IRCCS, Fondazione Bietti, Rome, Italy; [3]Sapienza University of Rome, Department of Human Neurosciences, Rome, Italy

Background: Little is known about the pathophysiologic bases of the clinical variability of migraine aura presentation. Previous spectroscopy studies during visual stimulation and functional magnetic resonance imaging at rest have shown differences between migraine patients with pure visual auras (MA), and patients with complex neurological auras (MA+), i.e. with the addition of at least one sensory and language symptom. Here, we aimed to study intracerebral white matter fiber bundles, using a tract-based spatial statistics (TBSS) analysis of diffusion tensor imaging (DTI), and grey matter cortical thickness from structural magnetic resonance imaging data in subgroups of migraine with aura patients.

Methods: 3T MRI data from 20 patients with pure visual auras and 15 with complex neurological auras were collected and compared with data from 19 healthy controls (HCs). For each subject, we performed DTI to calculate diffusivity metrics and we obtained cortical thickness maps from structural MRI.

Results: TBSS showed no significant differences in the diffusivity maps between both patients' groups and HCs. Compared to HCs, patients with MA and MA+ significantly showed thinner temporal cortices, frontal areas, insula, post-central area, and primary and associative visual areas. In the MA group, the high-level visual-information-processing areas, including lingual gyrus, were thicker, in contrast with the MA+ group where they were thinner than in HCs.

Conclusions: These findings suggest that clinical heterogeneity of migraine with aura is associated with common cortical surface morphological features as well as with an opposite morphological involvement of the high-level visual-information-processing areas.

References:

Sándor PS, Dydak U, Schoenen J, Kollias SS, Hess K, Boesiger P, Agosti RM. MR-spectroscopic imaging during visual stimulation in subgroups of migraine with aura. Cephalalgia. 2005;25(7):507-18.

Coppola G, Di Renzo A, Tinelli E, Petolicchio B, Parisi V, Serrao M, Porcaro C, Fiorelli M, Caramia F, Schoenen J, Di Piero V, Pierelli F. Thalamo-cortical networks in subtypes of migraine with aura patients. J Headache Pain. 2021;22(1):58.

Total pain burden in patients with treatment-resistant migraine: effects of galcanezumab in the CONQUER Phase 3b trial

J. Ailani[1], J.S. Andrews[2], A. Tockhorn-Heidenreich[3], R. Wenzel[3], M. Rettiganti[3], F. Torelli - Non-Author Presenter[4]

[1]Medstar Georgetown University, Washington DC, USA; [2]Takeda Pharmaceuticals, Cambridge, MA, USA; [3]Eli Lilly and Company, Indianapolis, IN, USA, [4]Eli Lilly and Company, Florence, Italy

Background: Total pain burden, a composite measure encompassing frequency of migraine headache days, duration, and severity, was previously used to characterize response to galcanezumab in patients with migraine. Here it is used to measure response in patients with treatment-resistant migraine.

Methods: CONQUER trial patients (N=458), 18-75 years old with 2-4 prior migraine preventive treatment category failures, were randomized (1:1) to monthly placebo or galcanezumab 120 mg with 240-mg loading dose. For each patient, monthly total pain burden in severity-weighted hours was calculated by multiplying daily migraine headache duration (hours) by maximum severity (0=none, 1=mild, 2=moderate, 3=severe) for each migraine day, then summing daily scores for the monthly score. Changes from baseline in monthly total pain burden across months 1-3 were analyzed post hoc using mixed-model repeated measures. Spearman correlations between total pain burden and Migraine Specific Quality-of-Life Questionnaire (MSQ) and Migraine Disability Assessment Scale (MIDAS) were assessed at baseline.

Results: Mean (standard deviation) baseline monthly total pain burden was 192.1 (158.3) and 188.2 (197.4) severity-weighted hours for galcanezumab-treated and placebo-treated patients, respectively. Across the 3-month double-blind period, galcanezumab-treated patients experienced significantly greater mean reductions from baseline in monthly total pain burden compared with placebo-treated patients, both for mean change [standard error (SE)] (galcanezumab: -82.7 (7.5), placebo: -15.8 (7.5), difference to placebo (95% confidence interval): -66.8 (-85.5, -48.2), $p<0.001$) and percent change (SE) (galcanezumab: -38.6% (5.7), placebo: 9.4% (5.7), difference to placebo (95% confidence interval): -48.1% (-62.3, -33.9), $p<0.001$). Furthermore, baseline total pain burden correlated with MSQ score ($r=-0.39$) and MIDAS score ($r=0.40$), suggesting good association of total pain burden with quality-of-life outcomes.

Conclusions: Total pain burden may be an additional meaningful measure for clinicians when discussing migraine preventive therapy.

Distortion Product Otoacoustic Emissions and their suppression as predictors of peripheral auditory damage in migraine: a case-control study

M. Albanese[1,2], S. Di Girolamo[3], L. Silvani[3], E. Ciaschi[3], B. Chiaramonte[4], M. Conti[1,2], F.M. Passali[3], B. Di Gioia[1,2], N.B. Mercuri[2,5], A. Di Stadio[6]

[1]Regional Referral Headache Center, Neurology Unit, University Hospital "Tor Vergata", Rome, Italy; [2]Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy; [3]Unit of Otorhinolaryngology, Department of Clinical Sciences and Translation Medicine, "Tor Vergata" University, Rome, Italy; [4]INAIL Consulenza Statistico Attuariale, Settore Tariffe, Rome, Italy; [5]Neurology Unit, University Hospital "Tor Vergata", Rome, Italy; IRCCS Santa Lucia Foundation, Rome, Italy; [6]Otolaryngology Department, S.M. della Misericordia University Hospital, University of Perugia, Perugia, Italy

Background: Although several cochleo-vestibular symptoms are commonly associated with migraine, only a limited number of studies have been done in this regard. Some reported abnormalities in audiometry, auditory brainstem response and caloric tests, considering these manifestations mainly related to central etiology. However, increasing evidence also suggests a peripheral involvement of the inner ear in migraine. The aim of this study was to investigate the peripheral auditory pathway in migraineurs by using transient-evoked (TEOAE) and distortion-product (DPOAE) otoacoustic emissions, to detect alteration of cochlear functioning and possible relationship with disease severity.

Methods: Fifty migraineurs and fifty-nine matched control subjects were enrolled in the study and underwent a routine neuro-otolaryngology evaluation including pure tone audiometry, acoustic immittance test and otoacoustic emission recordings (OAEs). Self-administered questionnaires were used to evaluate self-perception of hearing disability. Independent Student *t*-test was used for comparison of the means of normally distributed measures and unadjusted odds ratios with their 95% confidence intervals were used to compare variables between groups. Logistic regression analysis was performed to determine contributing factors for OAEs in migraineurs.

Results: Pure tone audiometric thresholds resulted within normal range in all patients and the hearing disability questionnaire did not reveal a subjective perception of auditory impairment during the attack-free periods. Significant difference was not found in the TEOAE responses with and without application of contralateral noise between the groups. DPOAE responses and their suppression were lower in migraineurs compared to controls and significantly related to the disease duration. Altered DPOAEs exposed migraineurs to the risk of migraine without aura, presenting with ocular and/or auditory symptoms during the attack and using more painkillers. Concomitant dopaminergic symptoms and/or allodynia such as the acute non-consumption of triptans were significant determinants of decreased contralateral suppression of DPOAE responses among migraineurs. Furthermore, OAE results were similar among patients categorized according to the side of pain.

Conclusions: Our study shows decreased DPOAEs and their suppression in migraineurs compared to controls, providing evidence for a subclinical cochlear impairment. The underlying detectable dysfunction of the outer hair cells by OAEs may represent a useful tool for the initial diagnosis and an opportunity to monitor disease course and treatment response over time.

References

Bolay H, Bayazit YA, Gündüz B, et al. Subclinical dysfunction of cochlea and cochlear efferents in migraine: an otoacoustic emission study. Cephalalgia. 2008;28(4):309-317.

Hamed SA, Youssef AH, Elattar AM. Assessment of cochlear and auditory pathways in patients with migraine. Am J Otolaryngol. 2012;33(4):385-394.

Joffily L, de Melo Tavares de Lima MA, Vincent MB, Frota SMMC. Assessment of otoacoustic emission suppression in women with migraine and phonophobia. Neurol Sci. 2016;37(5):703-709.

Ciuman RR. The efferent system or olivocochlear function bundle – Fine regulator and protector of hearing perception. Int J Biomed Sci. 2010;6(4):276-288.

Sarna B, Abouzari M, Harrison W Lin, Hamid R Djalilian. A hypothetical proposal for association between migraine and Meniere's disease. Med Hypotheses. 2020;134:109430.

A case of short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) responsive to anti-calcitonin gene-related peptide monoclonal antibody, galcanezumab: a new way to treat TACs?

D.V. Annese[1], D.E. Mampreso[2], D.R. Del Colle[1], D.M. Turazzini[1]

[1]Headache Centre, UOC Neurology, Legnago Hospital, AULSS9 Scaligera, Verona, Italy; [2]Headache Centre, Neurology, Piove di Sacco Hospital, AULSS6 Euganea, Padua, Italy

Background: Trigeminal autonomic cephalalgias (TACs), including SUNCT (short–lasting neuralgiform headache), SUNA (short-lasting neuralgiform headache attacks with cranial autonomic symptoms), HC (Hemicrania Continua), PH (Paroxysmal Hemicrania) and CH (Cluster Headache) according to the International Classification of Headache Disorders (third edition) often are conditions difficult to treat successfully.

Case Report: A 34-year-old woman, with a history of episodic high frequency migraine (a mean of 8 migraine days/month) with and without aura, recently experienced daily episodes of severe stabbing sharp pain, peri-orbital and temporal left region, accompanied by ipsilateral lacrimation, ptosis, eyelid edema and conjunctival injection, lasted between 10 seconds to 10 minutes and occurred on average 10-40 times daily. TC scan and a MRI of the brain resulted normal. She was treated with lamotrigine, corticosteroids, verapamil without significant benefit of the symptoms. Her medical history was remarkable for an episode of depression. A diagnosis of SUNCT was reached despite atypical features (response to indometacinan and sumatriptan). Galcanezumab 240-->120 mg every 4 weeks, according to migraine diagnosis, was prescribed, with excellent response to therapy both for migraine and for SUNCT (4 migraine episodes and 3 SUNCT / month in the seventh month of treatment).

Conclusions: The hypothetical physiopatological mechanism for SUNCT/SUNA is the activation of the trigemino-autonomic reflex due to activation of the posterior hypothalamus which results in autonomic features, possibly produced by the connection of the posterior hypothalamus to the trigeminal nucleus caudalis. There is no evidence-based treatment for SUNCT/SUNA but experimental approaches with anti-epileptic drugs, peripheral neuromodulation (greater occipital nerve region injections with corticosteroids and local anesthetics, occipital nerve stimulation) or central neuromodulation (deep brain stimulation in the ipsilateral posterior hypothalamus, high cervical spinal cord stimulation). Monoclonal antibody against calcitonin gene-related peptide could be a new opportunity for SUNCT/SUNA; this is the second case report regarding this treatment option; further larger case series are needed.

References:

Cohen AS, Matharu MS and Goadsby PJ. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or cranial autonomic features (SUNA) – a prospective clinical study of SUNCT and SUNA. Brain. 2006;129:2746–2760.

Maggioni F, Manara R, Mampreso E, Viaro F, Mainardi F, Zanchin G. Trigeminal neuralgia and trigeminal-autonomic cephalalgias: a continuum or simple co-existence? Cephalalgia. 2010;30(6):752-6.

Lambru G, Maharu MS. SUNCT/SUNA and trigeminal neuralgia: Different disorder or variants of the same disorder? Curr opin Neurol. 2014;27:325-331.

Wöber C. Tics in TACs: A Step into an Avalanche? Systematic Literature Review and Conclusions. Headache. 2017;57(10):1635-1647.

Bsteh G, Bsteh C, Broessner G. Refractory short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing responsive to anti-calcitonin gene-related peptide monoclonal antibodies: A case report. Cephalalgia. 2021;41(1):127-130.

Is detoxification still necessary in MOH patients receiving erenumab for the preventive treatment of chronic migraine complicated with medication overuse headache?

C. Baraldi, F. Lo Castro, M. Dal Porto, M.M. Cainazzo, L. Pani, S. Guerzoni

Medical Toxicology, Headache and drug abuse research center, University of Modena and Reggio Emilia, Modena, Italy

Background: Medication overuse headache (MOH) significantly contributes to the chronification process and treatment refractoriness of migraine [1]. Currently, abrupt discontinuation of the overused medication still represents the best management strategy for these patients, challenging public health system resources [2].

Methods: In this prospective study, chronic migraine and MOH sufferers with at least 28 days of analgesic consumption per month were included. Assessment of efficacy outcomes at three months were compared among patients who underwent in-hospital abrupt discontinuation of overused acute medication (YES-DETOX group) and patients who did not (NO-DETOX group) before starting an anti-CGRP monoclonal antibody.

Results: Of 401 patients who received either erenumab or galcanezumab, 28% (n=51) satisfied inclusion criteria (YES-DETOX n=18; NO-DETOX n=33). After three months of treatment, 59% patients reverted from MOH and 51 achieved ≥50% reduction in monthly headache days; yet no statistical differences were observed between the two groups (p=0.4788 and p=0.8393, respectively). A higher monthly consumption of pain medication was the only baseline negative prognostic factor in multivariate analysis in the overall cohort (p=0.016).

Conclusions: Our results strongly reinforce the emerging evidence that anti-CGRP monoclonal antibodies may be effective in MOH patients irrespective of detoxification.

References:

1. Diener HC, Holle D, Solbach K, Gaul C. Medication-overuse headache: risk factors, pathophisiologya and management. Nat Rev Neurol. 2016;12:575-83.
2. Munksgaard SB, Madsen SK, Wienecke T. Treatment of medication overuse headache-A review. Acta Neurol Scand. 2019;139:405-414.

Cognitive amelioration of chronic migraineurs complicated with medication overuse headache during erenumab treatment

C. Baraldi, F. Lo Castro, A. Fiorini, M.M. Cainazzo, L. Pani, S. Guerzoni

Medical Toxicology, Headache and Drug Abuse Research Center, University of Modena and Reggio Emilia; Modena, Italy

Background: Chronic migraine (CM) is characterized by the recurrence of migraine attacks for ≥8 days in at least 3 months [1]. Chronic migraineurs' quality of life is not only compromised by the pain, but also by the cognitive symptoms that are associated with migraine [2]. Indeed, usually before or during a migraine attack, the patient suffers from low attention, low information processing speed and displays a deficit in executive functions and memory [3]. Additionally, in episodic migraine a cognitive impairment is present even in the inter-ictal phase [3]. The cognitive decline is present in CM as well and MOH is thought to worsen this condition [4]. Erenumab is a fully human monoclonal antibody acting against the calcitonin gene-related peptide that has demonstrated a good efficacy and a favourable safety profile in CM complicated with MOH [5]. The present study aimed to explore the variation in the Montreal Cognitive Assessment (MoCA) score during one year of therapy with erenumab.

Methods: In this prospective study, chronic migraine and MOH sufferers who were treated with Erenumab were enrolled. Cognitive functions were assessed through the Montreal Cognitive Assessment (MoCA) and MoCA scores were compared with the Kruskal-Wallis rank sum test every 6 months during the one-year period of treatment.

Results: Sixty-four patients completed the year of treatment. At the baseline MoCA value was 24.35±2.23. At month 6 the MoCA score was 27±2.37 and 28.12±1.98 at the month 12. The executive and memory domains of the MoCA questionnaire showed the highest amelioration.

Conclusions: Our results suggest that Erenumab treatment may be also effective in reducing cognitive impairment in chronic migraineurs complicated with MOH.

References:

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd Edition. Cephalalgia. 2018;38:1-211.
2. Gil-Gouveia R, Oliveira AG, Martins IP. The impact of cognitive symptoms on migraine attack-related disability. Cephalalgia. 2016;36:422-30.
3. Santangelo G, Russo A, Tessitore A, Garramone F, Silvestro M, Della Mura MR, Marcuccio L, Fornaro I, Trojano L, Tedeschi G. Prospective memory is dysfunctional in migraine without aura. Cephalalgia. 2018;38:1825-32.
4. Martins IP, Maruta C, Alves PN, Loureiro C, Morgado J, Tavares J, Gil-Gouveia R. Cognitive aging in migraine sufferers is associated with more subjective complaints but similar age-related decline: a 5-year longitudinal study. J Headache Pain. 2020;21:31.

Time lost due to an attack: a novel patient-reported outcome measure for acute migraine treatments

S. Benemei[1], H. Pohl[2], D. Garcia-Azorin[3], J. Dixon[4], E. Huzzey[5], M.D. Ferrari[6]

[1]Careggi University Hospital, Florence, Italy; [2]University Hospital Zurich, Zurich, Switzerland; [3]Hospital Clínico Universitario de Valladolid, Valladolid, Spain; [4]MEDIAN Kinzigtal-Klinik, Bad Soden-Salmünster, Germany; [5]Watford Osteopaths, London, United Kingdom; [6]Leiden University Medical Centre, Leiden, Netherlands

Background: Migraine attacks result in reduced fitness for personal, professional, and social activities by limiting the ability to function normally. Often these constraints are not only due to pain, but also to other features of migraine attacks such as fatigue. Therefore, acute migraine outcome measures should not just focus on the short-term analgesic effects of a treatment, but rather on improvement of all migraine symptoms and restoration of normal functioning, in addition to possible impairment caused by the therapy.
We propose a new outcome measure to assess the efficacy of migraine treatments translating the approach of the Global Burden of Disease studies from a societal to an individual level, instead of calculating "Years lived with Disability", we suggest estimating "Time Lost due to an Attack" (TLA).

Methods: TLA is calculated by multiplying the duration and the degree of impaired functioning during an attack. In the following formula, t denotes the time lost due to an attack. In addition, d represents the attack duration (in hours) and *f* the level of functioning. The duration of the attack is defined as the total duration of impaired function since the onset of pain – not just the duration of pain. Subtracting $\frac{f}{100}$ from 1 converts the level of functioning into the level of impairment on a scale from 0 to 1. Multiplying the level of impairment with the duration of the attack results in TLA.

$$t = d * (1 - \frac{f}{100})$$

Results: TLA, different from other outcome measures, does not just focus on the short-term analgesic effects of treatments, but rather on the improvement of all migraine symptoms and restoration of functioning, also considering therapy-related impairment. Importantly, TLA measures the entire time patients are not functioning normally, from onset to complete resolution.

Conclusions: TLA represents a new paradigm to assess migraine burden in single patients for a patient-centered evaluation of both acute and prophylactic treatments.

References:

Diener HC, et al. Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: Fourth edition. Cephalalgia. 2019;39:687-710.

James SL, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018;392:1789-1858.

Alexithymia and psychological distress in chronic migraine and fibromyalgia: A comparative study

S. Bottiroli[1,2], A. Ghiggia[3], F. Galli[4], L. Castelli[3], G. Sances[2], L. Ahmad[5], E. Guaschino[2], M. Allena[2], C. Tassorelli[2,5]

[1]Faculty of Law, Giustino Fortunato University, Benevento, Italy; [2]Headache Science and Neurorehabilitation Centre, IRCCS Mondino Foundation, Pavia, Italy; [3]Department of Psychology, University of Turin, Italy; Clinical Psychology Unit, AOU Città della Salute e della Scienza di Torino, Italy; [4]Department of Dynamic and Clinical Psychology, and Health Studies-Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy; [5]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy

Background: Alexithymia is a personality trait characterized by the inability to identify and express emotions [1]. Several studies evidenced a positive association between alexithymia and psychological distress in patients with chronic migraine (CM) [2] and fibromyalgia (FM) [2-4]. Here we evaluated the prevalence of alexithymia and psychological distress in FM and CM, compared to healthy controls (HC).

Methods: Two-hundred and fifty women with CM (age: 46.1 ± 11.5, disease duration: 7.9 ± 7.3 yrs) and 250 FM (age: 51.2 ± 10.5, disease duration: 7.9 ± 7.8 yrs) were assessed by the Toronto Alexithymia Scale (TAS-20), and the Hospital Anxiety and Depression Scale (HADS). A HC group (n = 280; age: 51.8 ± 9.0) was also enrolled and assessed by TAS-20 and HADS.

Results: Differences between groups showed significantly higher levels of alexithymia [$F(2,755) = 11.7$, $p<.001$] and psychological distress in FM patients [$F(2,763) = 31.7$, $p<.001$], compared to CM and HC. Post-hoc analysis showed that CM patients reported higher levels compared to HC group in total score ($p<.001$) and in the Difficulty Identifying Feeling subscale of the TAS-20 ($p<.001$). A moderation analysis was performed to examine the moderation effect of the group (CM vs. FM) on the relationship between alexithymia and psychological distress. Besides a strong relationship between alexithymia and distress, the group variable was not a significant moderator.

Conclusions: These findings suggest a common psychological dysregulation in patients suffering from chronic migraine and fibromyalgia, which manifests into a different expression of the physical symptom.

References:

1. Taylor GJ. Recent developments in alexithymia theory and research. Can J Psychiatry. 2001;45:134–142.
2. Bottiroli S, Galli F, Viana M et al. Traumatic experiences, stressful events, and alexithymia in chronic migraine with medication overuse. Front Psychol. 2018;9.

3. Galli F, Caputi M, Sances G, Vegni E, Bottiroli S, Nappi G, et al. Alexithymia in chronic and episodic migraine: a comparative study. J Ment Health. 2017;26:192–196.
4. Romeo A, Di Tella M, Ghiggia A, et al. Attachment style and parental bonding: Relationships with fibromyalgia and alexithymia. PLoS One. 2020;15:e0231674.

Psychological predictors of real-life experience with Erenumab in chronic migraine with or without medication overuse: data from a 1-year follow-up

S. Bottiroli[1,2], R. De Icco[2,3], G. Vaghi[2,3], G. Fiammingo[2,3], E. Guaschino[2], M. Allena[2], A. Putortì[2,3], N. Ghiotto[2], C. Tassorelli[2,3], G. Sances[2]

[1]Faculty of Law, Giustino Fortunato University, Benevento, Italy; [2]Headache Science and Neurorehabilitation Centre, IRCCS Mondino Foundation, Pavia, Italy; [3]Department of Brain and Behavioral Sciences, University of Pavia, Pavia; Italy

Background: Monoclonal antibodies (mABs) targeting the calcitonin gene-related peptide (CGRP) pathway represent the first disease-specific preventive migraine therapy [1,2]. Growing evidence shows that they are effective in the preventive treatment of difficult-to-treat patients [3,4]. In this study, we evaluated the psychological predictors of the outcome of real-life experience with the anti-CGRP monoclonal antibody Erenumab in a 1-year follow-up in chronic migraine (CM).

Methods: Seventy-one CM (ICHD-III criteria) patients (age: 49.1±9.5) with or without medication overuse who had already failed at least 3 preventive therapies received Erenumab (70 or 140-mg dose s.c.) for one year. At baseline, patients received a full psychological evaluation using The Structured Clinical Interview for DSM-5 Clinician Version (SCID-5-CV) to assess personality disturbances, mood and anxiety disorders, and as well as specific questionnaires to evaluate alexithymia traits, childhood traumas, and current stressors.

Results: At the 1-year follow-up, 50 patients (age: 49.0±9.5) reported a reduction of at least 50% in migraine days/month (Responders, R); whereas 21 (age: 49.3±9.7) did not (Non Responders, NR). When compared to R, NR were characterized by a higher prevalence of anxiety (90% vs 60%, p=.012) and Cluster C (avoidant, dependent, and obsessive-compulsive) personality disorders (87% vs 38%, p=.002). They also showed more alexithymic traits (53.2±12.9 vs 43.7±14.2, p=.03) and a higher number of stressors (1.2±2.5 vs 0.3±0.7, p=.012). The two groups were similar for mood disorders and childhood traumas.

Conclusions: Erenumab is an effective option for patients with difficult-to-treat migraine. Our findings show a further distinction within these patients, highlighting the impact of current stressors, anxiety and an “anxious-fearful” personality in those CM patients being refractory to many preventive treatments, including Erenumab.

References:

1. Charles A, Pozo-Rosich P. Targeting calcitonin gene-related peptide: a new era in migraine therapy. Lancet. 2019;394:1765–1774.
2. Goadsby PJ, Holland PR, Martins-Oliveira M et al. Pathophysiology of Migraine: A Disorder of Sensory Processing. Physiol Rev. 2017;97:553–622.

3. Ashina M, Tepper S, Brandes JL, et al. Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study. Cephalalgia. 2018;38:1611–1621.
4. Tepper SJ, Diener HC, Ashina M et al. Erenumab in chronic migraine with medication overuse. Neurology. 2019;92(20):e2309–e2320.

Familial hemiplegic migraine: a preliminary clinical and follow-up study in a pediatric sample

M. Capizzi[1], G. Quatrosi[1], F. Guccione[1], A. Santangelo[2], L. Vetri[3], R. Nardello[1], M. Elia[3], S. Mangano[1], F. Brighina[4], G. Santangelo[5], V. Raieli[5]

[1]Child Neuropsychiatry Unit Department Pro.M.I.S.E. "G D'Alessandro", University of Palermo, Italy; [2]Pediatric Clinic, Dept. of Clinical and Experimental Medicine, University of Pisa, Italy; [3]Oasi Research, Institute-IRCCS, Troina, Italy; [4]Department of Experimental Biomedicine and Clinical Neurosciences, University of Palermo, Italy; [5]Child Neuropsychiatry Dept., P.O. Di Cristina, ARNAS Civico Palermo, Italy

Objective: Familial Hemiplegic Migraine (FHM) is a rare clinical condition characterized by headache and motor weakness often unilateral, followed in most of cases by a large spectrum of visual, sensitive, motor and sometimes cognitive disorders. Follow-up studies are even rarer and there is the need to increase the observations of the pediatric population affected by FHM to better clarify the prognosis and possible treatment. Aim of our study was to carry out a follow-up activity in a group of 7 children affected by FHM.

Methods: A study was conducted retrospectively to select all genetically proven cases of FHM, collecting data based on clinical and genetic documentation. The selected subjects were interviewed on the clinical course of hemiplegic migraine, other possible types of headache and clinical disorders.

Results: Our children consisted of 5 males and 2 females (median age onset: 7 ys 8 m, age range 3.3-15.2; median age follow-up 13 ys 6 m; follow-up duration 5 ys 9 m., range 3 ys 4 m -9 ys). We found a CACNA1A mutation in 3 children and a ATP1A2 in 4. At follow-up they had complained of 1.86 attacks per year. Moreover, clinically 57% presented speech disorders, 28.57% sensory disorders, 14.28% visual disorders and 57.14% an impairment of consciousness. Only 1 child presented a diagnosis of epilepsy and intellectual disability. Three children showed recurrent attacks of migraine with and without aura.

Conclusions: Our data support the recent data of other Italian multicentric studies on 14 subjects showing a low frequency of hemiplegic attacks. Furthermore our cases were rarely associated to other disorders and had a good prognosis in short-term follow-up.

Improving our detection of patients' migraine related disability and impact on daily life: an observational study

V. Caponnetto[1], R. Ornello[1], G. D'Aurizio[1], I. Olivieri[2], L. Lancia[2], S. Sacco[1]

[1]Department of Applied Clinical and Biotechnological Sciences, and [2]Department of Health, Life, and Environmental Sciences, University of L'Aquila, L'Aquila, Italy

Background: High disability and reduced functionality associated to migraine are relevant issues that affect middle-aged subjects. Their accurate detection may orient therapeutic strategies. We compared the picture provided by a prospective migraine diary and two widely used validated questionnaires regarding these aspects.

Methods: We prospectively observed migraine patients for three months, providing them with a diary where they reported, for each migraine day, the impact of symptoms on daily functionality, defined as generally preserved (D0), impaired (D1, i.e., 'presenteeism' at work, school, or home), or totally impaired (D2, i.e., 'absenteeism' at work, school, or home). After three months, patients filled in the 'Migraine Disability Assessment Score Questionnaire' (MIDAS) and the 'Six-item Headache Impact Test' (HIT-6). Through the Kruskal-Wallis test, we compared median migraine days spent in D0 and D1 or D2 in three months with disability and impact categories defined through the questionnaires.

Results: We collected data from 92 migraine patients, mostly female (85.9%), with a median age of 43 (IQR 31-53) years. Forty-nine (53.3%) had chronic migraine and 67 (72.8%) were taking migraine preventives. In 90 days, patients reported 20 (IQR 12-29) median migraine days, with 8 (IQR 3-15) median migraine days in D0 and 3 (IQR 3-17) median migraine days in D1 or D2. MIDAS identified disability as minimal in 32.6% of patients, low in 13.0% of patients, medium in 16.3% of patients, and high in 38.0% of patients. HIT-6 identified migraine impact as low in 16.3% of patients, medium in 26.1% of patients, substantial in 8.7% of patients, and high in 48.9% of patients.
Median migraine days spent in D0 were similar according to MIDAS and HIT-6 categories ($p=0.341$ and $p=0.086$, respectively). Indeed, according to MIDAS categories, median migraine days spent in D1 or D2 were 3 (IQR 1-7) in patients with minimal disability, 6 (IQR 1-7) in patients with low disability, 7 (IQR 4-12) in patients with medium disability, and 19 (IQR 9-29) in patients with high disability ($p\leq0.001$). According to HIT-6 categories, median migraine days spent in D1 or D2 in three months were 3 (IQR 1-5) in patients with little impact, 13 (IQR 5-23) in patients with some impact, 10 (IQR 4-18) in patients with substantial impact, and 9 (IQR 4-16) in patients with high impact ($p=0.010$).

Conclusions: In accordance with MIDAS and HIT-6 measurements, our diary identified patients' high disability and impact related to migraine. However, the prospective observation of patients allowed to detect migraine days with preserved functionality that the instruments seem to not identify.

References:

Steiner TJ, Stovner LJ, Jensen R, Uluduz D, Katsarava Z; Lifting The Burden: the Global Campaign against Headache. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. J Headache Pain. 2020;21:137.

Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. Neurology. 2001;56:S20-8.

Kosinski M, Bayliss MS, Bjorner JB, Ware JE Jr, Garber WH, Batenhorst A, Cady R, Dahlöf CG, Dowson A, Tepper S. A six-item short-form survey for measuring headache impact: the HIT-6. Qual Life Res. 2003;12:963-74.

Monoclonal antibodies against the CGRP receptor exert effects at the level of the caudal trigeminal nucleus and on the somatosensory cortex in migraine patients

F. Casillo, G. Sebastianelli, C. Abagnale, F. Pierelli, G. Coppola

Sapienza University of Rome Polo Pontino, Department of Medico-Surgical Sciences and Biotechnologies, Latina, Italy

Background: Subcutaneous injection of monoclonal antibody against CGRP receptor erenumab has been approved for the prophylactic treatment of migraine. Although different studies have shown that this treatment is highly effective and safe, the neurophysiological mechanisms underlying its clinical efficacy are still widely debated. In particular, it is not yet clear whether the neurophysiological effects of the drug are exclusively confined to the periphery of the trigeminal system or also occur centrally, at the cortical level. This study assessed the neurophysiological effects of erenumab injection in a group of patients with migraine unresponsive to at least 2 prophylactic treatments.

Methods: We prospectively enrolled 20 migraine patients (15 with chronic migraine and 5 with high-frequency episodic migraine). In all participants, we recorded the blink reflex (nBR), after stimulation of the right supraorbital nerve with a nociception specific concentric electrode, and the non-noxious somatosensory evoked potentials (SSEPs) after repetitive electrical stimulation of the median nerve at the wrist. We measured nBR R2 area-under-the-curve (AUC) and habituation, and SSEP N20-P25 amplitude and habituation. Neurophysiological measurements were recorded before and at month-1 (T1) and month-2 (T2) before each monthly erenumab injection.

Results: At T2, erenumab significantly reduced the mean monthly headache days, severity of headache (0-10), and the mean monthly tablet intake (all p=<0.001). Compared to baseline, the nBR AUC was significantly reduced at T1, but not at T2, without changing the habituation slope. A significant increase in delayed SSEP amplitude decrement (habituation), but not in the initial cortical activation, was noted at T1 and, more so, at T2 after the beginning of the treatment compared to the baseline (slope baseline = +0.103, T1 = -0.167, T2 = -0.229, p<0.05).

Conclusions: The results of our study show for the first time that the clinical improvement induced by Erenumab can be attributed to neurophysiological changes occurring at both the brainstem and cortical levels.

Cervical musculoskeletal impairments in the 4 phases of the migraine cycle

M. Castaldo[1], S. Di Antonio[1], M. Ponzano[2], F. Bovis[2], P. Torelli[3], C. Finocchi[4], L. Arendt-Nielsen[1]

[1]Department of Health Science and Technology, Center for Pain and Neuroplasticity (CNAP), SMI, School of Medicine, Aalborg University, Denmark; [2]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal Child Health, Genoa, Italy; [3]Headache Centre, Department of Medicine and Surgery, University of Parma, Italy; [4]Headache Centre, IRCCS, Ospedale Policlinico San Martino, Genoa, Italy

Background: Even if migraine patients showed an increased prevalence of cervical musculoskeletal impairments [1] there is still no consensus if these impairments are a characteristic of migraine patients independent of the migraine phase and the presence of concomitant neck pain [2]. The aims of this study were: 1) to assess cervical musculoskeletal impairments in patients with episodic migraine (EM) during the 4 phases of the migraine cycle controlling for the presence of neck pain, 2) correlate the presence of cervical musculoskeletal impairments with clinical characteristics of headache, disability, and signs of widespread sensitization.

Methods: This multicenter, cross-sectional, observational study was conducted in the Headache Centers of Parma and Genova. Differences in cervical musculoskeletal impairments were assessed during the 4 migraine phases in EM patients and compared with healthy controls controlling for the presence of neck pain (interictal neck pain in EM). Total cervical active range of motion (flexion, extension, left/right lateral flexion, left/right rotation), flexion rotation test (FRT), cranio-cervical flexion test, total number of active and latent myofascial trigger points (head/neck region), and pressure pain threshold (PPT) over the upper cervical spine were assessed. Signs of widespread sensitization were assessed evaluating PPTs over the dominant hand, and the tibialis anterior.

Results: A total of 199 subjects were included. Total active range of motion ($p<0.047$), FRT ($p<0.001$), cranio-cervical flexion test ($p<0.001$), and total number of myofascial trigger points ($p<0.001$) were reduced in all 4 phases of the migraine cycle versus healthy controls. PPT over the upper cervical spine was reduced in EM in the ictal phase versus controls ($p<0.023$), with no significant difference between EM in the interictal (0.302), preictal (0.117), and postictal (0.108) phase versus controls. Outside the ictal phase, the total active range of motion was positively correlated with PPT over tibialis anterior ($r=0.22$; $p=0.023$), FRT was positively correlated hand PPT ($r=0.19$; $p=0.045$), the number of active trigger points was positively correlated with longer headache duration ($r=0.26$; $p=0.005$), and with physical ($r=0.23$; $p=0.016$) and emotional ($r=0.21$; $p=0.021$) headache-related disability. PPT over the upper cervical spine was positively correlated with hand PPT ($r=0.51$; $p<0.001$) and PPT over tibialis anterior ($r=0.69$; $p<0.001$).

Conclusions: In all phases of the migraine cycle, independent of the presence of neck pain, EM patients showed a reduced cervical active range of movement, reduced passive

mobility of the upper cervical spine, reduced functionality of deep flexor muscle, and increased number of myofascial trigger points. These impairments are correlated with enhanced headache duration, headache-related disability, and signs of widespread sensitization. In addition, mechanical hyperalgesia of the upper cervical was consistent in ictal EM patients and the subgroups of EM patients with higher signs of widespread sensitization.

References:

1. Szikszay TM, Hoenick S, von Korn K, Meise R, Schwarz A, Starke W, Luedtke K. Which examination tests detect differences in cervical musculoskeletal impairments in people with migraine? A systematic review and meta-analysis. Phys Ther. 2019;99(5):549-569.
2. Liang Z, Galea O, Thomas L, Jull G, Treleaven J. Cervical musculoskeletal impairments in migraine and tension type headache: A systematic review and meta-analysis. Musculoskelet Sci Pract. 2019;42(April):67-83.

An observational study aimed to assess the presence of musculoskeletal dysfunctions and signs of sensitization in migraine patients with and without interictal neck pain

M. Castaldo[1], S. Di Antonio[1], M. Ponzano[2], F. Bovis[2], P. Torelli[3], C. Finocchi[4], L. Arendt-Nielsen[1]

[1]Department of Health Science and Technology, Center for Pain and Neuroplasticity (CNAP), SMI, School of Medicine, Aalborg University, Denmark; [2]Department of Health Sciences (DISSAL), Section of Biostatistics, University of Genoa, Italy; [3]Headache Centre, Department of Medicine and Surgery, University of Parma, Italy; [4]Headache Centre, IRCCS, Ospedale Policlinico San Martino, Genoa, Italy

Background: Interictal neck pain is a common symptom among migraineurs [1]. However, it is still unclear which physical and psychophysical characteristics differentiate migraine patients with interictal neck pain from migraine patients without mechanical neck pain [2]. This study aimed to assess cervical musculoskeletal dysfunction (CMD) and quantitative sensory testing (QST) in migraine patients with concomitant mechanical neck pain (MNP) and without concomitant mechanical neck pain (MwoNP).

Methods: In this multicenter, cross-sectional, observational study, episodic and chronic migraine patients were assessed interictally and compared with healthy controls. Migraine patients were divided into MwoNP or MNP according to the presence of concomitant interictal neck pain, and the following variables were assessed: CMD: cervical active range of motion (AROM) in flexion, extension, right/left lateral flexion, right/left rotation, flexion rotation test (FRT), activation pressure score (APS). QST: static pressure pain threshold (sPPT) over the trigeminal area; sPPT and dynamic PPT (dPPT) over the cervical area; sPPT and mechanical pain threshold (MPT) over the hand. Differences in QST and CMD among controls, MwoNP, and MNP were assessed performing General Linear Models (GLM) including age, gender, and body mass index as a covariate. A Bonferroni-adjusted post-hoc analysis was conducted to make single groups comparisons. The alpha level accepted for the significance of the results was $p<0.05$.

Results: A total of 127 subjects were included (51 healthy controls, 31 MwoNP, 44 MNP). FRT and APS were reduced in MwoNO and MNP compared to controls ($p<0.001$). Compared to controls, MwoNP had reduced AROM in left lateral flexion ($p=0.025$) while MNP had reduced AROM in flexion ($p<0.001$), extension ($p<0.001$), and in right rotation ($p=0.002$), reduced trigeminal sPPT ($p=0.001$), cervical dPPT ($p<0.001$) and sPPT ($p<0.006$), and hand sPPT ($p=0.001$) and MPT ($p=0.002$). No other differences were found between the groups.

Conclusions: Interictal migraine patients, independent of the presence of concomitant neck pain, presented a reduction in functionality of deep neck flexors muscles and reduced passive mobility of the cervical spine. On the other hand, impairment of active cervical

movement and increased trigeminal, cervical, and widespread sensitization were consistent only in a subgroup of migraine patients with concomitant neck pain.

References:

1. Ashina S, Bendtsen L, Lyngberg AC, Lipton RB, Hajiyeva N, Jensen R. Prevalence of neck pain in migraine and tension-type headache: A population study. Cephalalgia. 2015;35(3):211-219.
2. Liang Z, Thomas L, Jull G, Minto J, Zareie H, Treleaven J. Neck pain associated with migraine does not necessarily reflect cervical musculoskeletal dysfunction. Headache. 2021;61(6):882-894.

Association between Primary Headaches and Dementia: A systematic review and meta-analysis

A. Cermelli[1], L. Giorgis[1], S. Boschi[1], E. Gallo[1], A. Grassini[1], A. Marcinnò[1], F. Roveta[1], E. Rubino[2], I. Rainero[1]

[1]Dipartimento di Neuroscienze "Rita Levi Montalcini", Università degli studi di Torino, Torino, Italy; [2]Dipartimento di Neuroscienze, A.O.U. Città della Salute e della Scienza, Torino, Italy

Background: In the last decade, several studies suggested that headache may be a risk factor for developing dementia [1-2]. However, results are, at present, inconclusive. The purpose of this study was to perform a meta-analytic review of all the studies that investigated association between Primary Headaches and dementia of all causes.

Methods: PubMed, Scopus, Science Direct, Web of Science and BMC databases were searched for articles reporting percentage of dementia in patients with a history of primary headaches by two independent revisors. In order to perform the review, we used the guidelines proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [3]. Risk of bias was evaluated using Newcastle Ottawa Scale (NOS). Pooled effect size was determined using random effects model. Binary data were extracted from each study and total Risk Ratio was calculated in order to determine the risk of develop dementia in patients with headache disorders.

Results: The initial search identified 4363 articles. After exclusion criteria were applied, 19 articles were included in the systematic review. Of these, 17 articles were included in the meta-analysis. Statistical analysis showed a total effect size of 1.19, p=0.035. Even if this result is statistically significant, it is also affected by Heterogeneity (I^2 =93.85). Analysis of funnel plot and Eggers regression test indicate a low level of publication bias (p=0.896).

Conclusions: Our review suggests that patients with primary headaches have a greater risk of developing dementia compared with controls. Nevertheless, statistical analysis showed significant heterogeneity. Additional studies, evaluating also comorbidities of primary headaches, are needed in order to better elucidate this complex relationship.

References:

1. Sharif S, Saleem A, Koumadoraki E, Jarvis S, Madouros N, Khan S. Headache - A Window to Dementia: An unexpected twist. Cureus. 2021;17;13(2):e13398.
2. Wang J, Xu W, Sun S, Yu S, Fan L. Headache disorder and the risk of dementia: a systematic review and meta-analysis of cohort studies. J Headache Pain. 2018;11;19(1):95.
3. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. PLOS Med. 2009;6(7):e1000097.

CGRP inhibition and plasmatic oxidative stress biomarkers in resistant migraine

L. Curto[1], S. Mazzucchi[1], A. Della Vecchia[2], C. De Luca[3], F. Baldacci[1], I. Lombardo[1], M. Ulivi[1], L. Chico[1], M. Papa[3], G. Siciliano[1], S. Gori[1]

[1]Neurologia, Università di Pisa, Pisa, Italy; [2]Psichiatria, Università di Pisa, Pisa, Italy; [3]Dipartimento di Anatomia, Università della Campania Luigi Vanvitelli, Naples, Italy

Background: The prophylactic treatment of resistant migraine is still a challenge in clinical practice. Migraine with or without aura is one of the most frequent and disabling neurological diseases. Overall, high frequency migraine and chronic migraine have a great impact in everyday life, and they have a strong association with psychiatric pathologies.
The discovery of Monoclonal antibodies against the calcitonin gene-related peptide (CGRP) and its receptor paved the way for a concrete change in this area, thanks to their specific target and their better tolerability profile.

Methods: We carried out a prospective study to observe how biological and clinical features of resistant migraineurs responded to anti-CGRP(R) mAbs.
We recruited 42 patients, between 26 and 64 years of age, fulfilling the (ICHD-3) criteria for high frequency episodic migraine without or with aura or chronic migraine, and medication-overuse headache, without comorbid chronic systemic diseases, pregnancy or breastfeeding during the study. Patients underwent baseline, 1-month, 3-month, and 6-month follow-up visits. At the end of each visit (T0, T1, T2 and T3) a blood sample was collected to study how plasmatic levels of AOPP, FRAP, and -SH (biomarkers of oxidative stress) changes before and after treatment.
Clinical features of migraine were measured through the following scales: Migraine Disability Assessment (MIDAS) Allodynia Symptoms Checklist 12 (ASC-12), the Fatigue Severity Scale (FSS), the Generalized Anxiety disorder (GAD-7), Patient Health Questionnaire (PHQ-9) and the Pittsburgh Sleep Quality Index (PSQI).
The comparison between non-parametric quantitative variables was performed employing the Wilcoxon test. The statistical significance threshold was set at $p>0.05$. A correction for multiple comparisons with Bonferroni was applied for biochemical analysis ($p=0.016$). The comparison between categorical dichotomous variables was performed by the chi-square test with continuity.

Results: We found the reduction of advanced oxidation protein products (AOPP) as a biomarker of improved redox state after 6 months of treatment. We also confirmed treatment efficacy finding that 7 out of 10 patients achieved a reduction of 50% from the baseline at 3 months, maintained it at 6 months, while about 1 out of 4 patients experienced a 75% reduction of the headache frequency after the first month of treatment. The migraine disability assessment (MIDAS), the associated fatigue and anxiety also significantly improved. The allodynia symptom dropped as a sign of central sensitization reduction.

Conclusions: Our study confirmed that anti-CGRP(R) mAbs are the first tailored therapy for migraine and their use in migraine prophylaxis demonstrated an improvement in the

patients' quality of life. Additional evidence is needed to understand the role of oxidative stress as a migraine biomarker.

References:

Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd Edition. Cephalalgia. 2018;38:1–211.

Lipton RB; Silberstein SD. Episodic and Chronic Migraine Headache: Breaking down barriers to optimal treatment and prevention. Headache. 2015;55 Suppl 2:103–122;quiz 123–126.

Edvinsson L. Role of CGRP in Migraine. Handb Exp Pharmacol. 2019;255:121–130.

ICHD-3 criteria in the Emergency Department: a survey in the province of Trieste

L. D' Acunto[1], A. Granato[1], G. Garascia[1], F. Cominotto[2], P. Manganotti[1]

[1]Clinical Unit of Neurology, Headache Centre, Department of Medicine, Surgery and Health Sciences, University Hospital and Health Services of Trieste, University of Trieste, Italy; [2]Emergency Department, University Hospital and Health Services of Trieste, University of Trieste, Italy

Background: Not Otherwise Specified Headache (NOS) remains a frequent discharge diagnosis of self-referring patients to the Emergency Department (ED), that frequently do not coincide with the precise diagnosis provided by a re-evaluation in a Headache Centre. Aim of this survey was to analyse the reasons why Emergency Physicians (EPs) do not apply the correct diagnosis of headache according to ICHD-3 criteria in the ED setting.

Methods: In April 2021 a monocentric survey was conducted among EPs of the two University Hospital EDs of the province of Trieste. An anonymized questionnaire that tested the knowledge and application of ICHD-3 criteria in the ED setting was structured by two neurologists experienced in headaches and was delivered by hand to each emergency physician. The questionnaire included questions with five answer options and EPs could indicate multiple choices among the following: EP's knowledge and the application of ICHD-3 criteria, EP's difficulty in using the criteria in the emergency setting, the preference in contacting the specialist consultant, and EP's friendliness with medical software where to register headache diagnoses.

Results: Out of all the EPs (n=30), 25 (84%) completed the questionnaire. Twenty-four EPs (96%) did not know ICHD-3 diagnostic criteria, while only one physician answered that he knew the ICHD-3 criteria, but they were too complex to use in the emergency setting.

Conclusions: EPs lack of knowledge of ICHD-3 criteria may partially explain the high rate of NOS headache diagnoses in the ED. An ICHD-3 diagnostic criteria educational program tailored to the ED setting could increase the use of diagnostic criteria with reduction of unspecified headaches.

Efficacy of monoclonal antibodies targeting the CGRP on unilateral cranial autonomic symptoms

E. De Matteis[1], A. Casalena[2], G. Affaitati[3], M.A. Giamberardino[3], M. Assetta[2], M. Maddestra[4], S. Viola[5], C. Marini[6], F. Pistoia[1], R. Ornello[1], S. Sacco[1]

[1]Neuroscience Section, Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, L'Aquila, Italy; [2]Department of Neurology, 'G. Mazzini' Hospital, Teramo, Italy; [3]Department of Medicine and Science of Aging, 'G. D'Annunzio' University, Chieti, Italy; [4]Department of Neurology, 'F. Renzetti' Hospital, Lanciano, Italy; [5]Department of Neurology, 'S. Pio da Pietrelcina' Hospital, Vasto, Italy; [6]Department of Neurology, 'S. Salvatore' Hospital, L'Aquila, Italy

Background: Unilateral autonomic cranial symptoms (UACs) - conjunctival injection, tearing, nasal congestion or rhinorrhoea, eyelid oedema, miosis or ptosis, forehead or facial sweating ipsilateral to headache - are often reported by migraineurs during headache attacks, although being typical symptoms of trigeminal-autonomic cephalalgias. UACs are a consequence of the "autonomic reflex", which is the physiological parasympathetic reaction to nociceptive stimuli mediated by the trigeminovascular system [1]. As the trigeminovascular system is the target of monoclonal antibodies acting on the CGRP pathway, we hypothesize that patients with UACs might have a higher trigeminovascular activation and better response to anti-CGRP treatments.

Methods: We performed a prospective analysis including patients with episodic or chronic migraine treated with anti-CGRP monoclonal antibodies (i.e. erenumab, fremanezumab, and galcanezumab) between 2019 and 2020. The observation period included a 12-week baseline before treatment with anti-CGRP antibodies and the first 12 weeks of treatment. We evaluated the prevalence of UACs in our cohort and compared mean Monthly Headache Days (MHDs) reduction across patients with and without UACs using the $\chi 2$ test.

Results: Out of 107 patients, 78 (72.9%) had UACs. Specifically, 28 (26.2%) reported conjunctival injection, 43 (40.2%) tearing, 40 (37.4%) nasal congestion or rhinorrhoea, 24 (22.4%) eyelid oedema, 12 (11.2%) miosis or ptosis, and 23 (21.5%) forehead or facial sweating ipsilateral to headache. Overall, patients had a median age of 49 years (IQR 43-57); a median disease duration of 28 years (IQR 17-40); 91 (85%) were females; 85 (79.4%) suffered from chronic migraine, and 66 (61.7%) had medication overuse. During the 12-week treatment, patients with UACs registered a reduction from baseline in MHDs of - 10 (IQR 6-15) days, while patients without UACs registered a reduction of - 5 ([IQR 2.5-15-5] P=0.031) days.

Conclusions: In our cohort, the presence of UACs was associated with a greater response to monoclonal antibodies targeting the CGRP. Our analysis is limited by the small sample size which might justify broader studies. UACs, as well as response to triptans [2,3], could be a clinical marker of trigeminovascular activation and thus predict a response to anti-CGRP treatments.

References:

1. Möller M, May A. The unique role of the trigeminal autonomic reflex and its modulation in primary headache disorders. Curr Opin Neurol. 2019;32(3):438-442.
2. Barbanti P, Fabbrini G, Vanacore N, Pesare M, Buzzi MG. Sumatriptan in migraine with unilateral cranial autonomic symptoms: An open study. Headache. 2003;43(4):400-3.
3. Sarchielli P, Pini LA, Zanchin G, Alberti A, Maggioni F, Rossi C, Floridi A, Calabresi P. Clinical-biochemical correlates of migraine attacks in rizatriptan responders and non-responders. Cephalalgia. 2006;26(3):257-65.

Differences in Postural Alterations and in Musculoskeletal Dysfunctions between Chronic Migraine and Chronic Tension Type headache: a cross-sectional study

M. Deodato[1], M. Martini[2], G. Sgubin[2], A. Granato[2], P. Manganotti[2]

[1]Dipartimento di Scienze della Vita and [2]Dipartimento di Scienze Mediche e Chirurgiche e della Salute, Università degli Studi di Trieste, Trieste, Italy

Background: Extensive research has highlighted a correlation between primary headache and musculoskeletal dysfunctions, especially over trigemino-cervical complex [1-3]. The aim of the study was to compare postural alterations and musculoskeletal dysfunctions throughout the spine in patients with chronic migraine (CM) and chronic tension type headache (CTTH) respect to healthy controls (HC).

Methods: The Bio photogrammetric evaluation was performed using the postural assessment software PAS/SAPO [4], while unilateral passive accessory intervertebral motion (PAIM) and passive physiological intervertebral motion (PPIM) were applied for manual examinations of spine segments from C0 to L5 vertebra [5].

Results: 60 patients were consecutively enrolled in the Headache Centre of the University of Trieste (20 with CM [13F/7M; age 52+/- 13.4]; 20 with CTTH [14F/6M; age 48 +/- 19.5]; 20 HC [12F/8M; age 50+/- 12.1]). Patients with CM and CTTH had postural alterations in all postural parameters (cranio-vertebral angle, lumbar-pelvic angle and center of gravity) and musculoskeletal dysfunctions in cervical, dorsal and lumbar spine respect to healthy controls. No differences were found between CM and CTTH concerning the postural alterations nor the musculoskeletal dysfunctions.

Conclusions: Patients with chronic migraine and chronic tension type headache had postural alterations and musculoskeletal dysfunctions not only in the trigemino-cervical complex but also throughout the spine. These data suggest that musculoskeletal dysfunctions may play a role in the mechanisms of sensitization inducing chronicity. Therefore, several non-pharmacological treatments which target the musculoskeletal system may be a good option in the management of chronic primary headache, especially when these therapies integrate various techniques that involve the whole spine.

References:

1. Coppola G, Di Lorenzo C, Schoenen J, Pierelli F. Habituation and sensitization in primary headaches. J Headache Pain. 2013;14:65.
2. Liang Z, Galea O, Thomas L, Jull G, Treleaven J. Cervical musculoskeletal impairments in migraine and tension type headache: A systematic review and meta-analysis. Musculoskelet Sci Pract. 2019;42:67-83.
3. Ashina S, Lipton RB, Bendtsen L, Hajiyeva N, Buse DC, Lyngberg AC, Jensen R. Increased pain sensitivity in migraine and tension-type headache coexistent with low back pain: A cross-sectional population study. Eur J Pain. 2018;22:904–914.

4. Macedo Ribeiro AF, Bergmann A, Lemos T, Pacheco AG, Mello Russo M, Santos de Oliveira LA, de Carvalho Rodrigues E. Reference Values for Human Posture Measurements Based on Computerized Photogrammetry: A Systematic Review. Journal of Manipulative and Physiological Therapeutics. 2017;40(3):156-168.
5. Luedtke K, Boissonnault W, Caspersen N, Castien R, Chaibi A, Falla D, Fernández-de-Las-Peñas C, Hall T, Hirsvang JR, Horre T, Hurley D, Jull G, Krøll LS, Madsen BK, Mallwitz J, Miller C, Schäfer B, Schöttker-Königer T, Starke W, von Piekartz H, Watson D, Westerhuis P, May A. International consensus on the most useful physical examination tests used by physiotherapists for patients with headache: A Delphi study. Manual Therapy. 2016;23:17-24.

Trigeminal and extra trigeminal sensitization in patients with chronic and episodic migraine: a cross-sectional study

M. Deodato[1], M. Martini[2], G. Sgubin[2], A. Granato[2], P. Manganotti[2]

[1]Dipartimento di Scienze della Vita and [2]Dipartimento di Scienze Mediche e Chirurgiche e della Salute, Università degli Studi di Trieste, Trieste, Italy

Background: Central and peripheral sensitization are characterized by widespread pressure hyperalgesia that is manifested by a larger extent of the pain area and reduction in the Pressure Pain Threshold (PPT). PPT decreases in patients with migraine not only over trigeminal cervical complex but also throughout the body [1, 2]. The main aim of this study was to compare the PPT among patients with chronic migraine, episodic migraine and healthy controls. The second aim was to highlight the differences in PPT among different muscles assessed in patients with chronic migraine and episodic migraine.

Methods: A six-month cross-sectional study was conducted in migraineurs attending the Headache Centre of the University of Trieste. The guidelines of Andersen [3] were used to evaluate the PPT bilaterally over five muscles in the trigemino-cervical complex (temporalis, sub-occipitalis, levator scapulae, masseter, trapezius) and over one muscle far from this area (tensor fasciae latae) with the algometer Somedic. The measurements were conducted in pain free days and in the late follicular phase of the female patients [4].

Results: 27 patients with chronic migraine (24F/5M; age 52.4±13.4), 27 with episodic migraine (25F/4M; age 48.3±11.2) and 27 healthy controls (24F/5M; age 47.4±12.3) were enrolled. PPT was significantly lower in all muscles both in patients with chronic and episodic migraine than in healthy control ($p>0.001$). On the other hand, no differences were found between chronic and episodic migraine in any muscle. Significant differences ($p<0.0001$) were found in PPT among some muscles both in chronic and in episodic migraine (masseter vs tensor fascia latae or levator scapulae; temporalis vs tensor fascia latae or levator scapula; suboccipitalis vs tensor fascia latae or levator scapulae).

Conclusions: Patients with chronic and episodic migraine had lower PPT than healthy controls both in the trigeminal and in the extra trigeminal area suggesting that sensitization involves pathophysiology of migraine also in the episodic form. Masseter, temporalis and suboccipitalis were the most sensitive muscles in patients with chronic and episodic migraine. Even though the chronicity could lead to a larger extent of the pain area, patients with chronic migraine also present more local hyperalgesia in the trigeminal cervical complex rather than widespread hyperalgesia. Therefore, pharmacological and non-pharmacological approaches should target this area.

References:

1. Coppola G, Di Lorenzo C, Schoenen J, Pierelli F. Habituation and sensitization in primary headaches. J Headache Pain. 2013;14(1):65.

2. De Tommaso M, Sciruicchio V. Migraine and Central Sensitization: Clinical features, main comorbidities and therapeutic perspectives. Curr Rheumatol Rev. 2016;12(2):113-26.
3. Andersen S, Petersen MW, Svendsen AS, Gazerani P. Pressure pain thresholds assessed over temporalis, masseter, and frontalis muscles in healthy individuals, patients with tension-type headache, and those with migraine--a systematic review. Pain. 2015;156:1409–1423.
4. Russo A, Coppola G, Pierelli F, Parisi V, Silvestro M, Tessitore A, Tedeschi G. Pain perception and migraine. Front Neurol. 2018;9:576.

Quantitative sensory testing in the 4 phases of the migraine cycle

S. Di Antonio[1], M. Castaldo[1], M. Ponzano[2], F. Bovis[2], P. Torelli[3], C. Finocchi[4], L. Arendt-Nielsen[1]

[1]Department of Health Science and Technology, Center for Pain and Neuroplasticity (CNAP), SMI, School of Medicine, Aalborg University, Denmark; [2]Department of Health Sciences (DISSAL), Section of Biostatistics, University of Genoa, Italy; [3]Headache Centre, Department of Medicine and Surgery, University of Parma, Headache Centre, Parma, Italy; [4]IRCCS, Ospedale Policlinico San Martino, Genoa, Italy

Background: Migraine is a brain disorder characterized by cyclic changes in the pain thresholds in trigeminal, cervical, and distal pain-free areas [1-3]. However, it is still uncertain if signs of trigeminal, cervical, and widespread sensitizations are also present in the interictal phase of the migraine cycle
This study aims to assess mechanical pain thresholds from trigeminal, cervical, and distal pain-free areas during the 4 phases of a migraine cycle in episodic migraine patients (EM) [4].

Methods: This multicenter, cross-sectional, observational study was conducted in the Headache Centers of Parma and Genova. Differences in quantitative sensory tests were assessed during the 4 migraine phases in EM patients and compared with healthy controls. Temporal summation of pain (TSP) to repeated mechanical pain stimuli, pressure pain threshold (PPT), and mechanical pinprick pain threshold (MPT) were assessed from the trigeminal area; PPT assessed from the cervical area (upper cervical spine and lower cervical spine); and PPT and MPT over the hand. The correlations between the quantitative sensory tests and headache characteristics were analyzed.

Results: A total of 181 subjects were included. TSP was facilitated in ictal EM versus controls ($p=0.004$); the pain thresholds to all stimuli from the trigeminal and cervical areas were reduced in all 4 phases of the migraine cycle versus controls ($p<0.045$). As compared with controls, preictal EM had reduced hand PPT ($p=0.006$) and MPT ($p=0.016$), while EM in the other phases showed only a reduction in hand MPT (interictal EM vs control $p=0.002$; ictal EM vs controls $p=0.006$; postictal EM vs control $p=0.020$) without significant reduction in hand PPT ($p>0.089$). Outside the headache attack hand MPT was negatively correlated with longer disease duration ($r=-0.25$; $p=0.011$) and was negatively correlated with higher drug usage ($r=-0.31$; $p=0.002$). TSP during the ictal phase was positively correlated with the physical ($r=0.38$; $p=0.040$) and emotional ($r=0.53$; $p=0.003$) headache-related disability. TSP outside the ictal phase was negatively correlated with headache frequency ($r=-0.23$; $p=0.022$), intensity ($r=-0.21$; $p=0.040$), and the physical ($r=-0.29$; $p=0.003$) and emotional ($r=-0.34$; $p=0.001$) headache-related disability.

Conclusions: In all phases of the migraine cycle, EM patients show signs of sensitization in the trigemino-cervical area, with patients in the ictal phase showing the most prominent sensitization. Signs of widespread sensitization were consistent in preictal EM patients and

in the subgroups of EM patients with the longest disease duration and more usage of symptomatic drugs. Moreover, during the ictal phase of the migraine cycle, those migraine patients with a higher level of disability presented a more pronounced sensitization of second-order neurons in the spinal trigeminal nucleus.

References:

1. Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. Ann Neurol. 2000;47(5):614-624.
2. Peng KP, May A. Migraine understood as a sensory threshold disease. Pain. 2019;160(7):1494-1501.
3. Sand T, Zhitniy N, Nilsen KB, Helde G, Hagen K, Stovner LJ. Thermal pain thresholds are decreased in the migraine preattack phase. Eur J Neurol. 2008;15(11):1199-1205.
4. Russo A, Coppola G, Pierelli F, Parisi V, Silvestro M, Tessitore A, Tedeschi G. Pain perception and migraine. Front Neurol. 2018;9:576.

An observational study aimed to assess which risk factors could predict neck pain in migraine patients

S. Di Antonio[1], M. Castaldo[1], M. Ponzano[2], F. Bovis[2], P. Torelli[3], C. Finocchi[4], L. Arendt-Nielsen[1]

[1]Department of Health Science and Technology, Center for Pain and Neuroplasticity (CNAP), SMI, School of Medicine, Aalborg University, Denmark; [2]Department of Health Sciences (DISSAL), Section of Biostatistics, University of Genoa, Italy; [3]Headache Centre, Department of Medicine and Surgery, University of Parma, Italy; [4]Headache Centre, IRCCS, Ospedale Policlinico San Martino, Genoa, Italy

Background: Even if neck pain is one of the most common symptoms in the migraine population [1], it is still not clear which mechanism could underline the presence of interictal neck pain in the migraine population [2]. This study aimed to assess which risk factors could predict the presence of interictal neck pain in migraine patients.

Methods: In this multicenter, cross-sectional, observational study, episodic and chronic migraine patients were divided into migraine without interictal neck pain (MwoNP) or migraine patients with interictal neck pain (MNP). Interictally, the following variables were assessed: *Headache characteristic*: headache frequency, intensity, and duration, use of drugs, headache disability (headache disability index physical component (HDI-P), and HDI emotional component (HDI-E)) and quality of life (questionnaire to assess the physical health dimension: SF-36 physical dimension, and questionnaire to assess the mental health dimension: SF-36 mental dimension); *Cervical musculoskeletal dysfunction*: active range of motion (AROM) in flexion, extension, right/left lateral flexion, right/left rotation; flexion rotation test (FRT), activation pressure score (APS). Quantitative sensory testing: static pressure pain threshold (sPPT) over the cervical and trigeminal area; dynamic PPT (dPPT) over the cervical area; hand and leg sPPTs (widespread PPTs). A univariate logistic regression model was used to determine risk factors associated with neck pain. Then, a multivariate Stepwise logistic regression model including as predictors only the variables resulting with a p-value<0.05 in the univariate analysis was conducted.

Results: A total of 75 patients were included. The univariate logistic regression model revealed 9 variables associated with the presence of interictal neck pain: headache frequency (p=0.004), use of drugs (p=0.05), HDI-E (p=0.004), SF-36 physical dimension (p=0.002), SF-36 mental dimension (p=0.031), AROM in flexion (p=0.010), AROM in extension, (p=0.013), AROM in right rotation (p=0.002), and cervical dPPT (p=0.017). The stepwise backward logistic regression model, including these variables, indicated that at an alpha level of p<0.05, four predictors (frequency, SF-36 physical dimension; AROM in extension, cervical dPPT) could predict the presence of neck pain (Chi2 (4)=38.269; p<0.001).

Conclusions: Neck pain in migraine patients could be predicted by increased headache frequency, worst level of quality of life, impaired active cervical extension, and increased mechanical neck hyperalgesia.

References:

1. Ashina S, Bendtsen L, Lyngberg AC, Lipton RB, Hajiyeva N, Jensen R. Prevalence of neck pain in migraine and tension-type headache: A population study. Cephalalgia. 2015;35(3):211-219.
2. Liang Z, Thomas L, Jull G, Minto J, Zareie H, Treleaven J. Neck pain associated with migraine does not necessarily reflect cervical musculoskeletal dysfunction. Headache. 2021;61(6):882-894.

Does symptomatic treatment help children and adolescents with chronic migraine?

M.A.N. Ferilli[1], L. Papetti[1], F. Ursitti[1], R. Moavero[1,2], S. Tarantino[1], G. Sforza[1], M. Proietti Checchi[1], F. Vigevano[1], M. Valeriani[1,3]

[1]Headache Center, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; [2]Child Neurology and Psychiatry Unit, Tor Vergata University of Rome, Italy; [3]Center for Sensory Motor Interaction Aalborg University, Aalborg, Denmark

Background and objective: Chronic migraine (CM) is defined in the third edition of the International Classification of Headache Disorders (ICHD-3) as the presence of headaches on 15 days or more in a month, at least 8 days showing the migraine phenotype, for more than 3 months. CM affects from 0.6% to 1.8% of children and adolescents and determines a decrease of the quality of life. Aim of this study was to analyze the type of symptomatic drugs used and their efficacy for the treatment of acute migraine attacks in pediatric patients with CM.

Methods: We conducted a prospective study by selecting pediatric patients diagnosed with CM in our Department. We administered a questionnaire to the parents of all our pediatric patients with CM according to the ICHD-3; questions were focused on symptomatic drugs used for acute migraine attacks and their effectiveness.

Results: For the final analysis we considered 91 patients with CM. Only two patients responded to the initial therapy with acetaminophen and only 31% improved with ibuprofen. 53% of patients had relief with second-line NSAIDs drugs like ketoprofen, indomethacin, naproxen. 51% of patients did not respond to more than three drugs and 16% were resistant to all acute treatments. All patients underwent prophylaxis therapy.

Conclusions. In our study we have shown that the drugs for acute attack are not very effective in patients with CM and that some patients do not respond to any acute treatment.

Sixty-minute intravenous lidocaine infusions in refractory headache and facial pain: a retrospective case series

M. Fuccaro[1], C. Mullins[2], D. Pang[2], M. Liu[2], G. Lambru[1]

[1]Headache Centre, Guy's and St Thomas' NHS Foundation Trust, London, UK; [2]Pain Management and Neuromodulation Department, Guy's and St Thomas' NHS Foundation Trust, London, UK

Background: Facial pain can be a debilitating expression of various primary and secondary headache disorders. Despite the variety of available options, unmet needs remain in the transitional treatment of these conditions, particularly for status-like presentation or refractory pain. Intravenous (IV) Lidocaine infusion has gathered initial promising evidence in neuropathic pain including trigeminal neuralgia [1]. Sparse evidence is available in headache treatment [2]. Furthermore, treatment protocol usually involved patient admission for several days, thus increasing the risk of adverse effects and costs [3]. This study aims to evaluate the efficacy and the safety of a single 60-minute-long IV lidocaine infusion as a transitional treatment in patients with refractory chronic headaches with facial pain radiation.

Methods: We retrospectively collected data of patients with refractory chronic headache disorders with facial pain who underwent IV lidocaine infusion between March 2018 and July 2021. The treatment was performed as a day-care procedure and all patients were administered with lidocaine 5mg/kg in 60 ml saline within 1 hour with a cardiac monitor, following a protocol already used in trigeminal neuralgia [1]. Patient global impression of change (PGIC) and the duration of improvement in weeks were used as outcomes. Side effects were also collected.

Results: Thirteen patients (female=11), mean age of 47 (range 24-72), were analysed: n=5/13 had short-lasting unilateral neuralgiform headache attacks (SUNHA), n=3/13 had chronic facial migraine, n=2/13 secondary trigeminal neuralgia, n=2/13 chronic cluster headache, n=1/13 hemicrania continua. Each patient had failed a mean of 13 previous treatments (±6, range 5-25). 6/13 patients (46.2%) underwent more than one infusion (n=2/13 two, n=1/13 three, n=1/13 four, n=1/13 seven and n=1/13 nine). Two patients (15.4%) did not respond to the treatment. Among the 11/13 responders (84.6%), 6/11 (54.5%) became pain-free after every infusion, while 5/11 (45.5%) had a partial response, rated between 40% and 80%. Improvement after every single infusion lasted on average for 5.4 weeks, (±3.6, range 1-16) and 3/11 (27.3%) patients obtained a benefit ≥12 weeks after at least one infusion. The response was sustained in those who had multiple infusion, with some variability in improvement duration. No serious adverse events were reported. 6/13 patients (46.2%) reported mild and transitory adverse events during the infusion and in only one patient they led to a temporary suspension of the infusion.

Conclusions: IV lidocaine performed as per our protocol, may be a safe and effective transitional preventive treatment in patients with refractory headache disorders with facial pain.

References:

1. Bendtsen L, Zakrzewska JM, Abbott , Braschinsky M, Di Stefano G, Donnet D, Eide PK, Leal PRL, Maarbjerg S, May A, Nurmikko T, Obermann M, Jensen TS, Cruccu G. European Academy of Neurology guideline on trigeminal neuralgia. Eur J Neurol. 2019;26(6):831-849.
2. Marmura M, Rosen N, Abbas M, Silberstein S. Intravenous Lidocaine in the Treatment of Refractory Headache: A Retrospective Case Series Michael Marmura. Headache. 2009;49:286-291.
3. Lambru G, Stubberud A, Rantell K, Lagrata S, Tronvik E, Matharu MS. Medical treatment of SUNCT and SUNA: a prospective open-label study including single-arm meta-analysis. J Neurol Neurosurg Psychiatry. 2021;92:233-241.

Humidity-sensitive migraineurs: a new subpopulation for targeted therapies?

G. Garascia[1], A. Buoite Stella[1], A. Granato[1], D. Filingeri[2], L. D' Acunto[1], P. Manganotti[1]

[1]Clinical Unit of Neurology, Headache Centre, Department of Medicine, Surgery and Health Sciences, University Hospital and Health Services of Trieste, University of Trieste, Trieste, Italy; [2]THERMOSENSELAB, Clinical Academic Facility, School of Health Sciences, University of Southampton, Southampton, UK

Background: Weather change is a frequent referred trigger for migraine attacks, with humidity as the prime suspect among climatic and environmental factors. Hygrosensation is almost solely mediated by TRPM8 receptors. The aim of this study was to analyse the moisture sensitivity in patients with episodic migraine.

Methods: We enrolled patients diagnosed with episodic migraine without aura attending the Headache Centre of the University Hospital of Trieste from 01.04.2021 to 30.06.2021. All patients were prophylaxis-free. Three wet stimuli at different temperatures (warm, thermoneutral, cold) were administered to each subject by a single investigator according to a validated protocol for the assessment of the humidity sensation. All participants were blinded to the nature and application of stimuli and they were informed only about the localization of stimuli. They also were pain-free during measurements, which were performed at least 72 hours before or after the cessation of migraine and/or use of analgesic medications. Thermal and wetness perceptions were tested on the forehead and posterior neck. Data were compared to a group of healthy volunteers. All statistical analyses were performed with SPSS v.23.

Results: Twelve migraineurs (5 males; 7 females; mean age 44.5±13.2 years) and 36 healthy volunteers (18 males; 18 females; age 39±14.6 years) were evaluated. On the forehead, thermal perception was found not significantly different between migraineurs and healthy subjects during the warm (p=0.777), thermoneutral (p=0.935) and cold (p=0.910) stimuli. In addition, the humidity perception was not different between migraineurs and healthy controls for the warm wet stimulus (p=0.200) and thermoneutral wet stimulus (p=0.799). In contrast, higher humidity scores were reported by migraineurs during the cold wet stimulus compared to healthy controls (72.7±17.6 vs 49.9±26.6; p=0.016). On the posterior neck, no difference was found between the two groups neither in thermal perception during the warm (0.406), thermoneutral (0.386) and cold (0.314) stimuli, nor in humidity perception during the warm wet stimulus (p=0.762), thermoneutral wet stimulus (p=0.957), and cold wet stimulus (p=0.466).

Conclusions: For the first time, an accurate and reproducible procedure testing hygrosensation in episodic migraineurs has evidenced an actual sensitivity to cold-wet stimuli coincident with the major localization of pain. Sensory testing could support clinicians to identify the subpopulation of migraineurs who are more susceptible to humidity, helping them to avoid this trigger factor. These patients could be selected as possible better responders to potential future therapies involving the pathways of humidity sensation.

Treatment discontinuation and re-treatment of monoclonal antibodies anti-CGRP in resistant chronic migraine patients

L.F. Iannone[1], D. Fattori[1], S. Benemei[2], A. Chiarugi[1], P. Geppetti[1], F. De Cesaris[2]

[1]Section of Clinical Pharmacology and Oncology, Department of Health Sciences, University of Florence, Florence, Italy; [2]Headache Center and Clinical Pharmacology Unit, Careggi University Hospital, Florence, Italy

Background: General guidelines for migraine prophylaxis suggest stopping medication after 6–12 months to reevaluate treatment. Policies for the access to novel expensive treatments often entail restrictions that may affect disease management and the Italian medicine agency has established a rule to stop medication for 3 months after 1-year treatment. However, efficacy of anti-CGRP (calcitonin gene-related peptide) pathway monoclonal antibodies (anti-CGRP mAbs) after discontinuation has been scarcely investigated [1-3].

Methods: A monocentric, prospective, cohort study, enrolling 50 severe chronic migraine patients (98% with medication-overuse) treated with erenumab (56.0%) and galcanezumab (44.0%) for 12 months that discontinued treatment for at least 1-month. The study comprised of a 1-month baseline phase, a 12-months treatment phase, and up to 3 months observation phase (*i.e.*, 1-3 months after treatment completion). The primary outcome was changes from baseline in monthly migraine days (MMDs) during the observation phase (1-3 months).

Results: All patients (n=50) stopped treatment for one month, 41/50 for two months and 34/50 completed the 3-months of discontinuation at the end of the study. During the entire observation phase, MMDs (±SD) were significantly lower than at baseline. Decreases ranged from 12.3 (±8.6) at the last month of treatment to 16.5 (±8.2) at month-3 after discontinuation ($p<0.0001$). Number of analgesics, days with at least one analgesic used and HIT-6 total score showed a trend to increase overtime as compared to the last month of treatment but remained lower than baseline ($p<0.0001$). MIDAS was considerably lower at the last month of treatment and at month-3 of discontinuation compared to baseline ($p<0.0001$).
Overall, 27/34 (79.4%) patients fulfilled the criteria to restart treatment at the end of the mandatory observation period and 19 of them completed a 1-month follow-up at the time of analysis. A rapid reduction in MMDs (mean ± SD, -6.8 ± 6.2) compared to month-3 of discontinuation ($p<0.0001$) was achieved, but not with the last month of treatment ($p=0.46$). Number of analgesics, days with at least one analgesic used and HIT-6 total score were lower compared with month-3 of discontinuation ($p=0.001$, $p=0.001$ and $p=0.002$, respectively). No changes have been shown with the last month of treatment.

Conclusions: Our results indicate that after discontinuation anti-CGRP mAbs maintain effectiveness up to 3 months in the prevention of chronic migraine compared to baseline but not compared with the last month of treatment. A tendency to a progressive increase in

all outcome measures was observed from month-1 to month-3 of discontinuation. Thus, although a beneficial effect persists in the 3 months of discontinuation, this effect seems to fade over time.

References:

1. Raffaelli B, Mussetto V, Israel H, Neeb L, Reuter U. Erenumab and galcanezumab in chronic migraine prevention: effects after treatment termination. J Headache Pain. 2019;20:66.
2. De Matteis E, Affaitati G, Frattale I, Caponnetto V, Pistoia F, Giamberardino MA, Sacco S, Ornello R. Early outcomes of migraine after erenumab discontinuation: data from a real-life setting. Neurol Sci. 2021;42:3297-303.
3. Gantenbein AR, Agosti R, Gobbi C, Flügel D, Schankin CJ, Viceic D, Zecca C, Pohl H. Impact on monthly migraine days of discontinuing anti-CGRP antibodies after one year of treatment - a real-life cohort study. Cephalalgia. 2021;41(11-12):1181-1186.

Headache nurse intervention: an integrated approach to improve quality of life in chronic migraine

E. Mampreso, E. Pesce, A. Piron

Headache Centre, Neurology, Piove di Sacco Hospital, AULSS6 Euganea, Padua, Italy

Background: Chronic migraine is notoriously a highly disabling disease with high direct and indirect costs. For the management and treatment of chronic migraine, pharmacological and non-pharmacological strategies and integrative therapeutic education approaches can be adopted at Headache Centers. Fields of intervention of a specialized nurse in headaches (headache nurse) can be many, but are still poorly implemented, probably due to the lack of adequate trained resources. The purpose of this study was to evaluate the effectiveness of therapeutic educational interventions, carried out by a headache nurse, on patients with chronic migraine and under treatment with botulinum toxin at a Headache Center.

Methods: We studied a sample of chronic migraine patients, followed at the Piove di Sacco Hospital Headache Centre, AULSS 6 Euganea. Patients were treated regularly with botulinum toxin (PEEMPT protocol). We submitted the HURT (The Headache Under-Response to Treatment) questionnaire, validated and translated into Italian, in two moments: time 0 before the scheduled follow-up visit and at the next visit, carried out after 3 months. At the time 0 visit therapeutic educational interventions were carried out by a headache nurse and from that moment there was the possibility for the patient to contact the nurse by phone or dedicated email.

Results: 43 patients suffering from chronic migraine, mostly women (42), with an average age of 47.3 years, and the majority with a higher education degree completed the study. Patients who showed a decrease in the overall HURT score were clinically improved. In patients with chronic migraine, improvement occurred for all subdivisions of the HURT questionnaire (HURT 3 evaluates the frequency of attacks and disabilities; HURT 5 aspects of clinical and care management and HURT 8 evaluates the global aspect of the clinical-care pathway). The mean of the HURT 3 scores improved from 5.7 to 4.27; HURT 5 from 6 to 4; HURT 8 from 11.7 to 8.3. These data showed a significant improvement ($p<0.05$) in the outcomes of treatment and the quality of life.

Conclusions: A qualified support in the management of chronic migraine has the objective to allow patients to lead as normal a life as possible. The professional multidisciplinary approach can allow the patient to obtain, through the most appropriate clinical-care pathway, a decrease in the levels of disability and a better quality of life. By evaluating the data relating to HURT 5, it is possible to conclude that the knowledge acquired by the patient, regarding the disease and the correct use of drugs, through the action of the medical-nursing team, allow to improve the overall disability.

References:

Westergaard ML, Jensen RH, Steiner TJ. The HURT (Headache Under- Response to Treatment) questionnaire: utility in a specialist care center in Denmark. J Headache Pain. 2013;14(Suppl 1):P97.

Westergaard ML, Steiner TJ, MacGregor EA, Antonaci F, Tassorelli C, Buse DC, Lipton RB, Jensen RH. The Headache Under-Response to Treatment (HURT) Questionnaire: assessment of utility in headache specialist care. Cephalalgia 2013;33(4):245-55.

COVID-19 and pediatric headaches: Are admissions increasing in the Emergency Department?

A. Marino[1], F. Guccione[1], A. Santangelo[2], V. Raieli[3], D. Buffa[3]

[1]Child Neuropsychiatry Unit Dept. Pro.M.I.S.E. "G D'Alessandro", University of Palermo, Italy; [2]Pediatric Clinic, Dept. of Clinical and Experimental Medicine, University of Pisa, Italy; [3]Child Neuropsychiatry Dept., P.O. Di Cristina - ARNAS Civico Palermo, Italy

Background and objectives: Recent studies have showed that in the Emergency Department (ED) pediatric admissions for headache have been increasing in the last years. However, Covid-19 pandemic may have changed the use of health services for several reasons. Aim of this study was to analyze the rates of admission for pediatric headaches in the ED before and during Covid-19 Pandemic.

Methods: We collected retrospectively the records of children (range of age 5-14) admitted in the ED in 2012, 2019 and 2020. We selected the records including headache and headache associated to other symptoms (vomit, fever, dizziness, etc.), and also the use of computed tomography (CT) and neurological consultation.

Results: In 2012, 2019 and 2020 the cephalalgic children admitted to the ED were respectively 313/18806 (1.66%), 407/15605 (2.61%) and 234/9630 (2.43%). The admission rates for headaches shows highly significant differences between 2012 and the biennial 2019/2020. There are no differences in use of CT and neurological consultations. The only difference in access was the initial drop in the first months of lockdown (2020/80% vs 2019/50%).

Conclusions: Our data support the increase of admission for headache to the pediatric ED in the last ten years. However, the Covid-19 pandemic has not increased the admission rate compared to 2019 nor the use of CT or neurological consultations. The fear of using the EDs was unchanged for headache compared to other pediatric alarm symptoms.

Women with chronic headache and their gut microbiome

M. Nicolodi[1], M. Cerboneschi[2], M.S. Pinnaro[3], L. Di Puccio Sicuteri[4], V. Sandoval[5], A. Torrini[1]

[1]Foundation for Prevention and Study of Primary Headache and Primary Pain, Florence, Italy; [2]Next-Incubator Biology, University of Florence, Florence, Italy; [3]Human Nutrition and Food Science, University of Florence, Florence, Italy; [4]Cognitive Neuroscience and Clinical Neuropsychology, University of Padua, Padua, Italy

Background: Some years ago we proposed a therapeutic approach based on food supplementation that underwent gut processing and likely relieved migraine course. Recently, several researches have been devoted to the relevance of neurotransmitters regulating and produced by gut microbiome. The possible relevance of gut microbiota in migraine has been suggested in a recent review.

Aim: Observation of possible alterations of gut microbiota in women with regular menstrual cycle and no exogenous hormone administration (age range 30-45) suffering from chronic headache according to the ICHD3 criteria.
Exclusion criteria: Abuse of triptans, long-lasting extensive use of SSRI, indomethacin abuse, hormones assumption, immunotherapies, Parkinson disease, diabetes, heart, kidney, hepatic, celiac disease, cancer, dietary restriction.
Observation started in May 2019 had to include 2300 volunteers. First results concerned 531 women (age 38.6+7.9SD) with regular menses suffering from chronic headache.
DNA genome sequencing was carried out in the Laboratory of Next–Incubator, University of Florence and was performed by using NGS platform sequencing, which provided a much cheaper and higher throughput alternative, than the traditional Sanger sequencing exams.

Results: Results in the first group of 531 samples regarding the microbial community of chronic headache suffering females evidenced the following common pivotal characteristics:
1) Probiotics & Detoxification: a) Severe decrease ($p>0.0001$ vs standard values for sex-age) of both Lactobacillus (acidophylus, brevis, bulgaricus, casei, delbrueckii, fermentum, helveticus, paracasei, plantarum, rhamnosus, salivarius and Lactobacillus spp.) and Bifidobacterium (bifidum, breve, infantis, lactis, longum, Bifidobacterium spp.); *2) Enteric Bacteria & Dysbiosis:* a) Bacteriodes vulgatus spp., and b) Serratia spp., both Gram negative bacteria $p>0.001$ increase vs. standard values for sex-age), c) Blautia spp., Gram positive bacteria, $p>0.5$ increase vs. standard values for sex-age.

Conclusions: Serratia are often present in liver dysfunctions, cellulitis and anxiety. Bacteroides are said to relate to GABA-transmission linked to carbohydrates consumption. Blautia might be related to the very high-fiber nature of the mediterranean diet volunteers are suited to strictly maintain. The severe lack of probiotics, regulating immunity, might relate either to stress due to chronic pain or to complex changes in the levels of

neurotransmitters. These data, when confirmed might open new possibilities in the treatment of chronic and severe headache pain.

References:

Nicolodi M, Torrini A. From NMDA theory of chronic migraine to polyamines dietary implementation: Preliminary data. Cepalalgia. 2009;29(1):38.

Arzani M, Jahromi SR, Ghorbani Z, Vahabizad F, Martelletti P, Ghaemi A, Sacco S, Togha M; School of Advanced Studies of the European Headache Federation (EHF-SAS). Gut-brain Axis and migraine headache: a comprehensive review. J Headache Pain. 2020;15:21-33.

Otaru N, Ye K, Mujezinovic D, Berchtold L, Constancias F, Cornejo FA, Krzystek A, de Wouters T, Braegger C, Lacroix C, Pugin B. GABA Production by Human Intestinal Bacteroides spp.: Prevalence, regulation, and role in acid stress tolerance. Front Microbiol. 2021;4:1-15.

Increased (18)fluorodeoxyglucose uptake occurring in new daily persistent headache associated with anxiety and depression

M. Nicolodi[1], I. Taddei[2], F. Fanfani[2], L. Di Puccio Sicuteri[3], V. Sandoval[1]

[1]Foundation for Prevention and Study of Primary Headache and Primary Pain, Florence, Italy; [2]Istituto Manfredo Fanfani, Clinical Research, Florence, Italy; [3]Cognitive Neuroscience and Clinical Neuropsychology, University of Padua, Padua, Italy

Background: In primary headache MRI is often silent. A previous observation of our group evidenced peculiar metabolic alterations in the thalamic areas in juvenile chronic cluster headache that led us to perform 18-Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET)/Computed Tomography (CT) in new daily persistent headache sufferers, refractory to any prophylactic or acute/abortive medication. In these patients headache pain was associated with relevant mood disorders. Recent data indicate the cerebellar involvement in fear, anxiety and in pain perception/integration.

Method: 18-FDG-PET/CT were carried out in subjects suffering from refractory new daily persistent headache 153.4 days ± 16.5SD before investigation. Headache was associated with generalized anxiety (GAD) and depression recently evidenced (170+31.6SD days) before investigation. Observation started in October 2018. *Exclusion criteria:* personal history positive for dementia, for substance abuse, pre-existing primary headache that could be classified by using the ICHD-3, CNS pathologies evidenced by MRI. Four females (mean age 34.7±7.9SD) suffering from new daily persistent headache based on the ICHD-3 classification and also positive for GAD and Depression DSM5 criteria, accepted to undergo the observation. Comparisons were performed with normal results for sex and age.

Results: Increased 18-FDG uptake in the cerebellum [+65%-+55% (standardized uptake ratio to normalize tracer uptake doses/body weight) SUV vs. other brain regions].

Conclusions: Results seemingly support the assumptions and data indicating that cerebellum participates in pain perception/modulations and links this sensory discrimination also to mood alterations in headache disease.

References:

Nicolodi M, Torrini A, Sandoval V, Fanfani M, Taddei I. O013. Neuro-imaging and history of cases of refractory chronic cluster headache in young patients: a hint for reflections. J Headache Pain. 2015;16:A 95.

Apps R, Strata P. Neuronal circuits for fear and anxiety — the missing link. Nat Rev Neurosci. 2015;16(10):642.

Moulton EA, Schmahmann JD, Becerra L, Borsook D. The cerebellum and pain: passive integrator or active participator? Brain Res Rev. 2010;5-65(1):14-27.

Bogoian HR, King TZ, Turner JA, Semmel ES, Dotson VM. Linking depressive symptom dimensions to cerebellar subregion volumes in later life. Transl Psychiatry. 2020;10(1):201.

Late effects of SARS-CoV-2 disease in migraine and in lupus eritematosus sufferers: Perspective Cohort Observation - Preliminary data

M. Nicolodi[1], L. Di Puccio Sicuteri[2], M. Cerboneschi[3], M.S. Pinnaro[4], V. Sandoval[1], A. Torrini[1]

[1]Foundation for Prevention and Study of Primary Headache and Primary Pain, Florence, Italy; [2]Cognitive Neuroscience and Clinical Neuropsychology, University of Padua, Padua, Italy; [3]Next-Incubator Faculty of Biology, University of Florence; [4]Human Nutrition and Food Science, University of Florence, Italy

Cohort Observation: Preliminary data of 502 SARS-CoV-2 patients and 203 subjects, otherwise healthy, affected by SARS-CoV-2. Group A: n=172 Migraine without aura (ICHD-3) (48.2±11.9SD, 99 females); Group B: n=130 Lupus (49.4±9.9SD, 79 females); Group C: n=203 Controls infected by SARS-CoV-2 (47.6±15.9SD, 111 females).
Exclusion criteria: cancer, obesity, diabetes, cardiovascular, pulmonary, hepatic, kidney, psychiatric and neurologic diseases, HIV.
Time Plan: 20/3/2020, 8/11/2020, 4/7/2021, 10/3/2022 – yearly until 2027.
Examination: pain, internal medicine and neurological examinations, medications checklist.
Exams: L-citrulline, equimolar coproduct of nitric oxide (NO)-in catalysed metabolism of L-arginine, blood tests and hemostasis-thrombosis test, auto-antigens battery, endocrine exam, psychometric/memory tests.

Results: *SARS-CoV-2 late-onset effects and results of exams*
Variations vs. standard range:
- Pulmonary, enteric, myocardial symptoms: Hemostasis-trombosis test increase p>0.1 Groups A, B, C
- Pain worsening, pulmonary symptoms: Abnormal levels L-citrulline p>0.001 in Group A, p>0.01 in Group B, p>0.05 in Group C
- Asthenia, insomnia, weight gain: Hyposurrenalism: p>0.001 Group 1, p>0.01 Group B, Thyroid Hormones decrease: p>0.05 Groups A, B, C
- Olfactory loss, impaired memory functions: Autoantigens increase p>0.01 Group B
- Pulmonary, heart symptoms: thyroid and gonadic hypo-function p>0.01 Group A, p>0.05 Groups B, C

Possibly induced variation by pre-existing therapies:
a) Pain exacerbation, asthenia were blunted p>0.01 Groups A, B using NMDA antagonists/overusing FANs versus other therapies Groups A,B.
b) Worsening of severe pain, CNS symptoms lasting over 10 months: Immunotherapies/tissue targeted-therapies vs. other therapies p>0.01 Groups A, B.

Conclusions: SARS-CoV-2, like 2002 SARS, seemingly disrupts Hypothalamic-Pituitary-Thyroid and Hypothalamic-Pituitary-Adrenal Axis.
Nitric oxide synthesis markedly increased in painful conditions might suggest a role of NO in headache pain exacerbation.

Even though we supposed otherwise, lupus sufferers seemingly did not report so dramatic effects in this sample/observation-period.

References:

Leow MK, Kwek DS, Ng AW, Ong KC, Kaw GJ, Lee LS. Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). Clin Endocrinol. 2005;63:197–202.

Sleep disorders and chronic headaches in the developmental age: observational study

A. Onofri, L. Olivieri, E. Tozzi

Children Headache Center, Neuropsychiatric Clinic, Department of Life, Health and Environmental Sciences, University of L'Aquila, Italy

Background: National and international scientific literature show a correlation between sleep disorders and headache; however, this correlation is not always specified and analyzed in clinical researches. On the other hand, headaches, particularly chronic headaches, have a negative impact on sleep and create a vicious cycle that is more problematic to manage. The purpose of our study was to identify the presence and the type of sleep disturbances in a group of children and adolescents suffering from chronic headache belonging to one Children Headache Center in central Italy.

Methods: We recruited consecutively in the years 2018 and 2019, a cohort of children and adolescents aged 6 to 18 years suffering from chronic headache, presenting to the Children Headache Center, Neuropsychiatry Clinic of San Salvatore Hospital (L'Aquila, Italy). Headache diagnosis was made according to the criteria of the ICHD-3-beta (2018), sleep disturbances were evaluated by the SDSC test-Sleep Disturbances Scale for Children [1], statistical analysis with the Chi-square test and Fischer's test.

Results: Total sample was composed of 141 children (mean age 14.9 years): 65 males and 76 females, 106 with a diagnosis of Chronic Migraine (CM) (40 M and 66 F) and 35 with a diagnosis of Chronic Tension Headache (CTH) (20 M and 15 F). In males with CM, 57% had comorbid sleep disorders, specifically Bruxism (14%), Somniloquy (11%), Agitated sleep (11%), Insomnia and frequent awakenings (9%), Snoring (6%), Body Rolling (3%), and Sleep-Wake Cycle Alterations (3%). In females with CM, 63% had the following comorbid sleep disorders: Insomnia and Frequent Awakenings (30%), Bruxism (12%), Restless Sleep (6%), Sleepiness (6%), Snoring (5%), and Sleepwalking (4%). In the males with CTH, 56% had comorbidities with sleep disorders: Bruxism (17%), Insomnia and frequent awakenings (17%), Snoring (17%), and Agitated sleep (5%). In the females with CTC, 71% had comorbid with sleep disorders: Insomnia and frequent awakenings (29%), Bruxism (21%), Snoring (14%), and Sleepwalking (7%). Therefore, sleep disorders in CM are greater in males (Bruxism) than in females (Insomnia), instead in CTC insomnia, bruxism and snoring are equally distributed both in males and females.

Conclusions: Our study shows the presence of a high percentage of sleep disturbances in chronic headaches, and a difference in comorbidity between chronic migraine and tension headache regarding type of sleep disturbance and a different gender distribution [2-4].

References:

1. Bruni O, Ottaviano S, Guidetti V, Romoli M, Innocenzi M, Cortesi F, Giannotti F. The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. J Sleep Res. 1996;5(4):251-61.
2. Dosi C, Figura M, Ferri R, Bruni O. Sleep and Headache. Semin Pediatr Neurol. 2015;22(2):105-12.
3. Guidetti V, Dosi C, Bruni O. The relationship between sleep and headache in children: implications for treatment. Cephalalgia. 2014;34(10):767-76.
4. Korabelnikova EA, Danilov AB, Vorobyeva YD, Latysheva NV, Artemenko AR. Sleep Disorders and Headache: A Review of Correlation and Mutual Influence. Pain Ther. 2020;9(2):411-425.

Gender differences in 3-month outcomes of erenumab treatment – The Efficacy and Safety of Treatment with ErEnumab in Men (ESTEEMen) study

R. Ornello[1], C. Baraldi[2]*, S. Guerzoni[3], G. Lambru[4], M. Fuccaro[4], B. Raffaelli[5], A. Gendolla[6], P. Barbanti[7,8], C. Aurilia[7], S. Cevoli[9], V. Favoni[9], F. Vernieri[10], C. Altamura[10], A. Russo[11], M. Silvestro[11], E. Dalla Valle[12], A. Mancioli[12], A. Ranieri[13], G. Alfieri[13], N. Latysheva[14], E. Filatova[14], J. Talbot[15], S. Cheng[16], D. Holle[17], A. Scheffler[17], T. Nežádal[18], D. Čtrnáctá[18], J. Šípková[18], Z. Matoušová[19], L. Sette[1], A. Casalena[20], M. Maddestra[21], S. Viola[22], G. Affaitati[23], M.A. Giamberardino[23], F. Pistoia[1], U. Reuter[4,24], S. Sacco[1]*
**equal contribution*

[1]Neuroscience Section, Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, Italy; [2]Department of Biomedical, Metabolic and Neural Sciences; University of Modena and Reggio Emilia, Modena, Italy; [3]Medical Toxicology, Headache and Drug Abuse Research Center; Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; [4]The Headache Service, Guy's and St Thomas' NHS Foundation Trust, London, UK; [5]Charité, Universitätsmedizin Berlin, Department of Neurology, Berlin, Germany; [6]Private Practice: Essen, Germany; [7]Headache and Pain Unit, IRCCS San Raffaele, Rome, Italy; [8]San Raffaele University, Rome, Italy; [9]IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; [10]Headache and Neurosonology Unit, Policlinico Universitario Campus Bio-Medico, Rome, Italy; [11]Headache Center, Department of Medical, Surgical, Neurological, Metabolic, and Aging Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy; [12]Headache Centre, Ospedale S. Antonio Abate, ASST Valle Olona, Gallarate, Italy; [13]Headache Centre, Division of Neurology and Stroke Unit, "A. Cardarelli" Hospital, Naples, Italy; [14]Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation; [15]Southwest Neurology Audit and Research group (SoNAR), Department of Neurology, Derriford Hospital, Plymouth, UK; [16]Department of Neurology, Alfred Health, Melbourne, VIC, Australia; [17]Department of Neurology, West German Headache Center, University Hospital Essen, Essen, Germany; [18]Military University Hospital Prague, Department of Neurology, 1st Faculty of Medicine Charles University, Prague, Czech Republic; [19]Motol University Hospital Prague, Department of Neurology, 1st Faculty of Medicine Charles University, Prague, Czech Republic; [20]Department of Neurology, "G. Mazzini" Hospital, Teramo, Italy; [21]Department of Neurology, "F. Renzetti" Hospital, Lanciano (Chieti), Italy; [22]Department of Neurology, "S. Pio da Pietrelcina" Hospital, Vasto (Chieti), Italy; [23]Headache Center, Geriatrics Clinic, Department of Medicine and Science of Aging and Center for Advanced Studies and Technology (CAST), G. D'Annunzio University, Chieti, Italy; [24]Universitätsmedizin Greifswald, Greifswald, Germany

Background: Men account for <20% of patients included in observational and interventional studies on migraine [1]. This proportion is too low to allow adequate generalizability of overall results to male gender. The efficacy and safety of monoclonal antibodies acting on the calcitonin gene-related peptide (CGRP) pathway have been proven in large studies; however, the proportion of men included in those studies did not allow to

perform subgroup analyses according to gender. We aimed to provide reliable gender-specific results on the efficacy and safety of erenumab, a monoclonal antibody acting on the CGRP receptor. To this aim, we collected a large dataset of real-world data.

Methods: Our pooled patient-level analysis of real-world data included patients treated with erenumab and followed-up for 12 weeks. We considered the following outcomes at weeks 9-12 of treatment compared with baseline: 0-29%, 30-49%, 50-75%, and ≥75% responder rates, according to the decrease in monthly headache days (MHDs); rate of treatment stopping; change in MHDs, monthly migraine days (MMDs), monthly days of acute medication and of triptan use, and Headache Impact Test-6 (HIT-6) score from baseline to weeks 9-12. Outcomes were compared between men and women by the chi-squared test or t-test as appropriate. An analysis of covariance (ANCOVA) was performed to identify factors influencing the efficacy outcomes.

Results: We included 1410 patients from 16 centers; 256 (18.2%) were men. Men were older than women and had a lower number of MHDs at baseline. At weeks 9-12, compared with baseline, 46 (18.0%) men had a ≥75% response, 75 (29.3%) a 50-74% response, 35 (13.7%) a 30-49% response, and 86 (33.6%) a 0-29% response, while 14 (5.5%) stopped the treatment. The corresponding numbers for women were 220 (19.1%), 314 (27.2%), 139 (12.0%), 401 (34.7%), and 79 (6.8%). No gender difference was found in any of the outcomes. The ANCOVA showed that gender did not influence the efficacy outcomes.

Conclusions: We showed that erenumab is equally safe and effective in men compared with women after a 12-week period. We reported the first gender-specific data on a preventive drug that was designed for migraine. A gap of knowledge should be filled regarding the gender differences in response to migraine treatments and their clinical implications.

References:

1. Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. Lancet Neurol. 2017;16:76-87.

Paradoxical air microembolism and bioelectrical activity of the cerebral cortex in patients with migraine and right-to-left cardiac shunt: an electroencephalographic study

R. Ornello[1], M. Spezialetti[2], V. Caponnetto[1], I. Frattale[3], E. Colangeli[1], G. Ceccanti[4], E. De Matteis[1], M. Grappasonni[5], F. Pistoia[1], G. Placidi[2], S. Sacco[1]

[1]Department of Applied Clinical and Biotehnological Sciences, University of L'Aquila, L'Aquila, Italy; [2]Department of Information Engineering, Computer Science and Mathematics, University of L'Aquila, L'Aquila, Italy; [3]Department of Child Neurology and Psychiatry Unit, Systems Medicine Department, Tor Vergata University, Rome, Italy; [4]Department of Internal Medicine, Public Health, Life and Environmental Sciences, University of L'Aquila, L'Aquila, Italy; [5]Department of Neurology, SS Filippo e Nicola Hospital, Avezzano (L'Aquila), Italy

Background: In patients with migraine, paradoxical air microembolism through a right-to-left cardiac shunt (RLS) is a hypothetical mechanism of headache induction and can alter the activity of the cerebral cortex, especially in patients with migraine with aura [1]. In the present study, we searched for possible bioelectrical abnormalities induced by paradoxical air microembolism in patients with migraine and RLS, at rest and under sensory stimulation.

Methods: We included patients with migraine and known large RLS, defined as passage of >20 microembolic signals or “curtain effect” in transcranial Doppler ultrasound. All patients were evaluated interictally. To monitor bioelectrical activity, we used a 19-channel EEG cuff mounted according to the 10-20 international system. Bioelectrical activity was assessed at rest and during two activation procedures, i.e. visual stimulation (pattern reversal), and somatosensory stimulation (electric stimulation of the right wrist). We recorded the EEG signal for each of those three conditions before and after the intravenous injection of a mixture of 9mL saline and 1mL air microbubbles. Passage of microbubbles through cerebral arteries was monitored with transcranial Doppler ultrasound. Spectral EEG analysis was performed for each electrode and frequency band (theta: 5-8 Hz; alpha: 9-13 Hz; beta: 14-30 Hz); a total spectral power was also computed for each patient. A total ΔP was calculated for each condition (rest, visual, and somatosensory stimulation) with the following formula: ΔP(dB)=10xlog([EEG power after microbubble injection]/[EEG power before microbubble injection]). We compared each condition before and after microbubble injection with Wilcoxon signed rank test. Subgroup analyses according to the presence of aura and migraine preventive treatments were also performed.

Results: We included ten patients, nine women and one man, with a median age of 42 years (range 30-58); six patients had migraine with aura; six patients were treated with migraine preventatives. Air microembolism did not increase EEG power at rest (total ΔP: -0.46 dB; p=0.158), during visual stimulation (total ΔP: -1.07 dB; p=0.341), or during sensory stimulation (total ΔP: +1.18 dB; p=0.350). No significant increase in EEG power was detected in any EEG electrode, at any frequency band. Subgroup analyses by the presence of aura and migraine preventive treatments returned no significant results.

Conclusions: In our study, air microembolism did not change bioelectrical activity in patients with migraine at rest or under sensory stimulation. Our finding contrasts with previous findings of EEG power increase in patients with migraine with aura induced by air microembolism [1]. Our neutral results might depend on the inclusion of few patients with migraine with frequent aura, who are more susceptible than those without aura to changes in cortical activity induced by microembolism.

References:

1. Sevgi EB, Erdener SE, Demirci M, Topcuoglu MA, Dalkara T. Paradoxical air microembolism induces cerebral bioelectrical abnormalities and occasionally headache in patent foramen ovale patients with migraine. J Am Heart Assoc. 2012;1(6):e001735.

Which is the best transcranial direct current stimulation protocol for migraine prevention? A systematic review

R. Ornello, V. Caponnetto, S. Ratti, G. D'Aurizio, C. Rosignoli, M. Ferrara, S. Sacco, A. D'Atri

Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università degli Studi dell'Aquila, L'Aquila, Italy

Background: Transcranial direct current stimulation (tDCS) could counteract the pathophysiological triggers of migraine attacks by modulating cortical excitability. Several pilot randomized controlled trials (RCTs) assessed the efficacy of tDCS for migraine prevention, with overall positive results of heterogeneous stimulation schedules and tDCS montages. We reviewed and summarized the state of the art of tDCS protocols for migraine prevention, discussing the study results according to the stimulations parameters and patients' population.

Methods: We combined the keywords 'migraine', 'headache', 'transcranial direct current stimulation', and 'tDCS' and searched Pubmed, Scopus, and Web of Science, from the beginning of indexing to June 22, 2021. We only included RCTs comparing the efficacy of active tDCS with sham tDCS to decrease migraine frequency, intensity, and/or acute drug utilization. The risk of bias of each RCT was assessed by using the RoB-2 tool (Cochrane Collaboration).

Results: 13 RCTs (from 2011 to 2021) were included in the review. According to the RoB-2 tool, only four of the 13 RCTs had a low risk of bias, while the others presented some concerns. The included patients ranged from 17 to 135. Six RCTs used cathodal and five anodal tDCS, while two RCTs compared the efficacy of both cathodal and anodal tDCS with that of sham. The RCTs with cathodal tDCS included patients with both episodic and chronic migraine (N=3), with episodic migraine only (N=1), with chronic migraine without aura (N=1) or women with menstrual migraine only (N=1). The cathode was usually positioned across the occipital regions, with the reference electrode across the central areas, on the vertex. The RCTs with anodal tDCS included subjects with chronic migraine (N=2), with episodic migraine (N=2), or any form of migraine (N=1). In these RCTs, the anode is usually placed above the primary motor cortex (M1), with varying sides, and the cathode on the contralateral supraorbital area. All RCTs adopted repeated sessions (from 5 to 28) at variable intervals, while the follow-up length spanned from 1 day up to 12 months. Headache frequency, intensity, and acute medication consumption significantly decreased after both the anodal stimulation on M1 and the cathodal stimulation on occipital regions compared with sham.

Conclusions: Available RCTs of tDCS for migraine prevention are heterogeneous and used different neurostimulation protocols. Electrode montage in anodal-tDCS RCTs aims to induce a reflex inhibition of subcortical pain-generating areas. In cathodal-tDCS RCTs, the inhibitory stimulation of occipital areas aims to contrast the excessive cortical excitability in

the posterior regions. Both the anodal and cathodal tDCS interventions are promising for migraine prevention. There is a need for larger and rigorous RCTs as well as studies designed to identify targeted neurostimulation protocols for specific subgroups of patients. Studying the effect of tDCS could also provide some information on the pathophysiological mechanisms underlying migraine occurrence.

Does COVID-19 vaccination worsen headache in people with migraine?

I. Orologio[1], M. Silvestro[1], P. Sozio[1], G. Napolitano[2], M. Siciliano[1], A. Tessitore[1], G. Tedeschi[1], A. Russo[1]

[1]Headache Center, Department of Advanced Medical and Surgical Sciences (DAMS), University of Campania "Luigi Vanvitelli", Naples, Italy; [2]Intensity Care Unit, Department of Emergency and Acceptance "Antonio Cardarelli" Hospital, Naples, Italy

Background: Vaccines have represented the breakthrough in the fight against COVID-19. Based on the results from COVID-19 vaccines randomized control trials (RCTs), reporting headache attacks in a high percentage of subjects, we aimed to focus on the effects of COVID-19 vaccine administration in a large cohort of people with migraine.

Methods: An on-line questionnaire has been developed and published on Italian Facebook groups oriented towards headache patients to collect data about demographics and clinical parameters of migraine severity, COVID-19 infection and/or vaccination, and characteristics of headaches following COVID-19 vaccination.

Results: According to the results, out of 841 migraine patients filling-in the questionnaire, 559 (66.47%) and 237 (60.15%) patients experienced a headache attack (from 1 hour to 7 days) after the first and the second vaccine dose, respectively. The main finding concerns headaches perceived by 322 patients (57.60%) as characterized by higher pain intensity (50.62% of patients), longer duration (52.80% of patients) and lower responsiveness to painkillers (49.69% of patients) compared to the usually experienced migraine attacks.

Conclusions: COVID-19 vaccines administration can lead to more severe, long-lasting and hardwearing headache attacks in migraine patients, likely by inducing the production of inflammatory mediators such as type Iβ interferon (IFN-1β). Also considering the high prevalence of migraine in the general population, the awareness of the possibility of headache worsening following COVID-19 vaccine administration in these patients may allow both patients and clinicians to face this clinical entity with conscious serenity and reduce the waste of resources towards an inappropriate health-care.

Headache in children: a challenge for the paediatrician

M. Pace[1], L. Marino[2], R. Falsaperla[3], S. Marino[4]

[1]Foundation "Il Cireneo" Onlus for Autism, Vasto, ASL2 Lanciano-Vasto-Chieti, Italy; [2]Postgraduate Training Programme in Pediatrics, Department of Clinical and Experimental Medicine, University of Catania, Italy; [3]Neonatal Intensive Care Unit [NICU], Neonatal COVID-19 Center, AOU "Policlinico", PO "San Marco", University of Catania, Italy; [4]Unit of Pediatrics and Pediatric Emergency, AOU Policlinico", PO "San Marco", University of Catania, Italy

Background: Headache is one of the main pediatric disorders, with a prevalence of 37% in school age, it is the third cause of school absences. Up to 18% of patients in the pediatric emergency room are found to be migraine-related. The diagnosis of migraine in children and adolescents remains a clinical diagnosis. The diagnostic criteria of the IHS classification are based on clinical-epidemiological findings. The early identification of secondary forms is important as a recognition of the link between epilepsy and migraine/headache, being the latter a possible, unique, clinical, often misdiagnosed manifestation of epilepsy. The successful treatment of pediatric migraine includes an individually tailored regimen of both non-pharmacologic and pharmacologic measures.

Methods: A search was carried out on Pubmed and Cochrane databases, by reviewing clinical studies published between 2010 and 2020, focused on age group ranging from 0 to 18 years and elaborated according to criteria of the International Headache Society (ICHD-II and ICHD-III), the main reference for the diagnosis of primary headaches. Keyword words searched for were: pediatric headache, clinical features of childhood headache, pediatric headache treatment.

Results: 40 eligible publications were identified. In the acute treatment of migraine in developmental age, ibuprofen, paracetamol, sumatriptan are safe and effective. For migraine prevention, we considered non-pharmacological therapies, such as sleep hygiene patterns, diet, managing stress, exercise, avoiding triggers such as stressors, drugs, environmental stimuli, lifestyle and pharmacologic therapies used successfully in the pediatric population, including beta-blockers, calcium channel antagonists, serotonin antagonists, antidepressants and antiepileptics. The discrepancy of the results in some studies could be attributed to differences in the number of subjects enrolled, selection criteria, age, source of information (parent/child). In children differentiating headache from a non-specific state of intolerance is often difficult.

Conclusions: Pediatric headache studies highlight the needs for a public health problem with negative social impact. Early diagnosis and treatment reduce the risk of becoming chronic. Underdiagnose and under management are common and self-medication is frequent. The non-pharmacological approach is considered the first line of treatment. There is enough evidence that combination of pharmacological and non-pharmacological

approaches is the best solution. Further studies on larger groups are necessary for prophylactic drugs.

References:

Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211.

Papetti L, Spalice A, Nicita F, Paolino MC, Castaldo R, Iannetti P, Villa MP, Parisi P. Migraine treatment in developmental age: guidelines update. J Headache Pain. 2010;11:267–276.

Antonaci F, Voiticovschi-Iosob C, Di Stefano AL, Galli F, Ozge A, Balottin U. The evolution of headache from childhood to adulthood: a review of the literature. J Headache Pain. 2014;15:15.

O'Brien HL, Kabbouche MA, Kacperski J, Hershey AD. Treatment of pediatric migraine. Curr Treat Options Neurol. 2015;17:326.

Antonaci F, Voiticovschi-Iosob C, Di Stefano AL, Galli F, Ozge A, Balottin U. The evolution of headache from childhood to adulthood: a review of the literature. J Headache Pain. 2014;15:15.

Association of hypnic headache and migraine: a single centre study

A. Palmieri, L. Valentinis

Headache Centre, Division of Neurology, Portogruaro Hospital, Portogruaro (VE), Italy

Background: Hypnic headache (HH) is a rare primary headache disorder originally described by Raskin in 1988 [1]. It is characterized by recurrent attacks developing exclusively during sleep and usually occurs in individuals older than 50 years of age. The pathophysiology of this condition remains largely speculative [2]. Moreover, the relationship between HH and other primary headache disorders, above all migraine, has been poorly investigated to date. In this single-centre study we describe the clinical characteristics of a cohort of patients diagnosed as having HH and the prevalence of concurrent or previous migraine headaches.

Methods: All consecutive patients affected by HH according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) and admitted to our Headache Centre from July 2006 to June 2021 were retrospectively evaluated by reviewing the medical records. Demographic and clinical data concerning HH and migraine headaches were assessed.

Results: Twenty-five out of about 4500 (0.6%) patients were diagnosed with HH (including 9 individuals with probable HH), with a female predominance (18/25). HH patients showed a mean age of onset of symptoms of 60.9 years (range 33 to 80), age at presentation of 65.0 years (34-81), duration of symptoms of 3.6 years (3 months to 12 years), frequency of attacks of 16.2 days per month (5-30), and duration of attacks of 3.3 hours (1-10). Twenty-three patients presented the classic unremitting headache pattern while only 2 patients exhibited an "episodic" pattern (active periods separated by one or more pain free months)[3]. In most patients (17/25) the pain was bilateral or generalised, while in 8/25 patients the pain was reported as unilateral (side-locked or alternating). Migraine-like features (i.e. unilateral throbbing pain with associated vegetative symptoms) were observed in 7/25 patients. Caffeine and indomethacin were the abortive and/or preventive therapies more frequently associated to a good response [4]. Fifteen out of 25 HH patients (60%) had a history of migraine without aura or chronic migraine, with a mean age of onset of 19.5 years (10-35). In 10/15 patients (67%), migraine resolved before the HH onset with a mean interval of 7.0 years (1-27). In 5/15 patients (33%) migraine attacks persisted during the HH period.

Conclusions: The present study indicates a relatively high lifetime prevalence of migraine in HH patients (60% of cases). Our findings confirm previous results reporting a common association between HH and migraine [5]. Furthermore, migraine-like features are not uncommon during HH attacks. Taken together, these findings suggest possible shared mechanisms in the pathogenesis of both forms of primary headaches.

References:

1. Raskin NH. The hypnic headache syndrome. Headache. 1988;28:534-6.
2. Lanteri-Minet M. Hypnic headache. Headache. 2014;54:1556-9.
3. Lisotto C, Mainardi F, Maggioni F, Zanchin G. Episodic hypnic headache? Cephalalgia. 2004;24:681-5.
4. Silva-Neto RP, Santos PEMS, Peres MFP. Hypnic headache: A review of 348 cases published from 1988 to 2018. J Neurol Sci. 2019;401:103-9.
5. Ruiz M, Mulero P, Pedraza MI, de la Cruz C, Rodríguez C, Muñoz I, Barón J, Guerrero AL. From wakefulness to sleep: migraine and hypnic headache association in a series of 23 Patients. Headache. 2015;55:167-173.

A case of COVID-19-related new onset persistent headache: possible role of corticosteroid therapy

A. Palmieri, L. Valentinis

Headache Centre, Division of Neurology, Portogruaro Hospital, Portogruaro (VE), Italy

Introduction: Headache is one of the most frequent symptoms in the acute phase of the coronavirus disease 2019 (COVID-19). In most cases, the headache is associated with fever and other classical respiratory symptoms of the disease and resolves with them. Nevertheless, the headache may persist until six weeks after the onset of COVID-19 manifestations in a relevant percentage of cases [1]. Here, we describe a patient who developed a long-lasting headache after COVID-19 with complete response to corticosteroid therapy.

Case report: A 17-year-old girl was referred to our Headache Centre for a new onset persistent headache. Eight weeks before presentation the patient developed fever at 37.5°C, sore throat and hyposmia over three days. The fourth day she awakened with a headache localised in the occipital region radiating towards the orbit bilaterally, moderate to severe in intensity, compressive in quality, exacerbated by physical activity and accompanied by photophobia and phonophobia. A few days later the patient tested positive for SARS-Cov-2. The other symptoms disappeared after one week but headache persisted afterward on a daily basis. Simple analgesics and NSAIDs did not help. The patient's personal history was remarkable for a Hashimoto thyroiditis and, in the last 2 years, sporadic episodes of headache, considerably different from the current headache, and suggestive for migraine without aura. The general and neurological examinations were unremarkable, while brain MRI and laboratory tests were within the normal limits. She was placed on a 10-day prednisone taper at the initial dosage of 50 mg daily. The headache rapidly improved during the first 48 hours of treatment after that the patient became completely pain free by the end of the therapy, after more than ten weeks of unremitting headache. Three months later she was still asymptomatic, apart from 3 episodes of her previous migraine.

Discussion: Headache has been increasingly recognised as a cardinal symptom of COVID-19 [2]. COVID-19-related headache may display multiple phenotypes, the most frequently reported being a diffuse pain, moderate or severe in intensity, and not accompanied by vegetative symptoms, consistent with *9.2.2 headache attributed to systemic viral infection* in the ICHD-3. However, our patient experienced an abrupt-onset and long-lasting continuous headache, in that resembling new daily persistent headache (NDPH). Furthermore, a previous acute viral infection, above all Epstein-Barr virus (EBV), is one of the best known risk factors associated with NDPH [3]. The complete response to corticosteroid therapy in our patient could indicate a possible role of an immune-mediated inflammatory response induced by the virus at the level of the central nervous system in the pathogenesis of COVID-19-related headache. Further studies are warranted to define the

headache characteristics in COVID-19 as well as the underlying pathophysiologic mechanisms.

References:

1. Caronna E, Ballvé A, Llauradó A, Gallardo VJ, Ariton DM, Lallana S, López Maza S, Olivé Gadea M, Quibus L, Restrepo JL, Rodrigo-Gisbert M, Vilaseca A, Hernandez Gonzalez M, Martinez Gallo M, Alpuente A, Torres-Ferrus M, Pujol Borrell R, Alvarez-Sabin J, Pozo-Rosich P. Headache: A striking prodromal and persistent symptom, predictive of COVID-19 clinical evolution. Cephalalgia. 2020;40:1410-1421.
2. Poncet-Megemont L, Paris P, Tronchere A, Salazard JP, Pereira B, Dallel R, Aumeran C, Beytout J, Jacomet C, Laurichesse H, Lesens O, Mrozek N, Vidal M, Moisset X. High prevalence of headaches during Covid-19 infection: a retrospective cohort study. Headache. 2020;60:2578-2582.
3. Li D, Rozen TD. The clinical characteristics of new daily persistent headache. Cephalalgia. 2002;22:66-69.

New onset persistent headache after COVID-19 vaccination: a new clinical entity?

A. Palmieri, L. Valentinis

Headache Centre, Division of Neurology, Portogruaro Hospital, Portogruaro (VE), Italy

Introduction: Safe and effective vaccines are considered the main weapon for contrasting the global consequences of COVID-19 pandemic. Although approved vaccines have shown a favorable safety profile, mild adverse reactions are common. Headache is one of the most frequent side effects, having been reported by a high percentage of individuals. The post-vaccinal headache is usually mild and short-lived. Here, we report on a cohort of consecutive patients who developed a new onset persistent headache with a close temporal relation with COVID-19 vaccination.

Methods: After observing the first clinical case, that prompted us to look for other similar ones, we prospectively recruited all patients referred to our Headache Centre from February to July 2012 for new or changing persistent headache of moderate to severe intensity that started within 72 hours since the first or second dose of COVID-19 vaccination. In all patients alternative diagnoses, above all cerebral venous thrombosis (CVT), were actively searched and excluded by performing brain MRI and laboratory tests.

Results: Eight patients (7 F, 1 M) were included with mean age at presentation of 51.3 years (25 to 59 years). Altogether, 4 patients were vaccinated with Pfizer-BioNtech, 3 with Astrazeneca, and 1 with Moderna. The headache started after the first vaccine dose in 6 patients, and after the second in 1, while in 1 patient it developed after both doses but was more intense and prolonged after the second one. On average, headaches occurred 30.3 hours after vaccination (1 to 72 hours) and lasted 23.0 days (7 to 58 days). In all patients the headache was on a daily basis from onset, continuous unremitting in 6, intermittent with free intervals below 24 hours in 2. The pain was described as bilateral (located in the orbital, frontal, and/or temporal regions) in 6 patients, and unilateral without side shift in 2 (left frontal and parieto-occipital areas respectively). The mean pain intensity during exacerbations was 8.9/10 (7-10), while the pain character was reported as pressing in 5 patients and pulsating in 3. Vegetative symptoms associated with headaches, such as nausea, photophobia, and/or phonophobia, were referred by 6 patients. Four patients gave a history of migraine without aura, but the current vaccination-related headache was reported as clearly different from the previous one.

Discussion: Although post-vaccinal headache is not included in the International Classification of Headache Disorders, 3rd ed. (ICHD-3), our study indicates that a new onset persistent headache may be a rare consequence of COVID-19 vaccination. The pathophysiological mechanisms underlying such clinical entity remain obscure. However, a role played by proinflammatory cytokines released as a response of the immune system to vaccines appears plausible [1], as hypothesized even for the pathogenesis of headache in the acute phase of COVID-19 [2]. Further studies are needed to confirm the distinctive clinical and temporal phenotype of headache associated with COVID-19 vaccination.

References:

1. Hervé C, Laupèze B, Del Giudice G, Didierlaurent AM, Tavares Da Silva F. The how's and what's of vaccine reactogenicity. NPJ Vaccines. 2019;24:39.
2. Trigo J, García-Azorín D, Sierra-Mencía Á, Tamayo-Velasco Á, Martínez-Paz P, Tamayo E, Guerrero AL, Gonzalo-Benito H. Cytokine and interleukin profile in patients with headache and COVID-19: A pilot, CASE-control, study on 104 patients. J Headache Pain. 2021;22(1):51.

Cortical abnormalities in pediatric patients with migraine without aura: analysis of gyrification morphology and cortical thickness

L. Papetti[1], G. Sforza[1], A. Guarnera[2], R. Moavero[1], F. Ursitti[1], M.A.N. Ferilli[1], S. Tarantino[1], A. Napolitano[3], D. Longo[2], M. Valeriani[1]

[1]Pediatric Headache Center, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; [2]Neuroradiology Unit, Imaging Department, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; [3]Medical Physics Department, Bambino Gesù Children's Hospital, Rome, Italy

Background: Migraine is the most common neurological disease, with a high social-economic burden. Although there is growing evidence of brain structural and functional abnormalities in patients with migraine, few studies have been conducted on children and no studies investigating cortical gyrification have been conducted on pediatric patients affected by migraine without aura.

Methods: Seventy-two pediatric patients affected by migraine without aura and eighty-two controls aged between 6 and 18 were retrospectively recruited with the following inclusion criteria: MRI exam showing no morphological or signal abnormalities, no systemic comorbidities, no abnormal neurological examination. Cortical thickness (CT) and local gyrification index (LGI) were obtained through a dedicated algorithm, consisting of a combination of voxel-based and surface-based morphometric techniques. The statistical analysis was performed separately on CT and LGI between: patients and controls; subgroups of controls and subgroups of patients.

Results: Patients showed a decreased LGI in the left superior parietal lobule and in the supramarginal gyrus, compared to controls. Female patients presented a decreased LGI in the right superior, middle and transverse temporal gyri, right postcentral gyrus and supramarginal gyrus compared to male patients. Compared to migraine patients younger than 12 years, the ≥ 12-year-old subjects showed a decreased CT in the superior and middle frontal gyri, pre- and post-central cortex, paracentral lobule, superior and transverse temporal gyri, supramarginal gyrus and posterior insula. Migraine patients experiencing nausea and/or vomiting during headache attacks presented an increased CT in the pars opercularis of the left inferior frontal gyrus.

Conclusions: Differences in CT and LGI in patients affected by migraine without aura may suggest the presence of congenital and acquired abnormalities in migraine and that migraine might represent a vast spectrum of different entities. In particular, ≥ 12-year-old pediatric patients showed a decreased CT in areas related to the executive function and nociceptive networks compared to younger patients, while female patients compared to males showed a decreased CT of the auditory cortex compared to males. Therefore, early and tailored therapies are paramount to obtain migraine control, prevent cerebral reduction of cortical thickness and preserve executive function and nociception networks to ensure a high quality of life.

Safety, efficacy and sleep effect of Erenumab in Chronic migraine: 12 months real-life data

L. Pilati, A. Torrente, S. Di Marco, G. Notaro, S. Ferlisi, M. Romano, F. Brighina

Università degli studi di Palermo, Palermo, Italy

Background and aims: Erenumab, human monoclonal antibody directed against CGRPr, is the first approved specific treatment for migraine. In this real-life study, we evaluated the efficacy and safety of erenumab associated with a multidisciplinary impact including sleep and circadian effect in 12 months treatment.

Methods: Data were collected from the Headache Centers in the Policlinico of Palermo and Messina, IRCSS Neurolesi Center "Bonino Pulejo". Patients with chronic refractory migraine received 140 mg or 70 mg of Erenumab every 28 days. A neurologist administered MIDAS, HIT-6 and BDI and scales to study sleep impact of erenumab (MEQ-SA, PSQI, SCI, ESS), every month for the first 3 months of treatment, and then every 3 months.

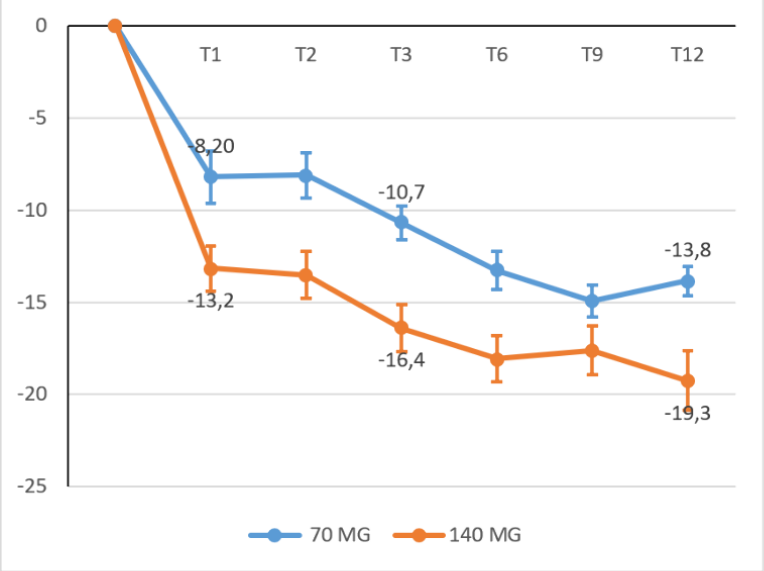
Results: We enrolled 88 patients: 38 migraineurs were given 140 mg and the remaining 50 patients 70 mg. Erenumab reduced significantly monthly migraine days (MMD) from month 1 to month 12 of treatment, improving disability and depression. Drug overuse was eliminated in 80% of patients as early as month 3 of the treatment. Dosage of 140 mg was more effective than 70 mg at 6-month treatment in reducing MMD. At month 3 there was a reduction of the morning chronotype in favor of the intermediate one and in insomnia. The most common adverse event was constipation, which was observed in 9 patients (10%). No adverse events led to withdrawal from the treatment.

Conclusions: Our real-life data confirm the efficacy and safety of erenumab in chronic migraine with one-year treatment with a significant improvement on quality of life. It is the first study that has evaluated the effect of Erenumab on sleep: a result of improvement in headache or the result of the action in CGRP, that is implicated in circadian rhythm?

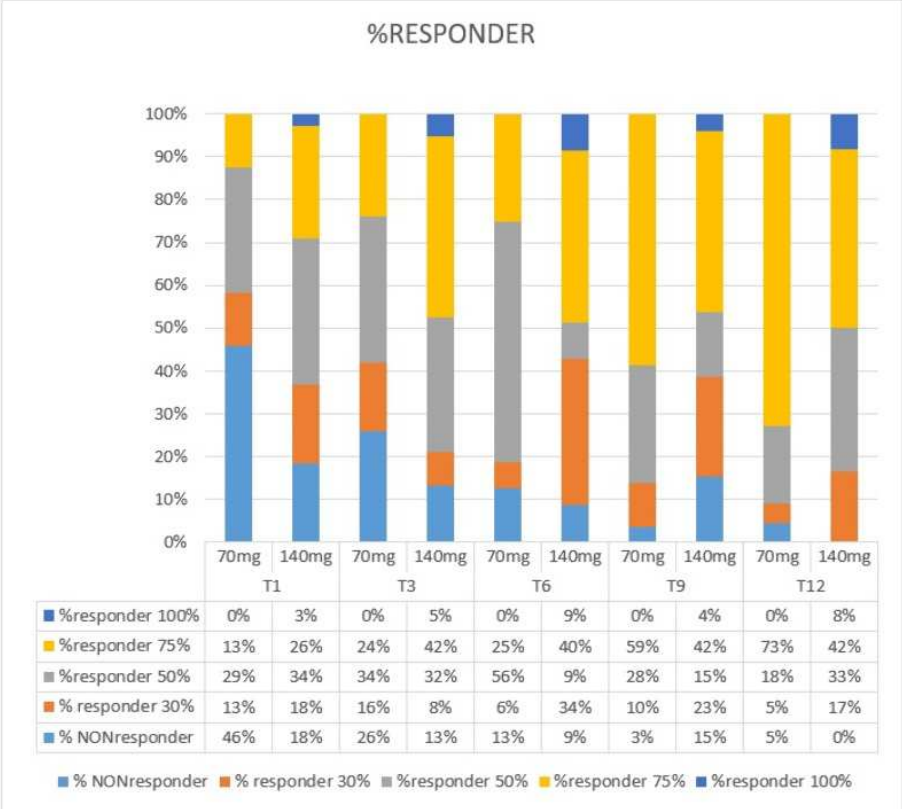
References:

Tepper S, Ashina M, Reuter U, Brandes JL, Doležil D, Silberstein S, Winner P, Leonardi D, Mikol D, Lenz R. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017;16:425–34.

Kunst M, Hughes ME, Raccuglia D, Felix M, Li M, Barnett G, Duah J, Nitabach MN. Calcitonin gene-related peptide neurons mediate sleep-specific circadian output in Drosophila. Curr Biol. 2014;24:2652–2664.

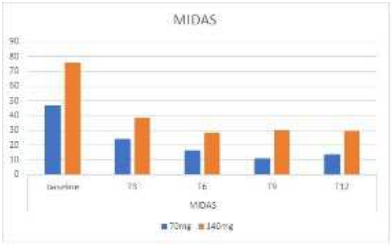


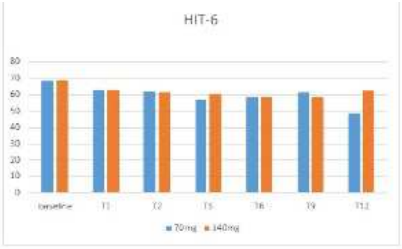
Graph 1: Decrease in MMDs compared to baseline

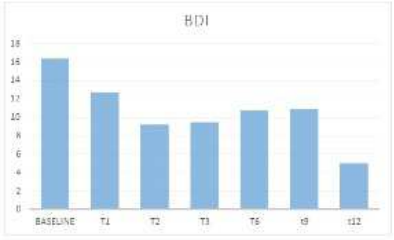


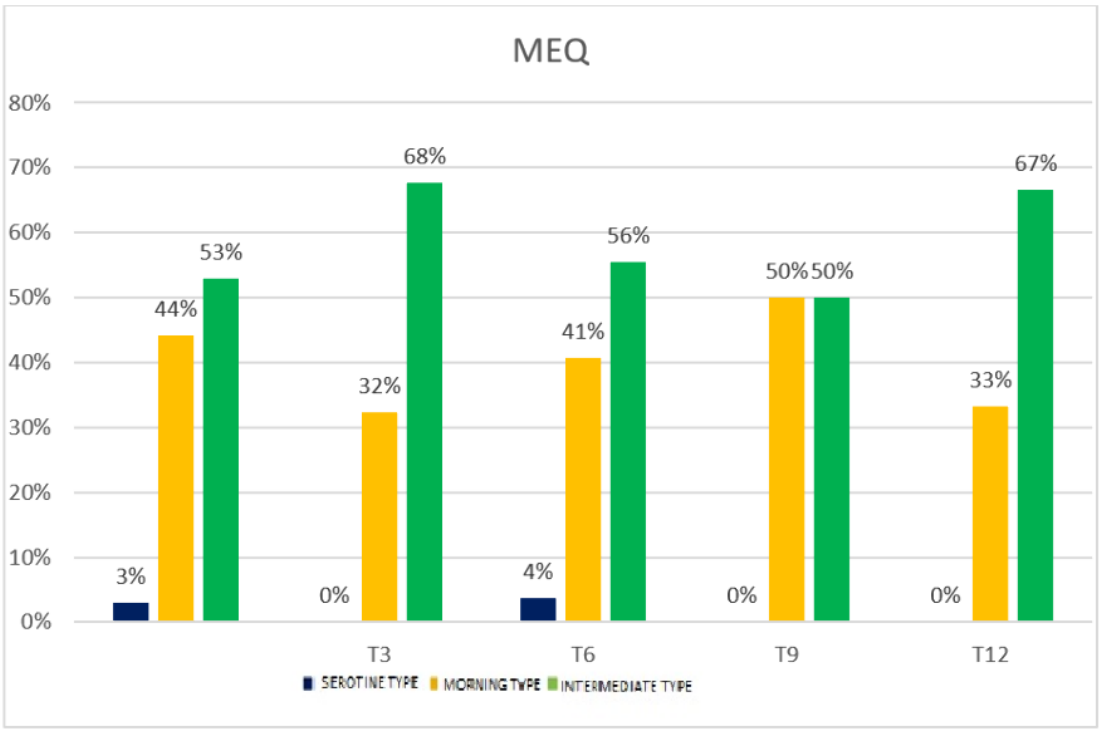
	70mg T1	140mg T1	70mg T3	140mg T3	70mg T6	140mg T6	70mg T9	140mg T9	70mg T12	140mg T12
%responder 100%	0%	3%	0%	5%	0%	9%	0%	4%	0%	8%
%responder 75%	13%	26%	24%	42%	25%	40%	59%	42%	73%	42%
%responder 50%	29%	34%	34%	32%	56%	9%	28%	15%	18%	33%
% responder 30%	13%	18%	16%	8%	6%	34%	10%	23%	5%	17%
% NONresponder	46%	18%	26%	13%	13%	9%	3%	15%	5%	0%

Graph 2. Responder 70mgvs 140mg









Graph.4 Chronic migraine, chronotype and erenumab

Long-term effects of Covid-19 pandemic on migraine features and psychological symptoms in adolescents

M. Proietti Checchi[1], S. Tarantino[1], L. Papetti[2], M.A.N. Ferilli[2], F. Ursitti[2], R. Moavero[2,3], G. Sforza[2], T. Grimaldi Capitello[1], F. Vigevano[2], M. Valeriani[2,4]

[1]Unit of Clinical Psychology, Bambino Gesù Hospital, Rome, Italy; [2]Headache Center, Division of Neurology, Bambino Gesù Hospital, Rome, Italy; [3]Child Neurology and Psychiatry Unit, Tor Vergata University of Rome, Italy; [4]Center for Sensory-Motor Interaction, Aalborg University, Aalborg, Denmark

Background: Covid-19 pandemic has changed the lifestyle of children/adolescents, influencing family organization, social relationship, and school attendance. A previous study showed the role of lifestyle modification, in particular the reduction in school-related stress during the lockdown, on improvement of migraine attacks. We aimed to compare the clinical characteristics of migraine, the use of prophylactic treatment and psychological symptoms between patients who referred to our Headache Center before and those who were evaluated during the pandemic. We, moreover, compared the clinical features and psychological symptoms according to the first and acute and the second and long-lasting phases of pandemic of Covid-19.

Methods: We studied 300 adolescents with migraine (m.a. 14.11 ± 1.79; 85 M and 215 F). According to the period, patients were grouped in "Before Covid" or "Covid"; in particular, the second group was divided into "Covid-1" (from March to October 2020, characterized by lockdown, starting of telematic lessons and summer holidays) and "Covid-2" (from November 2020 to June 2021, characterized by returning to school and/or telematic lessons). We, moreover, grouped patients in: 1) high frequency (from weekly to daily episodes) and low frequency patients (≤3 episodes per month); 2) mild and severe pain; 3) recent (≤ 6 months before the consultation) or late migraine onset; 4) finally, we divided patients who needed a prophylactic treatment from those who did not. PHQ-9 and GAD-7 questionnaires were used to evaluate adolescents' symptoms of anxiety and depression.

Results: We found a significantly lower migraine frequency in the "Covid" period (p=0.011), in particular in the "Covid-1" period (p=0.000). Our data did not show any significant difference in migraine frequency between the "Before Covid" and "Covid-2" (p=>0.05) groups. We found that a higher number of patients needed a prophylactic treatment in the "Covid-2" compared with the "Before Covid" period (p=0.006). Moreover, our results evidenced a significantly higher severity of pain in "Covid-2" compared with "Covid-1" (p=0.012). When we analyzed the psychological symptoms, we observed higher levels of anxiety and depression in adolescents evaluated during the pandemic of Covid-19 (GAD-7, p=0.015 and PHQ-9, p=0.036). The onset of migraine did not show any significant association with the two main periods of Covid-19.

Conclusions: Our finding suggested that although the pandemic of Covid-19 could have had an initial positive influence, it may have a negative long-term effect on migraine

severity. We support the hypothesis of a negative influence of school-stress on migraine in pediatric age. Moreover, our data evidenced a negative impact of the pandemic on anxiety and depression symptoms in adolescents with migraine.

Prevalence of primary headaches in a group of hospital workers during Sars-COV2 infection

E. Pucci[1], L. Campi[2], V. Nava[2], M. Lagorio[2]

[1]ASP IDR S. Margherita, Pavia and Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy; [2]ASP IDR S. Margherita, Pavia, Graduate School of Geriatrics and Gerontology, University of Pavia. Pavia; Italy

Introduction: Headaches represent at the same time the symptom and the disease, while the secondary ones are the expression of an ongoing pathology that can be systemic, locoregional or distant.

Aim: The aim of this study was to determine the prevalence rate in the workplace in a ward (Nucleo Alzheimer) during the period of Sars-COV2 infection. This survey was carried out using 2 questionnaires: 1) work activity sheet and 2) headache sheet according to IHS criteria.

Materials and methods: All health personnel belonging to the Alzheimer Nucleus of the IDR S. Margherita of Pavia were asked to complete the questionnaires during the Sars-COV2 infection period.

Results: From the analysis of the questionnaires administered, it was found that out of 15 workers, 10 were women and 5 were men: 4 (all women with migraine without aura) and 7 tension-type headache (5 women and 2 men). Before the Sars-COV2 period, only 2 workers had migraine without aura and 2 tension-type headaches (all women). All 11 workers reported stress, insomnia, and concern for family members and their own health. None of the workers at the time of testing had been vaccinated.

Conclusions: Factors related to the work environment are able to increase the frequency and/or intensity of pre-existing headaches. It is also likely that particular situations can give rise to or cause some forms of headache under certain working conditions. Excessive responsibility or, on the contrary, disaffection and incongruous work rhythms should be considered among the occupational risk factors.

Atypical migraine: sentinel symptom for Sars-COV2 infection

E. Pucci[1], L. Campi[2], V. Nava[2], M. Lagorio[2]

[1]ASP IDR S. Margherita, Pavia and Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy; [2]ASP IDR S. Margherita, Pavia and Graduate School of Geriatrics and Gerontology, University of Pavia, Pavia, Italy

Introduction: Migraine without aura is the most frequent of the forms of migraines (about 60% - 80% of all forms of migraines). There are many causes that can trigger migraines, including infections (IHS ICDH-3).

Materials and methods: A 69-year old woman, professional nurse with a family history of migraine (maternal line) arising in school age. Diagnosis was made according to the IHS ICDH-3 criteria. The patient presented 2-3 crises per month with pulsating pain in the bilateral frontotemporal region, medium-strong intensity, associated with photo-phonophobia, nausea, sometimes vomiting. Duration 24-36 hours. Triggering factors: menstruation and psychophysical stress. After menopause (49 years) reduction of intensity, duration and frequency with 1-2 crises per month stress related lasting 12-24 hours and responsive to NSAID intake. No preventive therapy was performed. On November 29th 2020 she presented with an episode of atypical headache (described as different from other episodes) with very strong, throbbing, stabbing, burning pain in the bilateral front-temporal region, unresponsive to the intake of NSAIDs with a duration of 24 hours. No other symptoms were reported, apyretic. The day after (November 30th 2020): TNF fast: +. Molecular TNF: patient was positive for SARS COV-2. During the period of infection headache presented whenever the patient had fever and was unresponsive to paracetamol.

Conclusions: In our case report, atypical migraine could be considered a sentinel symptom of an initial infection. The patient works as a professional nurse in the ward (Nucleo Alzheimer) which had become a Covid ward on November 3rd 2020.

Menstrual and non-menstrual migraine and the influence of preventive treatments: a diary-based study in a tertiary Headache Center

S. Ratti, G. Marini, V. Caponnetto, R. Ornello, E. De Matteis, F. Pistoia, S. Sacco

Neuroscience Section, Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, L'Aquila, Italy

Background: In fertile women, migraine is influenced by the periodic fluctuations of estrogen levels across the ovarian cycle [1]. Compared with those in the intermenstrual period, migraine attacks during the perimenstrual period of the ovarian cycle are longer, more severe, and less responsive to medication [2]. However, it is unclear whether migraine preventive treatments have any effect on the menstrual pattern of headache. The present observational study aimed to compare headache frequency and acute medication consumption in fertile women during their perimenstrual and intermenstrual period, stratified according to preventive medication use.

Methods: We prospectively collected data from headache diaries of fertile women treated at the Headache Center. We included patients with at least three-month headache diaries including a report of menstrual days, frequency and intensity of migraine attacks, doses and days of acute medication. Preventive migraine treatment classes were also recorded. Perimenstrual period was defined as day -2 to day +3 of the ovarian cycle. Intermenstrual period included the remaining days. The proportion of headache days was defined as the number of headache days divided by total diary days.

Results: We included 50 fertile women with a mean age of 38.5±11.4 years, contributing for a total of 11,172 days of diary and 343 ovarian cycles. The proportion of headache days was higher in the perimenstrual than in the intermenstrual period (45.3% vs. 31.5%, respectively; $p<0.001$). We found the same proportion in women who were not under any preventive treatment (45.7% vs 27.6%; $p<0.001$), in women treated with antidepressants (44.0% vs 28.6%; $p<0.001$), antiepileptics (60.9% vs 47.1%; $p=0.024$), calcium channel blockers (51.7% vs 33.6%; $p=0.042$), ACE-inhibitors or angiotensin receptor blockers (36.7% vs 13.6%; $p=0.006$), onabotulinumtoxinA (62.5% vs 44.0%; $p<0.001$), monoclonal antibodies acting on the CGRP pathway (37.0% vs 25.8%; $p<0.001$), and combined treatments (52.2% vs 36.4%; $p<0.001$). The difference was not significant in women treated with beta-blockers (57.1% vs 36.2%; $p=0.246$) possibly due to the low numbers. Days of acute medication consumption were also higher in the perimenstrual than in the intermenstrual period (31.7% vs. 19.9%; $p<0.001$). The same proportion was maintained in women treated with antidepressants (32.8% vs 17.1%; $p<0.001$), antiepileptics (44.9% vs 31.6%; $p=0.024$), ACE-inhibitors or angiotensin receptor blockers (36.7% vs 13.8%; $p=0.006$), onabotulinumtoxinA (37.5% vs 31.0%; $p<0.001$), monoclonal antibodies acting on the CGRP pathway (30.3% vs 19.8%; $p<0.001$), or combined treatments (33.4% vs 23.4%; $p<0.001$). In women treated with beta-blockers (57.1% vs 27.5%; $p=0.119$) or calcium channel blockers (24.1% vs 16.4%; $p=0.209$), the difference was not significant due to the low numbers.

Conclusions: Our study confirmed that perimenstrual migraine attacks are more frequent and require a higher acute medication consumption compared with intermenstrual attacks; besides, it suggests that, despite preventive treatments, the menstrual pattern of migraine attacks is maintained in many women.

References:

1. Vetvik KG, MacGregor EA. Menstrual migraine: a distinct disorder needing greater recognition. Lancet Neurol. 2021;20:304–315.
2. Ornello R, Frattale I, Caponnetto V, De Matteis E, Pistoia F, Sacco S. Menstrual headache in women with chronic migraine treated with erenumab: an observational case series. Brain Sci. 2021;11:370.

Diagnosis of trigeminal neuralgia and other orofacial pain conditions: patients' point of view

F. Reina[1], G. Salemi[2], F. Brighina[2], V. Raieli[3], C.A. Costa[4]

[1]Child Neuropsychiatry Unit Department, University of Palermo, Palermo, Italy; [2]Department of Biomedicine, Neuroscience and Advanced Diagnostics, University of Palermo, Palermo, Italy; [3]Child Neuropsychiatry Department, ISMEP, ARNAS Civico, Palermo, Italy; [4]Pain Management Department, Humanitas, Catania, Italy

Background: Trigeminal neuralgia (TN) is a disorder characterized by frequent and intense pain attacks along the trigeminal nerve distribution [1]. Although the diagnosis is determined clinically, imaging studies or specialized tests might be necessary for a differential diagnosis for other diseases that cause orofacial pain (OFP). Doing the correct diagnosis could be difficult since signs and symptoms might not be specific. For this reason, subjects with OFP often turn to more specialists without obtaining a definitive diagnosis. This could result in the loss of confidence in physicians by patients. Moreover, the persistence of the pain due to a misdiagnosis or ineffective treatment could involve negative psychosocial and functional consequences in multiple areas of the patients' life [2]. The purpose of the study was to assess the patient's level of satisfaction regarding the first diagnosis of OFP.

Methods: This study was based on the responses to a survey questionnaire administered to patients affected by OFP (especially TN) members of an association. Score was based on a 0 (poor) to 10 (excellent) rating system. Moreover, high score (>6) was referred to a specialist physician who made the diagnosis. The questionnaire was filled in by 320 subjects using a free online tool. Specifically, the sample included subjects who affirmed to be affected only by TN, or in comorbidity with another disease that caused OFP, subjects with a pathology that caused OFP without TN and finally subjects without a specific diagnosis but with OFP symptoms.

Results: Patients reported a quite low level of satisfaction equal to 4.62, on average (Fig.1a). Physicians who obtained a high score were neurologists in 34% of cases, dentists in 25.5%, family doctors in 19.1%, emergency room doctors and neurosurgeons in 6.3%, maxillofacial surgeons in 4.2%, oculists and pain therapists in 2.1%, whereas other specialists obtained a lower score (Fig.1b).

Conclusions: Unfortunately, several painful facial conditions have overlapping symptoms, thereby delaying the correct diagnosis. Some of these, such as dentoalveolar or musculoskeletal pain, could be easily differentiated from TN, but some types of headaches, neuropathic pains and other types of neuralgia, require more attention and experience by physicians. As demonstrated by the low level of satisfaction, the condition that causes OFP represents a clinical challenge. Moreover, considering that most of these diseases are chronic and strongly debilitating, physician attention in the diagnosis and follow-up could improve the patient's level of satisfaction. Further studies are necessary to better define diagnostic measures and support the differential diagnosis.

References:

1. Araya EI, Claudino RF, Piovesan EJ, Chichorro JG. Trigeminal neuralgia: basic and clinical aspects. Curr Neuropharmacol. 2019;18:109–119.
2. Turk DC, Fillingim RB, Ohrbach R, Patel KV. Assessment of psychosocial and functional impact of chronic pain. J Pain. 2016;17:21–49.

Figure 1a and 1b

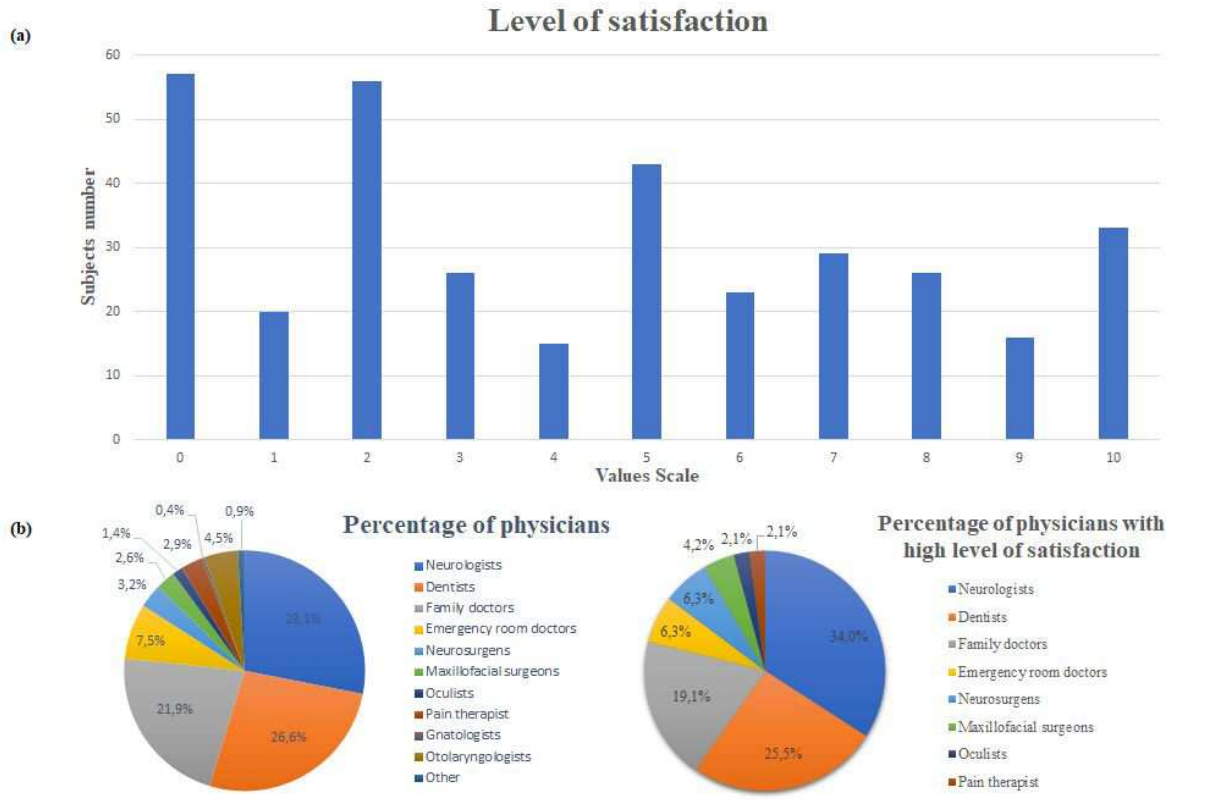


Figure 1: Rappresentation of rating system for each subjects (a); pie charts of consulted physicians for the first diagnosis and of physicians with highter score than 6 (b).

Lasmiditan is effective in the acute treatment of migraine in patients with insufficient response to triptans: findings from the CENTURION study

U. Reuter[1], L. Lombard[2], J. Krege[2], E. Gomez Valderas[2], J. Krikke-Workel[2], G. Dell'agnello[2], S. Dowsett[2], D. Buse[3], F. Torelli, Non-Author Presenter[4]

[1]Department of Neurology, Charité-Universitätsmedizin Berlin, Berlin, Germany; [2]Eli Lilly and Company, Indianapolis, IN, USA; [3]Albert Einstein College of Medicine, Bronx, NY, USA; [4]Eli Lilly and Company, Florence, Italy

Background: The objective of the study was to assess the efficacy of lasmiditan in triptan insufficient responders (TIRs). Lasmiditan is a selective 5-HT_{1F} receptor agonist, approved by the FDA for the acute treatment of migraine. It may be an option for TIRs, a group with potentially unmet medical need.

Methods: CENTURION was a modified-parallel, placebo-controlled, double-blind, Phase 3 consistency study of patients with migraine, with or without aura, randomized to lasmiditan (LTN) 200 mg for 4 attacks, LTN100 for 4 attacks, or placebo for 3 and LTN50 for 1 attack. TIRs were a pre-defined subset with an inconsistent response to their most recent triptan, were taking a triptan and had a poor/very poor migraine Treatment Optimization Questionnaire (mTOQ-6) score, or had discontinued their most recent triptan because of efficacy/tolerability issues or contraindications. Pain freedom at 2 hours (h) in the TIR population was a gated secondary endpoint. Results are provided for the first attack through 2h post dose and for sustained effects, through 48h, and for consistency of response defined as achieving the outcome at 2h in ≥2/3 attacks.

Results: During the first attack, both lasmiditan doses showed statistically-significant benefit over placebo for pain freedom beginning at 1h, and for pain relief beginning at 0.5h (LTN200) or 1h (LTN100)($p<0.05$). For pain freedom at 2h (gated): placebo, 8.8%; LTN100, 24.0% (OR 3.3 [1.8-6.0]; LTN200, 25.6% (OR 3.6 [2.0-6.4])($p<0.001$). Both lasmiditan doses showed statistically-significant benefit for consistency of effect across attacks for pain freedom and pain relief at 2h. Statistically-significant differences from placebo were evident for one or both lasmiditan doses for migraine-related disability freedom at 2h, much/very much better on the Patient Global Impression of Change at 2h, most bothersome symptom freedom at 2h, need for rescue medication, and sustained pain freedom at 24 and 48h ($p<0.05$).

Conclusions: Lasmiditan was efficacious across multiple clinically relevant endpoints in TIRs.

CACNA1A-p.Thr501Met mutation associated with Familial Hemiplegic Migraine: A family report

M. Romozzi[1], G. Primiano[1], E. Rollo[1], L. Travaglini[2], P. Calabresi[1], S. Servidei[1], C. Vollono[1]

[1]Dipartimento Universitario di Neuroscienze, Università Cattolica del Sacro Cuore, Rome, Italy; [2]Dipartimento di Neuroscienze e Neuroriabilitazione, Unità di Malattie Neuromuscolari e Neurodegenerative, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy

Background: Hemiplegic migraine (HM) is a rare form of migraine characterized by the presence of a motor and other types of aura. HM can be sporadic or familial. Familial hemiplegic migraine (FHM) is an autosomal dominant disorder, classified into 3 subtypes, based on the gene involved (CACNA1A in FHM1, ATP1A2 in FHM2 and SCN1A in FHM3). The clinical presentation is highly heterogeneous and some attacks may be severe. We report the clinical characteristics and genetic analysis of 12 patients belonging to a family with CACNA1A-p.Thr501Met gene mutation.

Methods: We screened for mutations in CACNA1A gene 15 patients belonging to the same family. The exonic sequences of CACNA1A were analyzed using a Tru-seq® Custom Amplicon (TSCA) (Illumina Inc., San Diego, CA) targeted capture and paired end library kit. Sanger sequencing was used to confirm CACNA1A variants and segregation analysis.

Results: CACNA1A-p.Thr501Met mutation was found in 12 of the 15 patients screened, which was compatible with the diagnosis of FHM1 [1]. The 12 patients were 7 women (58.33%) and 5 men (41.67%). Mean age at diagnosis was 14.4 ± 5.2 (range 6-24) and the mean age at examination was 50.4 ± 21.3 (range 22-76).
Attacks of hemiplegic migraine were reported by 10 of the 12 subjects (83.33%). All subjects affected by HM also reported attacks of migraine with non-hemiplegic aura and attacks of migraine without aura. According to the ICHD-3 criteria [1], one subject carrying p.Thr501Met mutation (8.33%) was diagnosed with migraine without aura and one subject (8.33%) with episodic tension-type headache. Emotional stress, menstruations and sleep deprivation were the most frequent triggering factors.
Only one subject developed persistent mild cerebellar symptoms and none of the subjects developed cerebellar atrophy.

Conclusions: The variant p.Thr501Met was described previously in association with episodic ataxia [2] and rarely with FHM related to cerebellar symptoms [3].
FHM1 has a broad clinical spectrum and about half of the families have cerebellar involvement [4]. In our study, only one patient developed persistent cerebellar deficits. These data suggest that CACNA1A-p.Thr501Met mutation can occur prevalently as hemiplegic migraine.

References:

1. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211.
2. Mantuano E, Romano S, Veneziano L, Gellera C, Castellotti B, Caimi S, Testa D, Estienne M, Zorzi G, Bugiani M, Rajabally YA, Barcina MJ, Servidei S, Panico A, Frontali M, Mariotti C. Identification of novel and recurrent CACNA1A gene mutations in fifteen patients with episodic ataxia type 2. J Neurol Sci. 2010;291(1-2):30-36.
3. Carreño O, Corominas R, Serra SA, Sintas C, Fernández-Castillo N, Vila-Pueyo M, Toma C, Gené GG, Pons R, Llaneza M, Sobrido MJ, Grinberg D, Valverde MÁ, Fernández-Fernández JM, Macaya A, Cormand B. Screening of CACNA1A and ATP1A2 genes in hemiplegic migraine: clinical, genetic, and functional studies. Mol Genet Genomic Med. 2013;1(4):206-222.
4. Russell MB, Ducros A. Sporadic and familial hemiplegic migraine: pathophysiological mechanisms, clinical characteristics, diagnosis, and management. Lancet Neurol. 2011;10(5):457-470.

Headache and Chiari I malformation in children: a retrospective study in a Pediatric Headache Centre

R. Rossi[1], G. Grasso[1], B. Lauria[1], A. Versace[1], A. Gambarotta[1], C. Bondone[1], P. Peretta[2], A.F. Urbino[1]

[1]A.O.U. Città della Salute e della Scienza di Torino, Regina Margherita Children's Hospital, Department of Pediatric Emergency, Pediatric Headache Centre, Turin, Italy; [2]A.O.U. Città della Salute e della Scienza di Torino, Regina Margherita Children's Hospital, Department of Neurosurgery, Pediatric Headache Centre, Turin, Italy

Background: The rate of brain abnormalities in paediatric patients with headache is 14-28%; the majority of the abnormal findings do not change the headache management. Chiari I malformation (CMI) is a condition characterized by downward displacement of the cerebellar tonsils through the foramen magnum into the spinal canal and it is identified in about 5.8% of patients imaged for headache. It has a variable clinical presentation with headache being the most common initial symptom. Although diagnostic criteria for headache attributed to CMI (CMH) are listed in the International Classification of Headache Disorders 3rd Edition (ICHD-III), the co-existence of a primary headache disorder and CMI, or whether CMI is causative of the headache is a challenge to many medical providers. The purpose of our study was to analyse abnormal neuroradiological findings in a population of children with headache and in particular describe clinical characteristics of patients with cerebellar ectopia.

Methods: We retrospectively studied all children that made their first visit in the Paediatric Headache Centre of the Regina Margherita Children's Hospital of Turin between January 2016 and June 2018 and that underwent neuroimaging.

Results: In the study period 480 children made their first visit for headache (male 47%, female 53%). A magnetic resonance imaging (MRI) was performed in 119 patients (25% of total) with rate of abnormal findings of 13% (16 patients); six of these showed a cerebellar tonsils ectopia (TE): two patients had a downward displacement of more than 5 mm. The majority of patients (5 of the total) with TE was diagnosed with primary headache (4 migraine and one mixed form) and only one showed diagnostic criteria for CMH. This patient had a cerebellar ectopia of more than 5 mm and underwent neurosurgical correction with clinical improvement of headache.

Conclusions: Headache is the most common symptom in children with CMI and CMH and show a peculiar clinical presentation. Nevertheless primary headaches have a high prevalence in children and in most cases CMI is an incidental finding. The coincidental association between primary headaches and asymptomatic CMI is therefore very frequent and clinical management of children with headache and CMI could be difficult. For these patients a multidisciplinary approach and a careful follow-up is mandatory, also to avoid unnecessary surgical procedure.

References:

Toldo I, Tangari M, Mardari R, Perissinotto E, Sartori S, Gatta M, Calderone M, Battistella PA. Headache in children with Chiari I malformation. Headache. 2014;54:899-908.

Victorio MC, Khoury CK. Headache and Chiari I Malformation in Children and Adolescents. Semin Pediatr Neurol. 2016;23(1):35-9.

Aitken LA, Lindan CE, Sidney S, Gupta N, Barkovich AJ, Sorel M, Wu YW. Chiari type I malformation in pediatric population. Pediatr Neurol. 2009;40:449-454.

Is there an association between primary headache as a risk factor for dementia? Results of a systematic review and meta-analysis of 15 cohort studies

N. Salvadori, E. Chipi, P. Eusebi, F. Paolini Paoletti, L. Parnetti, P. Sarchielli

Clinica Neurologica, Università di Perugia, Italy

Background: Several studies have investigated the association between primary headaches and risk of dementia. However, systematic reviews and meta-analyses available until now are limited and focused mainly to migraine, giving mixed results. This meta-analysis aimed to evaluate whether primary headache (i.e., migraine and tension-type headache) is a potential risk factor for dementia.

Methods: Our systematic review and meta-analysis were conducted according to the PRISMA guidelines. We searched MEDLINE (via PubMed) for cohort studies from databases from inception to September, 2021. The following information was independently extracted by two investigators (NS and EC): first author, year of publication, country of study, study design, statistical measures of association, target group, sample size, age of patients, diagnostic criteria of primary headache and dementia, years of follow-up, type of dementia, and adjustment. The methodological quality of the included studies was evaluated with a 9-point checklist for assessment of risk of bias. Heterogeneity was reported with I^2. Due to the number of studies available and the amount of heterogeneity, the measures of association were pooled with a random-effect model. The primary analysis was the meta-analysis of Hazard Ratios (HR), either adjusted or crude. Other analyses were planned for the pooling of: adjusted HRs; adjusted or crude Odds Ratios (OR); adjusted ORs. The R package *meta* was used for all the analyses. Reporting bias was assessed with visual inspection of funnel plots.

Results: Fifteen published cohort studies (10 retrospective, 5 prospective) covering a total of 4.488.252 individuals were selected from all articles identified by the search. Twelve of the selected studies were classified as high quality, 3 as moderate quality. Primary headache was associated with increased risk of all causes of dementia (n=9, HR=1.32, 95% CI=1.13-1.56, I^2=86%). The association was the same in retrospective (n=7, HR=1.34, 95% CI=1.12-1.61, I^2=87%) and in prospective studies (n=2, HR=1.35, 95% CI=0.72-2.54, I^2=78%). A significant increase of dementia risk was found also with the sensitivity analyses pooling only adjusted HR (n=7, HR=1.28, 95% CI=1.05-1.57, I^2=89%), adjusted and crude OR (n=13, OR=1.24, 95% CI=1.08-1.43, I^2=80%), only adjusted ORs (n=4, OR=1.22, 95% CI=1.02-1.47, I^2=49%). The funnel plots showed no evidence of reporting bias.

Conclusions: Our systematic review and meta-analysis confirm an association between primary headache (migraine, tension-type headache, non migraineurs-headache) and risk of developing dementia. The pathophysiologic substrate of such an association is less clear. Neuroinflammation, brain microstructural changes, subcortical white matter abnormalities, psychiatric comorbidity and/or other underlying mechanisms may probably play a potential role. Since our results confirmed high heterogeneity in data considered,

further investigation on the association between different types of primary headache and specific causes of dementia deserve is needed.

References:

Wang L, Wu JC, Wang FY, Chen X, Wang Y. Meta-analysis of association between migraine and risk of dementia. Acta Neurol Scand. 2021 Sep 15.

Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, Baker P, Smith E, Buchbinder R. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65(9):934-9.

Association between behavioral factors and episodic or chronic migraine: A Cross-Sectional Study

G. Saporito, G. D'Aurizio, R. Ornello, V. Caponnetto, A. Splendiani, S. Sacco, F. Pistoia

Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Italy

Background: Specific behavioral factors and sleep quality have been reported to influence the clinical course of migraine. However, the directionality of this association is not yet well defined. Migraine negatively affects the daily life of patients often leading to stress and discomfort, which, in turn, increases the frequency and severity of the migraine. Anxiety, mood alterations and depression are the psychiatric comorbidities most frequently associated with migraine, being two to ten times more common in migraineurs than in the general population. Our aim was to better investigate the relationship between behavioral factors and the clinical characteristics of migraine.

Method: In this cross-sectional study, consecutive female patients diagnosed with migraine and referring to a tertiary headache center were included in the study and asked to complete a self-report neuropsychological battery. Quality and quantity of sleep were evaluated through the Pittsburgh Sleep Quality Index (PSQI), the Insomnia Severity Index (ISI) and the Epworth Sleepiness Scale (ESS). Intolerance of uncertainty and personality were investigated using the Intolerance of Uncertainty Inventory (IUI-10), the Intolerance of Uncertainty Scale-12 (IUIS12), the URS Scale, the IA Questionnaire and the Eysenck Personality Questionnaire (EPQ-R). Anxiety symptoms were assessed using the State-Trait Anxiety Inventory (STAI-2) and the Anxiety Sensitivity Index-3 (ASI-3). Depression was assessed through the Beck Depression Inventory (BDI) while patients' attitudes and temperament through the brief TEMPS-M temperament questionnaire. Decision making style and tendency to magnify the threat value of pain were assessed through the General Decision Making Style (GDMS) questionnaire and the Pain Catastrophizing Scale (PCS) respectively. Healthy controls, matched by age and sex, were also included for comparison. Comparisons among groups were made through Univariate Anova and Tukey post-hoc tests.

Results: Sixty-five patients (mean age±SD 43.9±7.2) with Episodic Migraine (EM), 65 patients (mean age±SD 47.8±8.5) with Chronic Migraine (CM) and 65 Healthy Controls (HC) (mean age±SD 43.7±9.3) were included in the study. In patients with CM, we identified, poor sleep quality (PSQI Mean±SD CM 8.25±3.39, EM 6.75±3.60, HC 5.70±3.19; p<.001, ISI (Mean±SD CM 8.98±5.92, EM 7.70±5.86, HC 5,51±4.57; p=.002), as well as higher levels of anxiety (STAI-2 Mean±SD CM 46.03±12.04, EM 42.05±10.02, HC 38.78±10.70; p=.002; ASI-3-PH Mean±SD CM 6.15±5.89, EM 4.66±4.15, HC 3.63±3.55; p=.01; ASI-3-ME Mean±SD CM 5.58±6.38, EM 4.66±3.95, HC 3.63±2.36; p<.001; TEMPS TOT (Mean±SD CM 128.95±82.97, EM 75.92±19.65, HC 74.88±18.03; p<.001) and a tendency to accentuate the threat value of painful stimuli (PCS TOT Mean±SD CM 27.23±13.82, EM 20.84±12.13, HC 15.59±8.57;p<.001).

Conclusions: Our data show that patients with CM have poor quality of sleep as compared to patients with EM and HC. Additionally, CM patients may show mood instability and hypervigilance in response to environmental stimuli, resulting in an increased tendency to engage in rumination and to accentuate the perception of pain.

Enlarging the spectrum of cluster headache: extracranial autonomic involvement revealed by voice analysis

F. Scotto Di Clemente[1], M. Silvestro[1], F.M. Dovetto[2], V. Corvino[3], P. Apisa[3], M. Rita[3], A. Tessitore[1], P. Milizia[4], E. Marciano[3], G. Tedeschi[1], A. Russo[1]

[1]Headache Center, Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy; [2]Department of Humanistic Studies, University of Naples Federico II, Naples, Italy; [3]Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples Federico II, Naples, Italy; [4]Department of Asia, Africa and the Mediterranean, University of Naples l'Orientale, Naples, Italy

Background: People with cluster headache (CH) are frequently burdened by misdiagnosis or diagnostic delay. The peculiar somatic and behavioral changes characterizing patients with CH are not useful to improve diagnostic accuracy. In our clinical experience, we noticed a typical voice quality with low and croaking tone in patients with CH.

Methods: In the present cross-sectional study, we evaluated, by digital voice analysis, whether it is possible to identify a typical voice quality characterizing patients with CH when compared to healthy controls (HC). Furthermore, to investigate whether putative differences in voice characteristics could be underpinned by constitutional aspects or pathological processes of vocal cords, subjects underwent a video-laryngostroboscopy. Smoking habits and alcohol consumption were deeply investigated. After the digital recording of the voices from both patients with CH and HC conducted in a soundproof insulating cabin in the laboratory of the Audiology Department, a set of voice parameters was analysed. We included the measures of fundamental frequency, calculations of jitter and shimmer, and noise-to-harmonics ratios as well as quantities related to the spectral tilt (i.e., H1-H2, H1-A1, H1-A2, H1-A3) in 20 patients with CH and in 13 healthy controls (HC). A video-laryngostroboscopy, was performed in all subjects.

Results: Patients with CH, explored during the cluster-bout period, showed significantly lower second harmonic (H1-H2) values compared with HC (-6.9 ± 7.6 vs 2.1 ± 6.7, p=0.002), usually characterizing the so-called creaky voice. By using a laryngoscopy investigation, a significantly higher prevalence of mild to moderate vocal cords oedema and laryngo-pharyngeal reflux signs have been found in patients with CH (100% of patients with CH vs 15% of HC, p<0.001).

Conclusions: Creaky phonation is a "physiological mode of laryngeal operation" usually underpinned by shortened and thickened vocal folds. Creaky voice phonation can be due to a reduced vocal folds capability to become slack or flaccid secondary to vocal cords oedema underpinned by laryngo-pharyngeal reflux affecting the phonatory mechanisms in patients with CH. The laryngo-pharyngeal reflux may represent a dysautonomic sign related

to the increased parasympathetic tone during in-bouts period, reinforcing the hypothesis of an extracranial autonomic dysfunction as part of CH clinical picture.

References:

Hoffmann J, May A. Diagnosis, pathophysiology, and management of cluster headache. Lancet Neurol. 2018;17(1):75-83.

May A, Schwedt TJ, Magis D, Pozo-Rosich P, Evers S, Wang SJ. Cluster headache. Nat Rev Dis Primers. 2018;4:18006.

Keating PA, Garellek M, Kreiman J. Acoustic properties of different kinds of creaky voice. In: The Scottish Consortium for ICPhS 2015 (Ed.), Proceedings of the 18th International Congress of Phonetic Sciences. Glasgow, UK: The University of Glasgow. 2015.

Huang WJ, Shu CH, Chou KT, Wang YF, Hsu YB, Ho CY, Lan MY. Evaluating the autonomic nervous system in patients with laryngopharyngeal reflux. Otolaryngol Head Neck Surg. 2013;148(6):997-1002.

Snoer A, Vollesen ALH, Beske RP, Guo S, Hoffmann J, Fahrenkrug J. Calcitonin-gene-related peptide and disease activity in cluster headache. Cephalalgia. 2019;39:575–584.

Is the multisensory integration different between migraine patients and healthy subjects? A study of concurrent visual and somatosensory stimulation

G. Sebastianelli, C. Abagnale, F. Casillo, M. Serrao, G. Coppola

Sapienza University of Rome Polo Pontino, Department of Medico-Surgical Sciences and Biotechnologies, Latina, Italy

Background: Merging of sensory information is an important process for all species. Both in humans and in animal models, co-application of bi-modal stimulations results in greater neural activation than the sum of each unimodal stimuli delivered independently. We tested how the same process of multisensory integration took place in migraine patients, by evaluating the potential ability of concurrent visual and somatosensory stimulations to affect the mechanisms of habituation, an indirect hallmark of cortical responsivity.

Methods: We recorded somatosensory evoked potentials (SSEPs) in nineteen healthy volunteers and in nineteen migraine patients before, during, and after simultaneous visual stimulation with a black-and-white checkerboard pattern-reversal. Six hundred sweeps were acquired for each condition and partitioned off-line in 2 blocks of 100 sweeps for the calculation of habituation as the slope of the regression line between the 1st and the 2nd block of averaged N20-P25 SSEP amplitude response.

Results: In both groups the visuo-somesthetic stimulation changed the SSEP N20-P25 habituation seen at baseline. In healthy subjects the concurrent stimulation provoked a loss of habituation (amplitude increment). In migraine patients, who had a deficient habituation at baseline, the simultaneous stimulation produced an amplitude decrement between 1st and 2nd block (habituation).

Conclusions: There is ample scientific evidence which sustains that migraine patients have an atypical way of processing unimodal information. Our result suggests that the multisensory integration is also affected, and this process could influence the migraine cycle modifying habituation and cortical responsivity, which may lower the migraine threshold and might trigger an attack.

References:

Stein BE, Stanford TR. Multisensory integration: Current issues from the perspective of the single neuron. Nat Rev Neurosci. 2008;9:255–266.

Schwedt TJ. Multisensory integration in migraine. Curr Opin Neurol. 2013;26:248–253.

Coppola G, Pierelli F, Schoenen J. Habituation and migraine. Neurobiol Learn Mem. 2009;92:249–259.

Allen AE, Procyk CA, Brown TM, Lucas RJ. Convergence of visual and whisker responses in the primary somatosensory thalamus (ventral posterior medial region) of the mouse. J Physiol. 2017;595:865–881.

Coppola G, Vandenheede M, Di Clemente L, Ambrosini A, Fumal A, De Pasqua V, Schoenen J. Somatosensory evoked high-frequency oscillations reflecting thalamo-cortical activity are decreased in migraine patients between attacks. Brain. 2005;128:98–10.

Patient preferences for self-injectable preventive treatments for migraine

J. Seo[1], T. Tervonen[2], C. Thomas[3], N. Krucien[3], J.H. Ford[4], V.L. Stauffer[4], R.A. Nicholson[4], K. Harrison Duffy[4], A. Tockhorn-Heidenreich[4], F. Torelli, Non-Author Presenter[5]

[1]Patient-Centered Research, Evidera, Bethesda, MD, USA; [2]Patient-Centered Research, Evidera, London, UK - Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [3]Patient-Centered Research, Evidera, London, UK; [4]Eli Lilly and Company, Indianapolis, IN, USA; [5]Eli Lilly and Company, Florence, Italy

Background: Multiple preventive treatments for migraine are available, including three different injectable calcitonin gene-related peptide monoclonal antibodies (CGRP mAbs), and oral standard of care. Treatment selection requires weighting of multiple treatment attributes, including administration, but little is known about migraine patients' perspective to date. The objective of this study was to elicit preferences of patients with episodic (EM) or chronic migraine (CM) for CGRP mAbs, with a focus on administration.

Methods: Adults from the USA, the United Kingdom (UK) and Germany with moderate to severe EM or CM and experience with migraine preventive treatments completed an online discrete choice experiment (DCE). Participants repeatedly chose between two self-injectable CGRP mAb autoinjectors and an oral alternative. Self-injectable CGRP mAb autoinjectors were described by seven attributes introduced to respondents by a video: 1) dosing schedule, 2) storage requirements, 3) base (of autoinjector) and pinching, 4) injection steps, 5) injection duration, 6) needle removal (from skin), 7) dose confirmation. A description of common side effects was included. Attributes were identified from a literature review and nine face-to-face focus groups (N=47) that involved hands-on injection simulations of unbranded autoinjectors and prefilled syringes. DCE data were analyzed using an error-component logit model (EC-MNL). Relative attribute importance (RAI) scores were obtained, with higher values indicating larger effects on preferences. Predicted choice probabilities of attribute profiles comparable to erenumab (US label), fremanezumab and galcanezumab were calculated from the EC-MNL estimates and standard errors were bootstrapped.

Results: 1,067 participants (N=366 USA; N=351 UK; N=350 Germany; 51.3% with EM; 52.6% female; mean age 41.2 (SD 11.9) years) completed the DCE. Participants preferred the self-injectable CGRP mAb autoinjectors over oral medication (non-CGRP) in 86.3% of choices. Participants valued shorter injection duration (reduction from 30 seconds to 5 seconds) as the most important attribute (RAI: 37.0%), followed by auto-retractable needle removal (RAI: 30.8%), storage at room temperature for 14 days instead of 1 day (RAI: 15.2%), and a wide base that required no pinching over a narrow base that required pinching (RAI: 12.5%). The form of dose confirmation (RAI: 3.4%), type of injection steps (RAI: 0.6%) and dosing schedule (RAI: 0.4%) were less important. Elicited preferences suggested a 34.0% [95% CI; 31.5% - 36.4%] probability of participants preferring a profile

comparable to galcanezumab over profiles comparable to erenumab (23.8% [95% CI; 22.2% – 25.5%]) or fremanezumab administered monthly (20.3% [95% CI; 19.0% – 21.6%]) or every 3 months (22.0% [95% CI; 20.4% – 23.5%]).

Conclusions: Participants tended to prefer self-injectable CGRP mAbs over oral (non-CGRP) preventive treatments for migraine. Preferences for autoinjectors were driven by injection duration, auto-retractability of needle removal, storage requirements and the type of autoinjector base and pinching requirements. Among self-injectable migraine preventive treatments, participants preferred a profile similar to that of galcanezumab.

Migralepsy: the two-faced Janus of Neurology

G. Sforza[1], C. Ruscitto[2], R. Moavero[2], F. Ursitti[1], M.A.N. Ferilli[1], S. Tarantino[1], M. Balestri[3], F. Vigevano[3], M. Valeriani[1], L. Papetti[1]

[1]Pediatric Headache Center, Department of Neuroscience, Bambino Gesù Children Hospital, IRCCS, Rome, Italy; [2]Child Neurology and Psychiatry Unit, Tor Vergata University of Rome, Rome, Italy; [3]Child Neurology Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

Introduction: Migraine is the most common type of primary headache in the pediatric population and the prevalence varies according to presenting age, going from 3% in younger children to ~20% in adolescents. Pediatric epilepsy is another frequent neurological condition, with a prevalence of approximately 3.2-5.5/1000 in developed countries. There is a large range of comorbidity between migraine and epilepsy: among patients with migraine, epilepsy can occur in 1-17% of the cases (as in the healthy pediatric population) while, among epileptic patients, the prevalence of migraine ranges from 7% to 26%.
The International Headache Society (IHS) in the International classification of headache disorders (ICHD-3 edition) identified three main associations between headache and epilepsy, including migraine-triggered seizure (migralepsy), hemicrania epileptica and postictal headache.
Migralepsy is defined as a seizure triggered by a migraine attack with aura: in particular, the seizure must fulfill the diagnostic criteria for a specific seizure, it has to occur in a patient suffering from migraine with aura, during, or within 1 hour of a migraine attack with aura. To date several cases of patients with migralepsy have been described, many of which have turned out to be cases of occipital epilepsy.

Discussion: We report three cases of pediatric patients suffering from migraine aura triggered seizures. All patients had a prior history of migraine with visual aura. They later developed seizures preceded by the typical visual aura. All patients started anti-epileptic therapy with seizure regression but continued to present migraine with aura. In all patients MRI was normal and interictal EEG presents epileptiform alterations. No patient recorded ictal EEG.
The purpose of this abstract was to discuss the clinical and instrumental features of migralepsy through the description of three clinical cases in which the symptoms of the usual migraine aura developed into a generalized tonic-clonic or focal seizure.

Conclusions: The term migralepsy should be replaced by migraine aura-triggered seizure. However, the criteria for diagnosis should be specified better. In particular, the recording of the visual phenomenon with an EEG should be considered a major diagnostic criterion. However, considering that the episodes can be very rare, thus difficult to be recorded by EEG, some clinical elements should be necessary for the diagnosis: 1) previous history of migraine with aura before the onset of epilepsy; 2) the visual aura triggering the epileptic seizure must have the same clinical features as the migraine visual auras not followed by

epileptic manifestations; 3) there must be a recurrence in the association between the visual aura and the epileptic seizure; and 4) visual symptoms should meet the VARS criteria. In our cohort of patients all the afore mentioned criteria were met at the same time and we think that this may be congruous with the diagnosis of “migraine aura-triggered seizure”.

Functional connectivity changes in complex migraine aura: beyond the visual network

M. Silvestro, A. Tessitore, F. Di Nardo, F. Di Clemente, F. Trojsi, M. Cirillo, F. Esposito, G. Tedeschi, A. Russo

Università della Campania "Luigi Vanvitelli", Napoli, Italy

Objective: Although the majority of migraine with aura (MwA) patients experiences simple visual aura, a discrete percentage also reports somatosensory, dysphasic or motor symptoms (the so-called complex auras). The wide aura clinical spectrum led to investigate whether the heterogeneity of aura phenomenon could be subtended by different neural correlates, suggesting an increased visual cortical excitability in complex MwA. We aimed to explore whether complex MwA patients are characterized by more pronounced connectivity changes of the visual network and whether functional abnormalities may extend beyond the visual network encompassing also the sensorimotor network in complex MwA patients when compared to simple visual MwA patients.

Methods: By using a resting state-fMRI approach, we compared the resting state functional connectivity (RS-Fc) of both visual and sensorimotor networks in 20 complex MwA patients in comparison with 20 simple visual MwA patients and 20 migraine without aura (MwoA) patients.

Results: Complex MwA patients showed a significantly higher RS-Fc of the left lingual gyrus, within the visual network, and of the right anterior insula, within the sensorimotor network, when compared to both simple visual MwA and MwoA patients ($p<0.001$). The abnormal right anterior insula RS-Fc was able to discriminate complex MwA patients from simple aura MwA patients as demonstrated by logistic regression analysis (AUC: 0.83).

Conclusions: Our findings suggest that higher extrastriate RS-Fc might promote the CSD onset representing the neural correlate of simple visual aura that can propagate to sensorimotor regions, if an increased insula RS-Fc coexists, leading to complex aura phenotypes.

Predicting response to greater occipital nerve block in migraine: a real-world study

V. Taranta, R. Ornello, C. Di Felice, V. Caponnetto, E. De Matteis, F. Pistoia, S. Sacco

Dipartimento di Scienze Cliniche Applicate e Biotecnologiche Università dell'Aquila, Italy

Background: Greater occipital nerve block (GONB) is commonly used in migraine treatment [1]. GONB could significantly reduce pain severity, the number of headache days in migraine patients and analgesic medication consumption [2]. There is currently no predictive marker for the effectiveness of GONB [3]. The present study aimed to report the efficacy and evaluate possible outcome predictors of GONB for the preventive treatment of migraine in a single center.

Methods: This observational study prospectively included consecutive migraine patients of both sexes, without age limits, treated according to clinical indication with GONB in the Headache Centers of Avezzano-L'Aquila. Patients were treated with bilateral local injections of methylprednisolone 40 mg/lidocaine 10 mg for each nerve. Patients kept a headache diary. We reported the decrease in monthly migraine days, median headache intensity (on a 0-10 Numerical Rating Scale) and doses of acute medication during the month following the first-ever GONB compared with the previous month. The proportion of patients reporting a ≥50% reduction in migraine days from the month before to the month after GONB was also reported. We performed chi-squared or Wilcoxon-Mann-Whitney tests to assess outcomes according to type of pain (implosive, explosive, ocular), pain lateralization (unilateral vs bilateral), and the presence of occipital tender points.

Results: We included 32 patients (81% female) with a median age of 51 years (interquartile range [IQR] 37–72); 9 patients (28%) were on treatment with oral migraine preventatives. Referring to the type of pain, 16 patients (53%) had explosive, 8 (27%) implosive, and 6 (20%) stabbing pain; 18 patients (58%) had unilateral pain. Furthermore, 17 (65%) patients had occipital tender points. After the first GONB, compared with the previous month, median migraine days decreased from 20 (IQR 10-30) to 10 (IQR 7-20; $p < 0.001$), median headache intensity from 8 (IQR 7-9) to 6 points (IQR 5-8; $p < 0.001$), and median doses of acute medication from 16 (IQR 7-30) to 8 (IQR 7-18; $p=0.004$). Eleven patients (32%) reported a ≥50% reduction in migraine days. The decrease in migraine days was independent of the presence of occipital tender points (between-group $p=0.144$); the decrease in acute medication doses was also independent of the presence of occipital tender points ($p=0.317$), while the decrease in headache intensity was higher in patients with occipital tender points compared with those without ($p=0.041$). The presence of unilateral pain or pain type did not have any impact on response to GONB. Notably, GONB decreased migraine frequency, intensity and medication use in all subgroups.

Conclusions: In this observational study in patients with migraine, there were benefits after GONB. According to our data, there are no predictors of GONB response based on migraine characteristics.

References:

1. Ashkenazi A, Blumenfeld A, Napchan U, Narouze S, Grosberg B, Nett R, DePalma T, Rosenthal B, Tepper S, Lipton RB; Interventional Procedures Special Interest Section of the American. Peripheral nerve blocks and trigger point injections in headache management - a systematic review and suggestions for future research. Headache. 2010;50(6):943-52.
2. Zhang H, Yang X, Lin Y, Chen L, Ye H. The efficacy of greater occipital nerve block for the treatment of migraine: A systematic review and meta-analysis. Clin Neurol Neurosurg. 2018;165:129–133.
3. Inan LE, Inan N, Unal-Artık HA, Atac C, Babaoglu G. Greater occipital nerve block in migraine prophylaxis: Narrative review. Cephalalgia. 2019;39:908-920.

Psychological symptoms, coping strategies and maternal stress: which relationship with adolescents' migraine frequency?

S. Tarantino[1], M. Proietti Checchi[1], L. Papetti[2], M.A.N. Ferilli[2], F. Ursitti[2], B. Spagnuolo[1], R. Moavero[2,3], G. Sforza[2], T. Grimaldi Capitello[1], F. Vigevano[2], M. Valeriani[2,4]

[1]Unit of Clinical Psychology, Bambino Gesù Hospital, Rome, Italy; [2]Headache Center, Division of Neurology, Bambino Gesù Hospital, Rome, Italy; [3]Child Neurology and Psychiatry Unit, Tor Vergata University of Rome, Italy; [4]Center for Sensory-Motor Interaction, Aalborg University, Aalborg, Denmark

Background: Although several studies evidenced a relationship between maladaptive coping strategies and migraine severity, there is a lack of data on the association between coping strategies, psychological symptoms and migraine severity in pediatric age; in particular, no study focused on the role of maternal stress on children's coping strategies, psychological profile and migraine features. We aimed to explore: 1) the coping responses to stressful events and their possible association with migraine severity in adolescents; 2) the role of maternal stress on their children's coping strategies, psychological profile and headache.

Methods: We studied 47 adolescents (m.a. 13.7±1.6 years; 8 M and 39 F). Patients were classified in: 1) high frequency (from weekly to daily episodes), and 2) low frequency patients (≤ 3 episodes per month). To evaluate adolescents' anxiety, depression and coping strategies we used respectively SAFA-A, SAFA-D and CRI-Y questionnaires. Maternal stress was analyzed by PSI-SF.

Results: Our data evidenced that patients tend to use a cognitive/avoidant coping style. In particular, we found a significant higher score in «Cognitive Avoidance» compared with «Emotional Discharge» and «Seeking guide and support» scales. CRI-Y scales did not show significant differences between the two migraine frequency groups ($p>0.05$). When we explored the relationship between maternal stress and patients' migraine, we found an association between maternal PSI-Parental Distress scale and high frequency migraine attacks ($p=0.025$). Moreover, in our study, maternal stress (PSI-Total scale) showed a significant and positive correlation with patients' feeling of guilt ($p=0.016$) and hopelessness ($p=0.003$). SAFA Anxiety did not show any significant correlation with maternal PSI scales ($p>0.05$).

Conclusions: Adolescents with migraine tend to use cognitive strategies of coping, with an avoidance response. Coping response to stressful events and parental stress show a relationship with adolescents' feeling of guilt ($p=0.016$) and hopelessness, which in turn may impact on migraine severity.

Eating disorders symptoms and migraine in adolescents: which relationship with the frequency of attacks?

S. Tarantino[1], M. Proietti Checchi[1], L. Papetti[2], M.A.N. Ferilli[2], F. Ursitti[2], B. Spagnuolo[1], R. Moavero[2,3], G. Sforza[2], T. Grimaldi Capitello[1], F. Vigevano[2], M. Valeriani[2,4]

[1]Unit of Clinical Psychology, Bambino Gesù Hospital, Rome, Italy; [2]Headache Center, Division of Neurology, Bambino Gesù Hospital, Rome, Italy; [3]Child Neurology and Psychiatry Unit, Tor Vergata University of Rome, Italy; [4]Center for Sensory-Motor Interaction, Aalborg University, Aalborg, Denmark

Background: Over time, several studies evidenced the role of anxiety and depression in migraine severity, both in adult and pediatric age. There is also evidence that psychological factors may mediate the association between body weight and headache frequency. So far, data on eating disorders in pediatric migraine are sparse. We aimed to investigate: 1) the prevalence of eating disorders symptoms in adolescents with migraine and, 2) to analyze the possible relationship between eating disorders symptoms, anxiety, depression and migraine frequency.

Methods: Thirty-five adolescent girls with migraine were included (mean age 13.7 ± 1.6 years). Given the low number of patients we excluded male patients from our analysis. Patients were classified in: 1) high frequency (from weekly to daily episodes), and 2) low frequency patients (≤3 episodes per month). The Italian SAFA battery of tests (Psychiatric scales for self-administration for youths and adolescents) was used to investigate anxiety, depression and eating disorder risk

Results: Our data evidenced that 21% of patients had scores in the range of risk for eating disorders. We found significant higher bulimic behaviour symptoms in patients with high frequency of attacks ($p=0.04$). Anorexic behaviour symptoms did not show significant differences between the two migraine frequency groups ($p>0.05$). A correlation between depressive symptoms, bulimic ($p=0.00$) and anorexic ($p=0.00$) behaviour symptoms was found. In particular, in high frequency of attacks group, bulimic behaviour symptoms showed a significant positive correlation with patients' hopelessness feelings ($p<0.00$).

Conclusions: Our data suggest that depression may mediate the association between bulimic behaviour and migraine frequency. We suppose that depressive symptoms, and in particular hopelessness, may lead to bulimic behaviour; these symptoms may, in turn, influence the frequency of migraine.

Additive interaction between Onabotulinumtoxin-A and Erenumab in patients with refractory migraine

L. Tartaglione, M. Silvestro, A. Tessitore, F. Scotto Di Clemente, G. Battista, G. Tedeschi, A. Russo

Headache Centre, Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy

Background: In the last decade, notable progress has been observed in chronic migraine preventive treatments. According with the European Headache Federation and national provisions, Onabotulinumtoxin-A (BTX-A) and monoclonal antibody acting on the pathway of calcitonine gene-related peptide (CGRP-mAbs) should not be administered in combination due to supposed superimposable mechanism of action and high costs. On the other hand, preclinical observations demonstrated that these therapeutic classes, although operating directly or indirectly on the CGRP pathway, act on different fibers. Specifically, the CGRP-mAbs prevents the activation of the Aδ-fibers whereas BTX-A acts on C-fibers. Therefore, it can be argued that a combined therapy may provide an additive or synergistic effect on the trigeminal nociceptive pathway.

Methods: In the present study, we report a case series of 10 chronic migraine patients who experienced significant benefits with the combination of both Erenumab and BTX-A compared to each therapeutic strategy alone.

Results: A reduction in frequency and intensity of headache attacks was observed in migraine patients treated with a combined therapy with BTX-A and Erenumab compared to both BTX-A and Erenumab alone. Moreover, the combined therapy with BTX-A and Erenumab resulted in a statistically significant reduction in the symptomatic drugs intake and in migraine-related disability probably related to a reduced necessity or also to a better responsiveness to rescue treatments.

Conclusions: Present data suggest a re-modulation of current provisions depriving patients of an effective therapeutic strategy in peculiar migraine endophenotypes.

References:

Digre KB. What's New in the Treatment of Migraine? J Neuroophthalmol. 2019;39(3):352-359.

Pellesi L, Do TP, Ashina H, Ashina M, Burstein R. Dual therapy with Anti- CGRP monoclonal antibodies and botulinum toxin for migraine prevention: is there a rationale? Headache. 2020;60:1056–65.

Armanious M, Khalil N, Lu Y, Jimenez-Sanders R. Erenumab and Onabotulinumtoxin A combination therapy for the prevention of intractable chronic migraine without aura: a retrospective analysis. J Pain Palliat Care Pharmacother. 2020;30:1–6.

Do TP, Hvedstrup J, Schytz HW. Botulinum toxin: a review of the mode of action in migraine. Acta Neurol Scand. 2018;137:442–51.

Tessitore A, Russo A. Is targeting CGRP the right pathway to prevent migraine? Lancet. 2019;394:984–6.

Psychological impact and parental stress of primary headaches in pediatric age: a case-control study

I. Toldo[1], L. Galdiolo[1], S. Sartori[1], M. Nosadini[1], C. Angelico[2], M. Gatta[2], M. Miscioscia[2], D. Di Riso[3]

[1]Centro Cefalee dell'età evolutiva, Dipartimento della Salute della Donna e del Bambino, Università degli Studi di Padova, Padua, Italy; [2]UOC NPI, Dipartimento della Salute della Donna e del Bambino, Università degli Studi di Padova, Padua, Italy; [3]Dipartimento di Psicologia dello Sviluppo e della Socializzazione, Università degli Studi di Padova, Padua, Italy

Background: Primary headaches have a strong impact on the quality of life and on the family sphere and can be associated with anxious-depressive symptoms and difficulties in parenting and familial relationships.
The objectives of the present study are: to verify whether internalizing symptoms and separation anxiety symptoms are more frequent in subjects with primary headache than in controls, to understand if the headache affects functional and proactive coping strategies and if it determines greater emotional instability and, finally, to evaluate parental stress in subjects with primary headaches compared to controls.

Methods: Prospective case-control study: 50 cases (age 8-17 years) with primary headaches (migraine or tension-type headache according to the diagnostic criteria of ICHD-III, 2018) and 50 age- and gender-matched healthy controls.
Collection of clinical data, administration of questionnaires for children and adolescents: Children's Coping Strategies Checklist (CCCSC-R1); Emotion Awareness Questionnaire (EAQ-30); Positive and Negative Affect Schedule (PANAS); Separation Anxiety Assessment Scale (SAAS-C, 8-11 years) or Positive and Negative Affect Schedule (PANAS; 12-17 years); Strengths and Difficulties Questionnaire (SDQ); PEDmidas (only for cases). Administration of questionnaires for parents: Positive and Negative Affect Schedule (PANAS), Parenting Stress Index (PSI-SF), Strengths and Difficulties Questionnaire (SDQ).
Statistical analysis conducted with SPSS ("Statistical Package for Social Science") software. Level of test significance: $p \leq 0.05$.

Results: The SDQ questionnaire revealed a higher prevalence of emotional difficulties in cases (M=4.56; SD=2.54) compared to controls (M=3.37; SD=2.48) (p=0.02).
In the PANAS questionnaire, negative affect tended to be greater in cases (M=29.4; SD=6.7) compared to controls (M=26.8; SD=5.8) (p=0.06).
In the CCSC-R1 questionnaire, "Positive Cognitive Restructuring" correlated positively with disability (PEDmidas: disability 0.31; $p<0.05$). In the EAQ questionnaire, the "Analysis Own Emotion" subscale negatively correlated with disability (PEDmidas: disability -0.29; $p<0.05$), furthermore the "Differentiating Emotion" and "Verbal Sharing" subscales negatively correlated with headache frequency (respectively PEDmidas: frequency -0.36; $p<0.05$ and PEDmidas: frequency -0.37; $p<0.01$); finally, the "Not Hiding Emotions" subscale correlated

negatively both with headache frequency and disability (PEDmidas: frequency -0.44; $p<0.01$ and PEDmidas: disability 0.31; $p<0.05$).

Conclusions: In the present study, children and adolescents with primary headache, compared to healthy controls, had greater internalizing and emotional difficulties, which worsened with the aggravation of the headache in terms of disability and frequency, making the subject even more vulnerable in implementing internalizing strategies to cope with the situation.
Subjects with headache used dysfunctional coping strategies to cope with pain, in proportion to the increasing severity of the headache disorder.
Subjects with primary headache experienced more negative affects than controls, had greater difficulties in discriminating and analyzing emotions, sharing them verbally and not hiding them, which correlated with headache disability and frequency. This attitude leads the subject with headache to implement more internalizing behaviors in an attempt to manage the affective states that the patient does not know how to deal with effectively.
This study contributes to the relevant literature with a new assessment focused on the regulation and emotional awareness of subjects with primary headache in the developmental age, with possible relapses in the clinical management of these subjects.

Chiari 1 malformation-related headache in pre-school-aged children

F. Ursitti[1], L. Papetti[1], M.A.N. Ferilli[1], G. Sforza[1], R. Moavero[2], S. Tarantino[1], C. Ruscitto[2], F. Vigevano[1], M. Valeriani[1]

[1]Headache Center, Child Neurology Unit, Bambino Gesu' Children's Hospital, Rome, Italy; [2]Child Neurology and Psychiatry Unit, Tor Vergata University of Rome, Italy

Background: In children, the onset and the clinical characteristics of headache are fundamental for differential diagnosis between primary and secondary headache. Chiari I malformation (CM1) is a common incidental finding on neuroimaging studies. Studies suggest that approximately 1% of the population has CM1 and that most of these patients are asymptomatic. In a few cases CM1 can cause a variety of symptoms including headache, nystagmus, dysphagia, sensorimotor disturbances, and sleep disordered breathing. Surgery is recommended for the treatment of symptomatic CM. Literature regarding the natural history of CM1 is greatly limited. We report our experience of three children, mean age of 3.3 years, that were brought to our observation for a headache and showed CM1 at brain MRI. Particular attention was paid to the characteristics of the headache.

Methods: First case was a female, 2 years and 6 months of age, with headache localized in the occipital region, with daily frequency and severe intensity of pain; episodes were present during physical activity, running, loud laughter and started ten months before. No other symptoms were associated, as photo/phonophobia, nausea or vomiting; no alterations of sleep reported. No response to paracetamol. A brain MRI was performed and a Chiari malformation 1 was observed. Spinal cord MRI and sensorial potentials were normal.
Second case was a female, 2 years and 8 months of age, from 2 months suffered of headache localized at the occipital region. They lasted a few hours and had an intermittent pattern. Frequency unclear. Paracetamol not effective. Coughs and colds triggered headaches and the cough accentuated it even more. Equivalents and family history of headache were not reported. Brain MRI showed a MC1 with descent of cerebellar tonsils of 17 mm; spinal cord MRI showed alteration of the cervical medullary signal. She underwent occipito-cervical and duroplastic decompression surgery with improvement of symptoms.
The last case was a male, 4 years and 10 months of age, with a history of headache from the age of 3, with a variable frequency; pain localized in the occipital region and severe intensity; the symptoms associated were pallor, nausea, vomiting and photophobia. Paracetamol was partially effective. In his familial history the mother suffered from migraine. MRI showed a CM1 (8-9 mm) and spinal cord MRI was normal. Elevated frequency of headache, non-responder to paracetamol and ibuprofen and because of evidence of an increased space in the optic nerve due to the presence of cerebrospinal fluid, he underwent atlanto-occipital and duroplastic decompression intervention.

Results: Treatment of CM1-related headaches is difficult because pain in the occipital region or coughing headache suggests symptomatic CM1, but children may suffer migraine or tension-type headache. In our cases age of onset, clinical characteristics and triggers of headache are principal factors that could suggest performing neuroimaging.

Conclusions: Onset of headache at an early age, occipital localization during coughing and absence of familial history lead to suppose secondary causes, such as CM1.This can be treated surgically, although not in all cases headache resolves after surgery.

One-year treatment with erenumab in difficult-to-treat patients: how does it affect chronic migraine course?

G. Vaghi[1,2], R. De Icco[1,2], E. Guaschino[1], S. Bottiroli[1,3], N. Ghiotto[1], M. Allena[1] C. Tassorelli[1,2], G. Sances[1]

[1]Headache Science & Neurorehabilitation Center, IRCCS Mondino Foundation, Pavia, Italy; [2]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy; [3]Giustino Fortunato University, Benevento, Italy

Background: Recently, monoclonal antibodies (mAbs) targeting the CGRP pathway have deeply transformed the scenario of migraine preventive therapies. To date, four mAbs are available: three directed against the CGRP and one directed against the CGRP receptor, namely erenumab. The aim of this study was to evaluate migraine pattern in chronic migraineurs, with and without medication overuse headache, during one-year treatment with erenumab.

Methods: Our population was composed of 82 middle aged patients (F59, M23; mean age: 49.5±9.8 years) with a long history of chronic migraine (12.9±10.7 years) who had already failed at least 3 preventive therapies. The most represented comorbidities (59%) were psychiatric conditions (e.g. depression and anxiety). Erenumab (70-140mg) was administered monthly for 13 treatments (T1 through T13). Thirteen patients (16%) interrupted treatment: 11 subjects for poor efficacy, after a mean of 7.3 months. We collected clinical data on headache features (diaries), disability (MIDAS, HIT-6), allodynia, anxiety and depression scales (questionnaires e.g. HADS-A and HADS-D) at baseline (T_0) and quarterly. Statistical analysis was conducted using ANOVA for repeated measures and consequent post-hoc tests.

Results: Patients experiencing a reversal pattern from chronic to episodic migraine (i.e.>50% responders) were 31.5% at T_1, rising to 68.5% at T_{13}. Super-responders (i.e.>75% responders) were 9.7% at T_1, reaching 34.3% at T_{13}. A significant reduction in migraine days and symptomatic intake was already detected after T_1 and persisted over one-year treatment: monthly headache days (T_0 23.8 ± 5.4, T_{13} 10.5 ± 8.2), monthly acute medication doses (T_0 31.9 ±25.4, T_{13} 8.1±7.4) and days of drug intake (T_0 20.3+7.5, T_{13} 6.8+4.6), $p<0.001$ for all variables at all time points vs T_0. This data also had a repercussion in disability and quality of life. MIDAS and HIT-6 scores improved soon after the first months of treatment ($p<0.001$ T_3 vs T_0), allodynia intensity decreased significantly from T_6 (T_6 vs T_0: $p<0.001$). Whereas anxiety and depression self-questionnaires presented a significant reduction from the ninth treatment compared to baseline (T_9 vs T_0: HADS-A $p=0.03$, HADS-D $p=0.01$). The treatment was well tolerated as only mild side effects were reported by 50% of patients, predominantly constipation, fatigue and local cutaneous reaction.

Conclusions: Erenumab is related to a high percentage of pattern reversal in difficult-to-treat patients. This mAb determines an early improvement in clinical features already during the 1st month of treatment, and in headache-related disability just after a few months. Efficacy is maintained over the long-term showing a positive tolerability profile.

Galcanezumab effectiveness in chronic migraine with and without medication overuse headache

G. Vaghi[1,2], R. De Icco[1,2], E. Guaschino[1], M. Allena[2], C. Tassorelli[1,2], G. Sances[1]

[1]Headache Science & Neurorehabilitation Center, IRCCS Mondino Foundation, Pavia, Italy;
[2]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy

Background: At the end of 2018 the development of a new specific drug type against migraine shook up the existent preventive migraine therapy landscape. Nowadays, there are four known monoclonal antibodies (mAbs) directed against CGRP peptide, of which three act against the ligand (specifically: eptinezumab, galcanezumab, fremanezumab) and one against the receptor (namely erenumab). The aim of our work was to evaluate one-year effectiveness of galcanezumab in patients with chronic migraine (CM) with and without medication overuse headache.

Methods: Our starting population was composed of 26 patients (F22, M4) with a mean age of 53 years and a mean migraine history equal to 38 years. They all previously failed at least 3 preventive therapies. Galcanezumab was administered monthly for 12 treatments (T_1 through T_{12}) with a loading dose of 240 mg and a maintenance dose of 120 mg. Two patients interrupted treatment for inefficacy at T_7 and T_9. We collected clinical data on headache features (through daily diaries) and disability and allodynia (through standardized questionnaires) at baseline and quarterly. Statistical analysis were conducted using ANOVA for repeated measures and consequent post-hoc tests.

Results: After the 1st dose of treatment (T_1) an improvement was detected in all clinical parameters, the same trend persisted over one-year treatment. Specifically: monthly headache days T_0 24.9$\pm$1.1SE, T_1 16.1$\pm$1.7, $T1_2$ 12.8$\pm$1.9,), monthly acute medication doses (T_0 51.2$\pm$10.4, $T_1$7.6$\pm$1.4, T_{12} 10.4$\pm$1.7) and days of intake (T_0 25$\pm$2.2, T_1 6.9$\pm$1.2, T_{12} 8.2$\pm$1.6). Statistical analysis detected significance for all the above-mentioned parameters ($p<0.001$ for T_1 and T_{12} vs T_0).Patients presented a high percentage of pattern reversal from chronic to episodic migraine (categorised as the number of patients who showed a reduction in monthly migraine days higher than 50% compared to baseline). They were 42% at T_1, rising to 62% at T_{12}, with a growing percentage of super-responders (i.e. >75% responders) growing from 8% at T_1 to 21% at T_{12}. An improvement in MIDAS and HIT-6 scores was present from T_3 ($p<0.001$), while allodynia intensity decreased significantly from T_{12} ($p=0.03$). Only mild side effects were reported by 33% of patients, predominantly constipation, cutaneous reaction and fatigue.

Conclusions: Galcanezumab is related to a high percentage of pattern reversal in difficult-to-treat patients and to a significant improvement in clinical features, already during the 1st month of treatment, and in headache-related disability after a few months. Efficacy is maintained over the long-term showing a positive tolerability profile.

Three-month erenumab suspension in chronic migraineurs: a real life experience

G. Vaghi[1,2], V. Bitetto[1,2], R. De Icco[1,2], E. Guaschino[1], N. Ghiotto[1], C. Tassorelli[1,2], G. Sances[1]

[1]Headache Science & Neurorehabilitation Center, IRCCS Mondino Foundation, Pavia, Italy; [2]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy

Background: The growing evidence of CGRP monoclonal antibodies (mAbs) efficacy, and their wider use as migraine preventive therapies, have recently led to their prescription through the National Health System according to Italian local regulations (AIFA). Until June 2021, AIFA required a 3-month interruption period of mAbs after a 12-month course. Limited data were available on the persistence of their effect during interruption. Here, we report migraine pattern during the suspension period in chronic migraine patients.

Methods: We investigated 65 chronic migraineurs, mostly women (45 females and 20 males), with a mean age equal to 49.2+9.3 years and a long history of chronicity (mean: 11.4 years). All patients were administered a monthly dose of erenumab for over a year (mean treatment duration 17±5.6 months) before the mandatory suspension. We evaluated changes in monthly headache days, monthly medication doses and days of drug intake, as well as migraine related disability through MIDAS questionnaire. Analyses were conducted with ANOVA for repeated measures at baseline (T_0), at the end of treatment (T_{end}) and during the suspension period.

Results: We detected a significant improvement for all migraine features at the end of erenumab administration compared to baseline *(*$p<0.001$, for all): monthly headache days (T_0 23.6$\pm$5.5, T_{end} 10.1$\pm$7), monthly medication doses (T_0 30.1$\pm$25.3, T_{end} 8.2$\pm$5.8) and days of drug intake (T_0 19.7$\pm$7.7, T_{end} 7.1$\pm$4.3). Whereas, all parameters significantly worsened ($p<0.01$, for all) already in the 1st month of suspension when compared to T_{end} (monthly headache days 14$\pm$6.7, monthly medication doses 13.7$\pm$14.5, days of drug intake 10.5$\pm$6.1). They all maintained a worsening pattern over the subsequent 2 months. Though significantly worse, the clinical conditions observed in the last month of suspension were still better than T_0 values. Finally, MIDAS significantly worsened accordingly (T_{end} 18.9+26.1, after three-month- stop 45.3+37.2, $p<0.001$).

Conclusions: Erenumab suspension was associated with an early and progressive worsening of headache-related parameters and disability. Even though efficacy was partially maintained, MIDAS changes reflected a severe disability. Thus, our data strongly support the reduction of the suspension period down to 1 month, in order to allow prolonged treatment in migraine subjects resistant to other preventive therapies.

Headache occurrence after Covid-19 vaccination in migraine patients under treatment with anti-CGRP monoclonal antibodies

A. Vaiano, E. Cresta, A. Bellotti, G. De Vanna, I. Corbelli, P. Sarchielli

Clinica Neurologica, Dipartimento di Medicina, Università degli Studi di Perugia, Perugia, Italy

Background: Vaccination represents the cornerstone for contrasting the ongoing coronavirus disease 2019 (COVID-19) pandemia. Serious side effects are extremely rare following COVID-19 vaccination. Headache is one of the most frequent adverse events referred by vaccinated people.
In a recent research headache incidence after vaccination was significantly higher in migraine (69.2%) and non-migraine headache (71.4%) patients than in healthy controls [1].
According to the public Italian Medicines Agency (AIFA) database of Adverse Drug Reactions, the rate of headache/migraine episodes voluntarily reported by COVID-19 vaccine recipients, up to May 9, 2021, was 129, 103, and 21 per 100,000 for Astra Zeneca, Pfizer, and Moderna vaccines, respectively. The cumulative rate of headache/migraine episodes after receiving all COVID-19 vaccines was 2.25-fold higher than the daily frequency of headache disorders (37 per 100,000 people) [2].
The aim of the present study was to verify the occurrence of headache in migraine patients undergoing anti-calcitonin-gene-related peptides (CGRP) monoclonal antibodies (mAb) treatment after the first and second doses of the COVID-19 vaccination.

Methods: Fifty-nine migraine patients (19 M and 40 F; 23-74 years old) attending the Headache Center treated with anti-CGRP (mAb) for at least 3 months were enrolled. Patients failing to respond to at least 3 prophylactic drug classes were included in the anti-CGRP (mAb) treatment, of these, 35 suffered from high frequency episodic migraine and 24 complained of chronic migraine. They received erenumab (N=29) or fremanezumab (N=16) or galcanezumab (N=14). All patients included in the study received the first and second doses of one of the COVID vaccines authorized in Italy (9 Astra Zeneca, 41 Pfizer, 7 Moderna, 2 Johnson & Johnson).
The characteristics and duration of headache were recorded after the first and second doses of the COVID vaccine. Other concomitant side effects were also registered.

Results: Only a minority of migraine patients (N=14) under anti-CGRP (mAb) treatment complained of headache after receiving the first dose of vaccine: 7 Pfizer, 5 Astra Zeneca, 2 Moderna.
The same results were found in 12 patients after the second doses: 9 receiving Pfizer, 1 Astra Zeneca and 2 Moderna vaccines.
Headache was referred as very severe and long lasting only by a few patients after the first dose (N=2) and the second dose of COVID vaccination (N=2).
In a minority of cases, headache differed from the typical migraine attacks and was referred as dull holocranial, mainly with tension-type features by 2 patients after the first dose and by 4 patients after the second dose.

In the few patients complaining of headache after receiving the second dose of the COVID vaccination (N=4) a transient but slight increase in the frequency of migraine attacks was recorded in the following 2 months.

Conclusions: Based on these preliminary results treatment of migraine patients with anti-CGRP monoclonal antibodies appears to be protective against headache development as a side effect of COVID-19 vaccination. This is independent of the three currently approved COVID-19 vaccines administered.

References:

1. Sekiguchi K, Watanabe N, Miyazaki N, Ishizuchi K, Iba C, Tagashira Y, Uno S, Shibata M, Hasegawa N, Takemura R, Nakahara J, Takizawa T. Incidence of headache after COVID-19 vaccination in patients with history of headache: A cross-sectional study. Cephalalgia. 2021 Aug 18:3331024211038654.
2. Mattiuzzi C, Lippi G. Headache after COVID-19 vaccination: updated report from the Italian Medicines Agency database. Neurol Sci. 2021;42(9):3531-3532.

Società Italiana per lo Studio delle Cefalee

Tel. 075 585 8181
Fax 075 578 4229
sisc@sisc.it
www.sisc.it

SEGRETERIA ORGANIZZATIVA

Planning Congressi Srl
Via Guelfa 9
40138 Bologna
Tel. +39 051 300100
Fax +39 051 309477
r.cantelli@planning.it
www.planning.it