Focal gray matter decrease in the cerebral pain network of migraine patients

XX National Congress of the Italian Society for the Study of Headaches

Headaches: acquisitions and controversies

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PROCEEDINGS OF XX NATIONAL CONGRESS OF THE STUDY OF HEADACHES

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PREFACE

Like last year, it is a renewed privilege for me to introduce the proceedings of our annual scientific and social forum, the National Congress of the Italian Society for the Study of Headaches, *Headaches: acquisitions and controversies*, this year in its XXth edition.

The chosen topics cover many fields, the developments of which need to be reviewed critically, confronted with original results from the numerous different interdisciplinary research groups of our large and scientifically very productive society.

The main issues, from the genetics of primary headaches to the socioeconomic aspects; from the considerations regarding the ICHD-II criteria to the problem of cortical excitability; from headache as an emergency condition in childhood and adolescence to psychopathological factors, will be dealt with. On the frontline of therapy, the intriguing problem/resource of the placebo will also be discussed, along with the strategies in using triptans and the new perspectives of preventative therapies. The difficulties of managing the chronic patient and the often related problem of drug misuse/abuse will also be specifically addressed.

Along with invited lectures and round tables, a workshop and pros and cons sessions have been organised to expand the modalities of congressional debate. Two scientific sessions have been planned in cooperation with the Italian Society of Internal Medicine and with the Italian Association of Ambulatorial and Territorial Neurologists, underlying the multidisciplinary nature of our society and our commitment with other societies in order to provide more integrated answers to patients' needs.

This year's contributions emphasise the continuous growth of our society. The great increase in the number of submissions from a significantly larger number of members prompted the Scientific Committee to organise a new session entitled *Oral communications with posters*. Its aim is to give evidence both to the oral presentation and to the wealth of data that only a poster can offer, so that results can, firstly, be pointed out orally, in front of the plenary audience, and secondly, discussed at length individually with those colleagues who are specifically interested in the topic.

As you will have noticed, the Congress Proceedings are now peer-reviewed abstracts, in keeping with the modalities adopted by other large, authoritative societies. Furthermore, the abstracts of the Congress are no longer printed in a supplement, but within *The Journal of Headache and Pain*, which since last January has become the official journal of the European Headache Federation (EHF) – a significant gesture of esteem towards our society by the EHF and a

recognition of the quality of *The Journal of Headache and Pain*. Being hosted in a regular issue of the journal gives the congresses of the European national societies – in this case ours – a vast international audience, fostering mutual knowledge and cooperation.

The location of the Congress in Rome, after the previous one in Padua/Venice, continues a choice that connects science and culture. Along with an excellent scientific programme, participants will be able to enjoy the artistic and historical atmosphere that only the "Città Eterna" can offer. On this occasion, I wish to thank, also on behalf of our society, all those who have helped to organise this XXth SISC Congress and contributed to the preparation of the proceedings: my Co-President of the Congress, Professor Girolamo Di Trapani; the Scientific Committee and Secretariat; the Local Organizing Committee; the entire Executive Committee of the Italian Society for the Study of Headaches; and our generous Sponsors. And last, but not least, all of you, who continuously work with your patients and in your labs to promote new developments to relieve the burden of headache.

A warm, friendly welcome to Rome, with wishes of a very fruitful, scientifically and socially rewarding congress.

Giorgio Zanchin
President
Italian Society for the Study of Headaches

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ORAL PRESENTATIONS

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KEY LECTURES

GENETICS OF TENSION-TYPE HEADACHE

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Objective To analyze the importance of genetic and environmental factors in tension-type headache.
Subjects and methods Review of literature.
Results A family study of chronic tension-type headache suggested that genetic factors are important due to a 3-fold significantly increased risk of chronic tension-type headache among first degree relatives compared to the general population. A twin study suggested that tension-type headache is caused by 81% non-shared environmental effects and of 19% additive genetic effects. Another twin study suggests that no and frequent episodic tension-type headache is partly inherited due to a significant higher concordance rate among monozygotic than dizygotic twin pairs, while infrequent episodic tension-type headache is caused by environmental factors. Data for chronic tension-type headache were inconclusive.
Discussion The first twin study was based on twin pairs with co-occurrence of tension-type headache and migraine. This probably biased the result, since migraine increases the risk and frequency of tension-type headache. The family study of chronic tension-type headache was a clinic population and some of the probands had co-occurrence of migraine and tension-type headache, which may have caused overestimation of the family risk.
Conclusions Genetic factors are likely to play a role in no and frequent episodic tension-type headache. Infrequent episodic tension-type headache is caused primarily by environmental factors. Chronic tension-type headache may be inherited but the data are too limited to allow firm conclusions.

THE ROLE OF PLACEBO IN HEADACHE RESEARCH

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For a long time it has been known that almost any treatment or procedure used in headache patients will lead to an improvement. This is true for the treatment of headache attacks and the prevention of headache. The concept of controlled randomised trials revealed that placebos have a profound effect in headache patients. The consequence was that most modern trials in the treatment of headache use placebo groups. The responder rate to placebo depends on the endpoint and is around 20%–30% for improvement of headache in trials treating acute headache events and around 30% in prevention trials. Originally, it was assumed that the placebo effect would decrease over time. Long-term studies with topiramate or botulinum toxin, however, showed that the effect of placebo lasts over 6 or 9 months. Subcutaneous placebo is more effective than oral placebo. In the U.S.A. and in Southern Europe the placebo response is higher than in Northern Europe. Children and adolescents have a much higher placebo response than adults. Expectation will play a major role, when the randomisation ratio between placebo and verum is known. The quality of a trial has no influence on the placebo responder rate. Placebos can lead to side effects. In trials treating anxiety, placebo resulted in headache in 20% of the patients. Information about possible weight gain in a migraine prevention trial resulted in profound increase in body weight in the placebo run-in phase. Placebo might have a similar mode of action as "real" drugs. PET and functional MRI studies indicate that placebo will activate similar brain structures as opioids.

ICHD-2 AND ITS REVISION

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ICHD-2 features many improvements over the first edition of The International Headache Classification. Perhaps the single most important change is the introduction of the entity medication-overuse headache (MOH). The strengthening of the causal relations under secondary headaches, the changes regarding migraine with aura and the introduction of a number of new entities are also important. Subsequently, the introduction of chronic migraine was criticised because it was extremely demanding and very few patients would fit into these criteria. In order to include a reasonable number of patients with frequent migraine and headache on 15 days or more per month, new appendix criteria for chronic migraine were published. Also the criteria for MOH were changed. It is now a default rule that, if patients have a medication-overuse and a primary headache they must receive the diagnosis of medication-overuse headache.
A last major remaining problem is the Classification of secondary headaches, where improvement or disappearance of headache is requested after removal of the causative disorder. This means that patients cannot actually receive the diagnosis while they still have the headache.
This latter problem and other problems will be dealt with subsequently by the Classification Committee and revised appendix criteria will be printed in Cephalalgia. It is the hope that these appendix criteria will subsequently be tested and that results will justify the changes so that they can be included in a future revised version of the ICHD-2.

MIGRAINE HEADACHES: FROM MODELS TO MECHANISM

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Experimental and clinical findings established a firm scientific foundation for the notion that cortical spreading depression (CSD) underlies migraine visual aura and perhaps other migraine auras. Recent reports found that CSD activates trigeminal afferents innervating the meninges, and that this activation travels to the brainstem to trigger parasympathetic efferents promoting vasodilation within the dura mater. This provides strong evidence that neurovascular changes within the dura mater develop as a consequence of CSD in experimental animals. When acute abortive anti-migraine drugs were administered in this paradigm, the drugs suppressed evidence of CSD-induced trigeminovascular activation. Hence, intrinsic activity within the forebrain causes sustained vasodilation of meningeal blood vessels via parasympathetic reflex activation. We also found that CSD causes activation of a class of enzymes called "matrix metalloproteinases" (MMPs) in brain. These enzymes are activated within vessels early after CSD (contiguous depolarization of neurons and glia) and remain so for nearly 48 hours. MMPs are constituents of an inflammatory cascade within the brain triggered by the generation of reactive oxygen species (e.g. nitric oxide (NO)) and provide indirect evidence for upregulation of a pro-inflammatory state in brain and its connective tissue coverings. Evidence from Reuter and colleagues implicate meningeal inflammation as an important mechanism driving the delayed headache response to nitroglycerin. Infusion of

nitroglycerin caused upregulation of the inducible isoform of NO synthase (NOS) and NO within resident dural macrophages, meningeal oedema, cytokine activation and evidence implicating NF-kB, a proinflammatory transcription factor. CSD is not part of the pathophysiology of delayed nitroglycerin headache.

In some migraine subtypes, genes controlling translocation of Ca^{2+}, sodium and potassium ions have been implicated in migraine pathophysiology, perhaps altering the susceptibility to CSD. Environmental factors may modulate individual susceptibility by lowering the CSD threshold. Recently, mice carrying a human familial hemiplegic migraine-1 mutation were shown to express an abnormally low CSD threshold, and this phenotype was associated with enhanced neurotransmitter release.

More recent experimental data provide evidence that widely-prescribed migraine prophylactic drugs (topiramate, valproate, propranolol and amitriptyline, and methysergide) suppress CSD in experimental animals when administered chronically. These drugs dose-dependently suppress CSD frequency by 40%–80% and increase cathodal stimulation threshold. Acute treatment was ineffective. This previously unknown coherent action provides a potential common physiological target for the most widely used prophylactic compounds in migraine. It also opens up the possibility to develop more effective migraine prophylactic drugs to target specific cellular and molecular mechanisms underlying CSD or a physiological event in human brain closely related to it. Together these experimental data support the conclusion that CSD is an important underlying event in migraine pathophysiology.

NEUROGENIC INFLAMMATION: FURTHER THERAPEUTIC PERSPECTIVES

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Abnormal activation of neuropeptide-containing neurons of the trigeminal ganglia may initiate and/or maintain the pathophysiological processes that eventually result in migraine headache and associated phenomena [1]. A subpopulation of polymodal A-δ and C primary sensory neurons of dorsal root ganglia (DRG) and trigeminal ganglia is characterized by the ability to synthesize and release diverse neuropeptides, including calcitonin gene-related peptide (CGRP) and tachykinins, substance P (SP) and neurokinin A (NKA). CGRP, SP and NKA released from the peripheral endings of primary sensory neurons cause a series of proinflammatory responses at the vascular and extravascular levels collectively referred to as "neurogenic inflammation". If SP/NKA *via* activation of NK1 receptors increase the extravasation of plasma protein in meningeal postcapillary venules, CGRP via activation of specific receptors on vascular smooth muscle dilates intra- and extracranial arteries. Capsaicin has the unique ability to excite (and at high doses desensitize) an ion channel (TRPV1) expressed in sensory neurons, thus producing burning pain and releasing sensory neuropeptides. Triptans are specific antimigraine drugs, acting on serotonin 5-$HT_{1B/1D}$ receptors, which, among other actions, by this mechanism inhibit sensory neuropeptide release from peripheral and central endings of trigeminal neurons. It is possible that a major component of the efficacy of triptans in migraine is due to inhibition of neurogenic inflammatory responses. However, the role of plasma protein extravasation mediated by NK1 receptor activation by SP/NKA in migraine has been questioned by the negative results obtained in more than one clinical trial with selective NK1 receptor antagonists. In contrast, the high affinity nonpeptide antagonist for the human CGRP receptor, BIBN4096BS, has been found effective in reducing both the headache and the associated phenomena of the migraine attack without affecting cardiovascular baseline parameters [2]. Neurogenic vasodilatation promoted by CGRP released from perivascular endings of trigeminal sensory neurons significantly contributes to the migraine mechanism. Inhibition of CGRP release by triptans or blockade of the CGRP receptor are different strategies that successfully target a similar pathogenic mechanism.

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GENETICS OF PRIMARY HEADACHES

NEURONAL CALCIUM CHANNELS AND MIGRAINE

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Mutations in CACNA1A, the gene encoding the pore-forming subunit of $Ca_V2.1$ (P/Q-type) calcium channels, cause a group of dominantly inherited human neurological disorders, including familial hemiplegic migraine type-1 (FHM-1), a rare autosomal dominant subtype of migraine with aura. P/Q-type calcium channels are expressed in all brain structures that have been implicated in the pathogenesis of migraine and play a prominent role in controlling neurotransmitter release. Functional studies into FHM-1 may provide unique insight into the molecular and cellular mechanisms of migraine. We have investigated the functional consequences of eight FHM-1 mutations by expressing recombinant human $Ca_V2.1$ channel subunits in HEK293 cells and in cerebellar granule cells from *cacna1a*$^{-/-}$ mice lacking $Ca_V2.1$ channels. A consistent effect of FHM-1 mutations was to increase Ca^{2+} influx through single human $Ca_V2.1$ channels in a broad voltage range, as a consequence of an increased channel open probability mainly due to a shift to lower voltages of channel activation [1]. Recently, the generation of knockin (KI) mice carrying the R192Q [2] and S218L FHM-1 mutations allowed us to analyze for the first time mutant $Ca_V2.1$ channels expressed at their endogenous level in neurons, and evaluate the consequences of FHM-1 mutations on neurotransmission and cortical spreading depression (CSD, the phenomenon underlying migraine aura). Compared to wild-type mice, KI mice showed: 1) an increased P/Q-type Ca^{2+} current density in cerebellar granule cells in primary culture and dissociated cortical pyramidal cells in a broad voltage range and similar current densities at higher voltages; 2) an increased susceptibility to CSD as revealed by a lower threshold for induction and a higher velocity of CSD propagation *in vivo*. S218L KI mice also showed a higher incidence of recurrent waves of CSD after stimulation. Moreover, facilitation of CSD propagation was strikingly larger in S218L than in R192Q KI mice, in correlation with the more severe clinical phenotype of the S218L mutation. The gain-of-function effects on both P/Q-type Ca^{2+} current and CSD were about twice as large in homozygous as compared to heterozygous mice, revealing an allele-dose effect consistent with dominance of the mutation in FHM-1. Our data show an important role of $Ca_V2.1$ channels in the initiation and spread of CSD, and point to cortical hyperexcitability as the basis for increased susceptibility to CSD in migraine. The FHM-1 KI mice are promising animal models to study migraine mechanisms and treatments.

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GENETIC MUTATIONS AND POLYMORPHISMS IN MIGRAINE

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Migraine is an ictal neurological disorder, which frequently runs in families. It is supposed to be a complex genetic disorder, where additive genetic effects and environmental factors are interrelated. Genetic load can be seen as determining a critical migraine threshold that is modulated by external as well as internal factors and, if reached, leads to an attack.

At present, the only known monogenic subtype of migraine is familial hemiplegic migraine (FHM), a rare autosomal dominant subtype of migraine with aura. FHM patients have attacks of migraine associated with hemiparesis to a variable degree. The first FHM (FHM1) gene identified was CACNA1A on chromosome 19p13. This gene codes for the pore-forming subunit of voltage-dependent P/Q-type calcium channels. Only three years ago the second FHM (FHM2) gene was identified. FHM2 mutations have been found on the ATP1A2 gene on chromosome 1q23, which codes for the main subunit of the Na,K- ATPase. Both these genes have been supposed to play a role also in common forms of migraine, especially with aura, but results are still controversial. A mutation on the ATP1A2 gene has been described in a pedigree with basilar-type migraine, which is a form of migraine with aura clinically linked to FHM, although more common. Very recently, a third FHM gene (FHM3) has been identified on chromosome 2q24. It is the SCN1A, coding for the voltage-gated sodium channel. At present, only one mutation on this gene has been associated with FHM.

Although no mutations have been identified in common forms of migraine, some linkage studies revealed many migraine susceptibility loci. Significant linkages to chromosomes 1q23, 15q11-q13, 11q24, 6p12-p21, 4q24 and 19p13 were described in migraine with aura, and to chromosomes 5q21, 4q21, 14q21-q22, 1q31, Xq24-q28 and Xp22 in both types of migraine.

The prevalence of various gene polymorphisms may be higher in migraineurs than in controls. This was reported for dopamine D2 and D4 receptors, angiotensin converting enzyme, serotonin transporter, dopamine β hydroxylase, endothelin type A receptor, insulin receptor, methylenetetrahydrofolate reductase, estrogen receptor 1 and tumor necrosis factor β genes. The role played by these various polymorphisms remains to be determined; some of them may not be specific to migraine, but they could increase susceptibility to the disorder and induce endophenotypic vulnerability markers.

MOLECULAR GENETICS OF CLUSTER HEADACHE: A REVIEW

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Introduction In the past, cluster headache (CH) was not thought to be an inherited disorder. Recent studies have suggested that genetic factors play a role in the disease [1]. Genetic epidemiological surveys have clearly shown that first-degree relatives of CH patients are more likely to have CH than the general population. In addition, CH has been reported in some concordant monozygotic twin pairs. Recently, we have reported in an Italian population a significant association between the *HCRTR2* gene and the disease. This association was confirmed in a German study. The purpose of this review is to describe recent advances in the molecular genetics of CH.

Methods We searched MEDLINE (1966–2004) and reference lists of retrieved articles. The search terms "cluster headache", "genetics" and "molecular genetics" were used. Only original articles published in English were included.

Results Several studies reported lack of association between different candidate genes and CH. Excluded genes were: CACNA1A, NOS, HFE, Clock and elusive amine receptors (TAR 1, TAR 3, TAR 4, TAR 5, PNR, GPR58) genes. We reported a significant association between the 1246 G>A polymorphism of the gene encoding for the hypocretin receptor 2 (HCRTR2) and CH [2]. Patients homozygous for the G allele, in comparison with the remaining genotypes, have a five-fold higher risk of developing the disease. This association was confirmed in a large sample of 226 patients with CH from Germany.

Discussion At present, the type and the number of genes involved in cluster headache are still unclear. A significant association between the *HCRTR2* gene and the disease was found. This gene, however, is not a major gene but rather a disease-modifying gene. These findings suggest that the hypocretin/orexin system may be involved in the pathogenesis of CH. Hypocretins influence a wide range of physiological and behavioural processes like appetite regulation, sleep-wake cycle, neuroendocrine and sympathetic functions. Moreover, recent findings suggested that hypocretins modulate pain threshold and nociceptive transmission. Additional studies are needed to elucidate the role of the *HCRTR2* gene in the pathogenesis of CH and to search for major genes in this rare but severe headache disorder.

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MEDICATION-OVERUSE HEADACHE AS DEPENDENCE DISORDER: A DRD4 GENE POLYMORPHISM ANALYSIS

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Introduction Medication-overuse headache (MOH) is a chronic headache disorder developed from an episodic primary headache as a consequence of analgesic drug overuse. Characteristically, only drug discontinuation can substantially improve the clinical picture. MOH is currently regarded as a bio-behavioural disorder with drug dependence. Several genetic studies have highlighted the role of dopamine receptor subtype (DRD4) polymorphisms in illicit drug consumption and alcohol dependence. Furthermore, some DRD4 polymorphisms have been correlated with the variability of novelty seeking behaviour (NS), a personality dimension – determined by Cloninger's Tridimensional Personality Questionnaire (TPQ) – associated with substance abuse and dependence.

In our study we investigated the role of a DRD4 polymorphism in MOH.

Materials and methods Fifty-seven unrelated MOH patients were recruited and the diagnosis confirmed after 2 months of drug discontinuation. All patients were interviewed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), to obtain a categorical psychiatric diagnosis, and completed the TPQ. After obtaining written informed consent from the patients, their genotype with respect to a 120 bp "tandem duplication" in the 5'-untranslated region of the DRD4 gene was determined. Two types of polymorphism-lengths occurred: long (L), the commonest, and short (S), which have been correlated with high NS scores and substance dependence.
To find predictors of the monthly amount of drug consumption, in the statistical analysis we considered as independent variables: years of disease duration, type of analgesic drug, genotype, and the subscales of TPQ in the statistical analysis.
Results Twenty-eight patients were homozygous carriers for the L form (L/L), 26 were heterozygous (L/S) and 3 were homozygous for the S form (S/S).

- ANOVA analysis showed that in our patients the S/S and L/S genotypes predicted high scores of NS.
- Linear logistic regression indicated that only the persistence (P) score (a subscale of TPQ) and the presence of allele S (S/S and S/L) were factors predictive of the monthly amount of analgesic drug consumption.

Discussion As with disorders characterized by substance dependence, in MOH the S allele is related to NS. Moreover, the S allele seems to also be a predictor of increased drug consumption so that it can be regarded as an aggravating factor for this disease.
Conclusions In MOH patients the DRD4 polymorphism is linked to behavioural components like NS and is correlated with the extent of the drug overuse.

THE HEMOCHROMATOSIS (HFE) GENE INFLUENCES THE CLINICAL FEATURES OF MIGRAINE

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Introduction Several studies suggested that iron metabolism may be involved in the pathogenesis of migraine. Iron concentrations in the periaqueductal gray matter of migraine patients are significantly increased. A large population-based study showed a high migraine prevalence in women with hemochromatosis (HH), a disease associated with progressive iron overload in several organs. The hemochromatosis gene *(HFE)* is located in 6p21.3 and encodes for a HLA class I-like molecule involved in iron metabolism. Two principal polymorphisms in the *HFE* gene, C282Y and H63D, have been identified as the cause of HH. Using a case-control design, we performed an association study in a cohort of Italian migraine patients to evaluate whether a particular allele or genotype of the *HFE* gene would modify the occurrence and the clinical features of the disease.
Methods A total of 256 consecutive unrelated migraine patients (98 men, 158 women; mean age±SD=40.3±9.4 years) were involved in the study. The diagnosis of migraine was made according to the International Classification of Headache Disorders (ICHD-II) criteria. Two hundred and twenty-five patients fulfilled the diagnostic criteria for migraine without aura (MO) and 31 for migraine with aura (MA). A group of 237 sex-, age- and geographically (Northern Italy) matched healthy subjects (95 men, 142 women, mean age±SD=41.5±13.3 years) were used as controls. Patients and controls were genotyped for the C282Y and H63D polymorphisms of the *HFE* gene.
Results Phenotype and allele frequencies of both polymorphisms were similarly distributed in migraine patients and controls. The patients carrying the DD genotype of the H63D polymorphism showed a later age at onset of the disease and an increased number of migraine attacks.
Discussion Our data suggests that the *HFE* gene is not a major disease gene for migraine. However, the H63D polymorphism of the *HFE* gene may be considered a modifying genetic factor in migraine.

CYP 450 POLYMORPHISM CONTRIBUTES TO THE VARIABILITY OF THE RESPONSE TO PHARMACOTHERAPY IN PRIMARY HEADACHE

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Currently available treatments for primary headaches have a limited efficacy, due in part to the wide variation in individual responses. Variability in individual response to headache treatment may be due to several factors, including a patient's compliance with treatment, severity and type of headache and intercurrent illnesses, drug interaction with other medications taken concurrently, diet, and individual biological characteristics such as age, nutritional status, hepatic and renal functions. Hereditary differences may therefore be only one of the causes of the variable effect of pharmacotherapy in primary headache. However, genetic factors may underlie much of such variability.
Most drugs are subjected to more or less extensive metabolism. Only a few of the cytochrome P (CYP) 450 family enzymes are responsible for the majority of metabolic reactions involving drugs. They include the isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Several of the drug metabolizing enzymes are polymorphic, having more than one variant of the gene. This polymorphism is responsible for interindividual differences in the efficacy of drug treatment, side effects of drugs, and drug toxicity. Genetic polymorphisms with clinical implications have been described for 2D6, 2C19, 2C9, 1A2, and 3A4. Genetic polymorphism of CYP450 enzymes characterizes the general population into three groups: poor metabolizers, extensive metabolizers, and ultraextensive metabolizers. There are three ways to gain information on metabolizing enzyme activities: to study the genes that code for the enzyme, to study the level of enzyme expression in a certain tissue, and to assess the actual enzyme activity using an enzyme specific probe (phenotyping). Genotyping is a more simple procedure compared to phenotyping. Phenotyping might be helpful in detecting interethnic differences, or in studies aimed at detecting enzyme induction or inhibition. Probe substrates that may be used to assess the activity of specific cytochromes P450 *in vivo* are: caffeine for CYP 1A2, dextromethorphan for CYP 2D6, and midazolam for CYP 3A4.
Polymorphism of CYP450 enzymes may or may not have a clear clinical significance for the affected medications, depending on the importance of the enzyme for the overall metabolism of a medication, the expression of the other drug metabolizing enzymes in the patient, the therapeutic index of the drug, the presence of concurrent medications or illnesses, and other polygenic factors that impact drug response.

PATHOGENETIC ASPECTS OF HEADACHES: FROM THE EXPERIMENTAL MODEL TO MAN

CA-DEPENDENT EXOCYTOSIS AND CGRP RELEASE IN MICE TRIGEMINAL GANGLION NEURONS

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Introduction Activation of trigeminal ganglion (TG) nociceptors and consequent neurotransmitter release are centrally involved in the development of migraine headache. Calcitonin gene-related peptide (CGRP) is one of the most important vasoactive neurotransmitters in migraine. Major lines of evidence are: *i)* CGRP is found in human jugular venous during migraine attacks; *ii)* the administration of the antimigraine agent sumatriptan relieves headache and re-establishes normal CGRP levels; and *iii)* intravenous administration of CGRP induces headache and migraine in migraineurs. Elucidation of the release mechanism for CGRP in TG neurons may thus be critical in the understanding of migraine pathology [1, 2]. In dorsal root ganglia (DRG) neurons it has been recently shown that a significant component of exocytotic release and even a greater fraction of depolarization-induced CGRP release do not require Ca^{2+} influx. We then set out to assess the Ca^{2+} dependence of exocytosis and of CGRP release in TG neuron of mice. This investigation was carried out considering that a subtype of migraine with aura, familial hemiplegic migraine type 1 (FHM1), is caused by mutations of CaV2.1 channels, abundantly expressed in TG neurons [2].

Methods Depolarization-induced membrane capacitance changes were measured in the whole-cell configuration of the patch-clamp technique, by using the Neher-Lindau method. CGRP release was assessed by immunocytofluorimetric methods.

Results With 5 mM external Ca^{2+}, 200-ms depolarizing pulses to 0 mV evoked a Ca^{2+} current of -3.4±0.4 nA, and an increase in membrane capacitance of 292±67 pF (n=17). Bath application of 200 µM Cd^{2+} fully inhibited the Ca^{2+} current, but reduced the depolarization-induced capacitance change by only 24±6% (n=4). When neurons were stimulated with a train of 20 depolarizing pulses, the fraction of Cd^{2+}-sensitive capacitance change increased to 45±7% (n=4). Similar results were obtained when the inhibition of Ca^{2+} influx was attained by removing the external Ca^{2+}. K^+-induced depolarization of TG neuronal cultures in 2.5 mM external Ca^{2+} increased CGRP release by 19.4±2.1 fold of its basal level (n=8). When neurons were incubated in a medium containing 30 µM Ca^{2+}, the K^+-induced CGRP release was reduced to 5.4±1.1 fold of its basal level (n=4).

Conclusions Our data indicate that TG neurons possess both a Ca^{2+}-dependent and a Ca^{2+}-independent exocytotic release, and that the CGRP release is strongly controlled by the Ca^{2+}-dependent component.

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CEREBROSPINAL FLUID LEVELS OF OREXIN-A AND CORTICOTROPIN-RELEASING FACTOR SUGGEST THEIR INVOLVEMENT IN THE NEGATIVE MOTIVATIONAL STATE THAT DRIVES "DRUG DEPENDENCE" IN MEDICATION-OVERUSE HEADACHE

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Background Hypocretin-1 and -2 (Hcrt-1 and Hcrt-2), also referred to as orexin-A and -B, are two neuropeptides, which are considered critical components for maintaining and regulating the stability of arousal to mediate the hypothalamic response to stress. Experimental evidence suggests that corticotrophin-releasing factor (CRF) activates the hypocretin system, which relays orexin-A to brainstem nuclei as well as to the extended amygdala, a structure involved in the negative motivational state that drives addiction [1, 2].

No studies have been conducted until now to investigate the role of hypocretins, in particular orexin-A, in medication-overuse headache (MOH).

Objective The present study was aimed at investigating the levels of orexin-A and CRF in the cerebrospinal fluid (CSF) of chronic migraine (CM) and probable CM+probable medication-overuse headache (PCM+PMOH) patients.

Patients and methods Twenty-five patients affected by CM and 30 patients with a prior history of migraine without aura and diagnosed as having PCM+ PMOH were admitted to the study.

Control CSF specimens were obtained from 20 age-matched subjects who underwent lumbar puncture for diagnostic purposes and in all of them CSF and blood tests excluded CNS or systemic diseases.

Orexin-A and CRF were determined by radioimmunoassay methods. Clinical variables which were related to CSF levels of orexin-A and CRF were: number of days with headache per month; intensity of headache measured with the visual analogue scale; duration of chronic headache (years); daily drug intake; and Leeds Dependence Questionnaire (LDQ) scores.

Results Significantly higher levels of orexin-A and CRF were found in the CSF of PCM+PMOH patients and to a lesser extent in patients with CM compared with control subjects (orexin-A=p<0.001 and p<0.02, =p<0.002 and p<0.0003). A trend toward a significantly positive correlation between CSF levels of orexin-A and CRF emerged in the PCM+PMOH group, but did not reach the level of statistical significance. A significantly positive correlation was also found between CSF orexin-A values but not with CRF and daily drug intake and LDQ scores in the latter group (r=0.53, p<0.001 and r=0.48, p<0.002, respectively).

In both CM and PCM+PMOH patient groups there was no correlation between number of day with headache per month, intensity of headache and duration of chronic headache.

Discussion Results of the present study support the involvement in the orexin-A system mediated by CRF activation, in the negative motivational state that drives drug dependence in MOH. This is supported by the relationship between the number of drugs abused and the scores of a self-completion 10-item instrument (LDQ) to measure dependence upon a variety of substances. These findings suggest a potential role for this hypocretin in driving drug seeking also in MOH through activation of stress pathways in the brain, has been shown in experimental models.

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PRIMARY CULTURES OF RAT TRIGEMINAL GANGLIA NEURONS AS AN IN VITRO MODEL TO INVESTIGATE MIGRAINE MECHANISMS AND THERAPIES

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We are currently developing an *in vitro* model based on primary cultures of neonatal rat trigeminal ganglia neurons, with the aim to investigate the pathophysiological mechanisms underlying migraine, as well as the effects of putative antimigraine agents.

Primary cultures were prepared as follows: ganglia from 6–7 day-old rats were quickly removed and digested by collagenase and trypsin; cells were seeded on 24-well tissue culture plates, coated with poli-D-lysine and laminin at a density of 130–150 x 10^3 cells/well and incubated at 37°C in a humidified atmosphere containing 5% CO_2. The cul-

ture medium was changed within 24 h from seeding. Plating medium was enriched with 50 ng/mL of 2.5 S murine nerve growth factor. Cytosine arabinoside 10 μM was added to arrest non-neuronal cell growth. All experiments were performed from 3 to 6 days after dissection. In this model, we developed a radioimmunoassay (RIA) method to measure calcitonin gene-related peptide (CGRP) released in the incubation medium; this parameter can be taken both as an index of neuronal function as well as a pivotal mediator of migraine pathology. We found that CGRP was released in sizable amounts after 10–60 minutes experiments. Basal CGRP release was increased in a significant manner by depolarizing solutions (i.e., incubation media containing 56 mM KCl). Release was also increased by the Na^+-channel activator, veratridine, with significant increases from 10^{-8} M onward. Apart from non-specific depolarizing agents, CGRP release was also increased in a concentration-dependent manner by the vanilloid receptor agonist capsaicin, with an estimated EC_{50} of 0.3 μM.
Preliminary findings show the opioid-related peptide nociceptin, also referred to as orphanin, reduces basal CGRP release from cultured neurons. We are currently investigating the effects of nociceptin over specific (capsaicin) and non-specific (KCl and veratridine)-stimulated CGRP release.

FOCAL GRAY MATTER DECREASE IN THE CEREBRAL PAIN NETWORK OF MIGRAINE PATIENTS

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Introduction Migraine is considered a frequent, primary headache disorder due to transient abnormal brain function. According to the current classification of the International Headache Society, structural brain lesions are absent in primary headaches. However, recent studies with voxel-based morphometry (VBM) demonstrated selective brain alterations in both cluster headache (bilateral increase of gray matter in postero-lateral hypothalamus) and chronic tension-type headache (gray matter decrease in orbifrontal cortex, insula, and anterior cingulate cortex). The purpose of this study was to investigate the presence of structural abnormalities in patients with migraine using the optimized voxel-based morphometry method, a highly sensitive technique to detect focal gray and white brain matter abnormalities.
Methods A group of 27 right-handed migraine patients, diagnosed according to ICHD-II criteria, and 27 right-handed healthy controls underwent high resolution structural magnetic resonance imaging (MRI). Data was analyzed using MATLAB 6.5 and Statistical Parametric Mapping 2 (SPM2). Covariance analysis was used to detect local gray matter changes in migraine patients and between episodic and chronic migraine. Regression analysis was performed to search for a relationship between local gray matter changes with the clinical characteristics of migraine.
Results Significant gray matter volume reduction was found in the right superior temporal gyrus, right parietal operculum, right inferior frontal gyrus, left angular gyrus, left inferior parietal lobule and left precentral gyrus of migraine patients. In comparison with episodic migraine, patients with chronic migraine showed a significant bilateral reduction of gray matter concentration in the anterior cingulate cortex (AAC), right angular gyrus and right inferior frontal gyrus. Finally, we found a significant correlation between the frequency of migraine attacks and the reduction of gray matter concentration in AAC of migraine patients.
Discussion Our study shows a significant gray matter reduction in migraine patients of several cortical areas involved in pain processing and a selective alteration of AAC related to frequency of migraine attacks. Functional neuroimaging shows that several brain regions are activated by pain, including frontal and pre-frontal cortices, operculo-insular cortex, primary and secondary somatosensory cortices, AAC, thalamus and regions within the parietal and temporal cortices. In addition, AAC plays a key role in the affective and attentive processing of pain sensations. Our data supports the results of previous studies suggesting that migraine may be considered a progressive brain disorder and highlights the importance of prophylactic antimigraine therapy in order to avoid the progression of the disease.

EVIDENCE FOR SPINAL CORD HYPERSENSITIVITY AND ABNORMAL MODULATORY INFLUENCE OF DIFFUSE NOXIOUS INHIBITORY CONTROLS IN MEDICATION-OVERUSE HEADACHE

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Background It has been postulated that chronic exposure to antimigraine and/or analgesic treatment may interfere with the pain control system, leading to a central sensitization phenomenon responsible for chronic headache.
Diffuse noxious inhibitory controls (DNICs) are part of a central pain modulatory system that relies on spinal and supraspinal mechanisms. It has been postulated that chronic or frequent exposure to antimigraine and/or analgesic treatment may lead to a downregulation of specific receptors and may subsequently change central inhibitory (anti-nociceptive) pathways such as DNICs, leading to central sensitization phenomena responsible for chronic headache pain. Our previous study [1] showed that the temporal summation threshold (TST) of the nociceptive flexion reflex (RIII) represents a useful tool to evaluate both the central sensitization of pain pathways and the functional activity of DNICs.
Objective The present study investigated the TST of the RIII reflex in medication-overuse headache (MOH) patients before and after withdrawal therapy.
Methods Twenty-four MOH patients before and after withdrawal treatment and 25 age- and sex-matched controls were evaluated. TST of the RIII reflex and the subjective painful sensation were measured before, during and after activation of the DNICs by the cold pressor test (CPT), which involved immersing the hand in cold water (2–4°C). After 7–10 days of withdrawal treatment all patients were re-evaluated.
Results Significantly ($p<0.01$) lower RIII threshold and TST were found in patients versus controls. In patients, the CPT induced a significantly ($p<0.01$) lower TST increase with respect to controls. After the withdrawal therapy we found an improvement of the evaluated parameters, and a highly significant increase ($p<0.01$) in the TST during CPT.
Conclusions These data confirm the hypothesis of a lack of function of the DNICs and of a central sensitization phenomenon in MOH patients. The improvement after withdrawal treatment suggests that medication overexposure could interfere with inhibitory central pain mechanisms.
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EFFECT OF PREGABALIN IN A STRESS AND NITROGLYCERIN-INDUCED MODEL OF HYPERALGESIA IN THE RAT

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Introduction Nitroglycerin activates spinal and brain nociceptive structures via nitric oxide (NO) and plays an important role in the initiation and maintenance of pain. Chronic stress affects both pain threshold and behaviour, and unavoidable stress paradigms such as immobilization are used to study nociception. We have recently reported that chronic stress enhances the hyperalgesia induced by nitroglycerin in the rat. This may be particularly relevant to migraine, since nitroglycerin triggers spontaneous-like attacks in humans, and an unfavourable migraine outcome (transformation into a chronic daily headache) is associated with chronic stress and comorbid depression.
Pregabalin is an antiepileptic and analgesic drug with significant effects on thermal allodynia and mechanical hyperalgesia; we therefore investigated the effect of pregabalin in this experimental model of chronic migraine.
Materials and methods Pain perception was measured using the latency of response to a tail flick test (hot stimulus). Measures were made 1, 2 and 4 hours following nitroglycerin (10 mg/kg i.p.) in rats immobilized for 7 days using dedicated plexiglass restraining cages, and treated with pregabalin at the dose of 60 mg/kg per os or with vehicle.
Results Chronic stress caused hyperalgesia, which was further enhanced by nitroglycerin after 2 and 4 hours ($p<0.05$). By contrast, chronic stress-induced pain perception decreased in pregabalin treated animals ($p<0.05$); in the same group, the hyperalgesic effect of nitroglycerin was also found to be significantly dampened ($p<0.05$).
Discussion and conclusions These preliminary data suggest that pregabalin acts as an antinociceptive drug by affecting the mechanisms leading to hyperalgesia in the rat. Pregabalin may thus represent a novel therapeutic option in the management of chronic migraine in humans.

CEREBRAL EXCITABILITY IN MIGRAINE

ROLE OF THE BRAINSTEM IN MODULATION OF CORTICAL EXCITABILITY IN PRIMARY HEADACHE

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Neuroimaging and neurophysiological studies have done much to clarify the fundamental neurological basis of migraine. One of the most pivotal investigations in the history of migraine pathophysiology reported activations from a positron-emission tomography (PET) study of acute migraine. Brain activation was seen in the dorsal midbrain and dorsal pons during the acute attack. Remarkably, the same midbrain area was identified in a study of iron homeostasis in episodic and chronic migraine. Clinical reports have identified secondary migraine after disturbances in the brainstem, again in the same regions. From triangulation of these observations, a candidate region for a key defect in migraine would be the ventrolateral periaqueductal grey (PAG). The PAG is known to ordinarily inhibit trigemino-vascular nociceptive input and to remarkably facilitate it when voltage-gated calcium channels are blocked. It is largely involved in the modulation of pain transmission, being activated or deactivated by the cortical areas subtending the attentive and emotive compounds of pain. In this view, it has been shown that migraine patients are unable to modulate pain, for a lack of inhibition of the nociceptive cortex during distractive tasks [1]. There is controversy about the status of basal hypo- or hyperexcitability of the migraine cortex, leading to the phenomenon of reduced habituation to repetitive stimuli and cognitive tasks [2]. This basic abnormality seems to affect the nociceptive cortex, other than the cortical zones elaborating multimodal stimuli [2]. Whatever is its origin, reduced habituation results in cortical over-activity, with reduced efficacy of the cortical-subcortical reciprocal connections. Changes in cortical synchronization have been described in migraine as an underlying abnormality, which may also interfere with brainstem modulation [3].
Abnormal cortical information processing, probably based on the phenomenon of altered neuronal synchronization, may be a basic feature in migraine; the brainstem, particularly the zones corresponding to the PAG, may consequently change its ascending firing to the cortex and its descending control on the nociceptive afferents, with a self-maintaining circuit prone to the generation and the persistence of headache.
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CORTICAL EXCITABILITY AND HABITUATION MECHANISMS IN MIGRAINE

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Controversy has arisen about the excitability status of the cerebral cortex in migraineurs between attacks. Intuitively, some clinical features of migraine such as hypersensitivity to environmental light or noise, and the aura symptoms suggest hyperexcitability of the cerebral cortices. In the physiological sense, however, hyperexcitability would mean that the brain responds to a subliminal stimulus with an increased amplitude. This abnormality has never been precisely demonstrated studying cortical excitability in migraine patients.
Increased cortical excitability or decreased intracortical inhibition, as well as hypoexcitability or normal function of inhibitory cortical interneurons have been observed in migraine by using transcranial magnetic stimulation (TMS), thus providing ambiguous results.
It has been hypothesized that the finding of an interictal deficit of habituation of cortical evoked responses is probably not due to hyperexcitability or to underactivity of intracortical inhibition, but to a reduced preactivation excitability level of the sensory cortices, stated by activity in thalamo-cortical loops and aminergic projections from the upper brainstem. This low preactivation level, in conjunction with the cortical "ceiling theory", could indeed explain the low amplitudes found in the first blocks of several types of evoked responses and the lack of habituation in subsequent blocks, since it would offer a larger range for suprathreshold cortical activation before reaching the "ceiling".
Interestingly, this dishabituation phenomenon is reversible, since it normalizes just before and during an attack. It remains to be determined if activation of the dorsal rostral brainstem and of thalamo-cortical projections may contribute to ictal normalization of the cortical preactivation level.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN MIGRAINE: RECENT EVIDENCE

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Transcranial Magnetic Stimulation (TMS) has been employed to study the pathophysiology of migraine. All studies reported abnormal cortical activation in migraineurs during the interictal phase; the findings however were controversial, some authors describing hypo- and others hyper- excitability of the migraine visual cortex.
Repetitive TMS (rTMS) is able to modulate cortical excitability, with low frequency (≤1 Hz) decreasing while high frequency (> 1 Hz)

increasing activation of stimulated cortices.
A few rTMS studies have been conducted in migraine. We showed that low-frequency rTMS has paradoxical facilitatory effects on striatal and extra-striatal cortex in migraine and interpreted this result as due to reduced efficiency of cortical inhibitory circuits, unable to be up-regulated by rTMS. According to this hypothesis, we found dysfunction of inhibitory circuits also in the motor cortex of migraineurs. Through paired pulse TMS we showed that migraineurs present reduced intracortical inhibition at baseline. After 1 Hz stimulation, parodoxical potentiation of intracortical facilitation (ICF) occurs, opposite to the suppression of ICF induced by the same trains in healthy controls.
In contrast, Bohotin et al. [1] in a rTMS experiment found that the facilitatory frequency 10 Hz favours the recovery of habituation of visual evoked potentials that is reduced in migraine. The authors speculated that migraineurs have a reduced cortical activation that can be reversed by facilitatory rTMS. Moreover, in the authors' view, the relationship between reduced-activation and deficient-habituation is also confirmed by the results of 1 Hz rTMS application in healthy subjects; in this group, in fact, reducing activation through 1 Hz rTMS that normally exerts an inhibitory effect gives similar habituation impairment compared with migraine.
However, the effects of rTMS greatly depend on the basal excitability state of stimulated cortex. In fact, in a recent paper [2] we found that during visual deprivation, a condition known to increase visual cortical excitability, rTMS can exert opposite effects, with low frequencies increasing while high frequencies decreasing excitability of the occipital cortex. This means that rTMS should be interpreted cautiously when investigating cortical excitability, to avoid a circular reasoning, i.e., the same rTMS effects are conditioned by the basal excitability state of the stimulated cortex.
rTMS if given in repeated stimulation sessions is also able to induce persistent plastic changes of the stimulated cortex, and this is the rationale for its use in experimental treatment of various neurological and psychiatric diseases.
Recent findings about this rTMS application seem to open interesting therapeutic perspectives in migraine.

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VISUAL EVOKED GAMMA BAND RESPONSES IN SUBGROUPS OF MIGRAINE WITH AURA

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Background Visual stimuli evoke high frequency oscillations in the gamma band range (GBOs, 20–35 Hz) generated both by pre- (early GBOs) and post-synaptic (late GBOs) mechanisms. Recently, Sandor et al. [1], with MR-lactate spectroscopy, observed that a pattern of dishabituation, as previously found with evoked potentials, was present in a subgroup of migraine patients with associated paraesthesia, paresis or dysphasia as aura (MAplus), while in the subgroup with high resting lactate, the aura seems to be limited to the visual cortex.
Taking into account that a close relationship was observed between oscillatory response and metabolic cortical demand [2], we searched for pathophysiological differences in the clinically distinct subgroups of migraine with aura (MA) exploring visual evoked GBOs during the interictal period.
Materials and methods Eighteen patients affected by migraine with typical aura (ICHD-II code 1.2.1, 2004) were enrolled in this study: 8 with pure visual aura (MA) and 10 with visual aura associated with paraesthesia or dysphasia (MAplus). Migraineur groups were compared to 15 healthy volunteers (HV).
We extrapolated the GBOs from the broad-band visual evoked potentials (VEPs), with an off-line band pass digital filter (20–35 Hz). We analyzed peak-to-peak amplitude and habituation (the amplitude change (%) between the 1st and 6th block of 100 sequential averaged responses) of the conventional broad-band N1-P1 and of each of 6 peaks of GBO burst evoked by the checkerboard pattern. We considered as early GBOs the first 3 oscillatory peaks, and as late GBOs the last 3.
Results The conventional broad-band VEPs showed the well-known pattern of dishabituation in both MA (p=0.038) and MAplus (p=0.001) patients when compared to HV.
After digital filtration, there was a significant habituation deficit of the later two, but not of the earlier GBO peaks in MAplus patients compared to HV (respectively p=0.035 and p=0.032). In contrast, the MA group with pure visual aura showed an increased early oscillatory peak activity compared to HV (2nd p=0.024 and 3rd p=0.013), without habituation deficit of the later GBO peaks.
Discussion We found different patterns of visual oscillation responses in two subgroups of MA patients, which seem to mimic those observed with MR-lactate spectroscopy in patients with the same diagnosis. We hypothesized that an abnormal metabolic demand due to repetition of visual stimulus leads to dishabituation, which exists in MAplus patients, and to a predominant energetic metabolism dysfunction in MA patients.

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HYPEREXCITABILITY OF THE SOMATOSENSORY SYSTEM IN CHILDREN WITH MIGRAINE

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Introduction Although migraine represents the most common primary headache in childhood, its pathophysiology is poorly understood. In spite of the bulk of studies dealing with this problem in adults, the pathophysiological base of paediatric migraine has been only rarely investigated. As in adults, children with migraine show a reduced habituation to repetitive sensory stimuli [1, 2]. Although this characteristic neurophysiological phenomenon suggests an abnormal excitability of the cerebral cortex in this disease, whether cortical excitability in migraine is reduced or increased is still far from demonstrated.
Materials and methods We investigated cerebral cortex excitability in 15 children (mean age 11.7±1.6 years, 5 males, 10 females) affected by migraine without aura (MO) and in 10 age-matched control subjects (CS) (mean age 10.9±2.1 years, 6 males, 4 females). We calculated the somatosensory evoked potential (SSEP) latency and amplitude modifications after paired electrical stimuli at 5, 20 and 40 ms interstimulus intervals (ISIs), comparing it with a single stimulus condition taken as baseline.
Results In MO patients, the amplitudes of the cervical N13 and of the cortical N20, P24 and N30 responses at 20 and 40 ms ISIs showed a higher recovery than in CS (two-way ANOVA, p<0.05).
Discussion Since the SSEP recovery cycle depends on inhibitory interneuron function, our findings suggest that a somatosensory system disinhibition occurs in migraine. This is a generalized phenomenon, not limited to the cerebral cortex, but involving also the cervical grey matter.
Conclusions The shortened SSEP recovery cycle in migraine children,

besides showing that the somatosensory system is hyperexcitable in this disease, might represent a useful marker to control the effect of prophylactic pharmacological treatments.

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THE PREVALENCE OF EPILEPSY IN MIGRAINE PATIENTS: A CLINIC-BASED STUDY

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Introduction Comorbidity of migraine and epilepsy has long been suspected, but the nature of this association is still unresolved. The prevalence of epilepsy in migraine patients is reported to range from 1% to 17%, with a mean of 5.9%. We evaluated the prevalence of epilepsy in a large population of migraineurs.

Materials and methods We analysed the clinical charts of 1098 consecutive patients referred to our Headache Centre completely fulfilling the ICHD-II diagnostic criteria for migraine, with specific attention to those patients diagnosed also with epilepsy.

Results We identified 16 migraine patients affected by epileptic syndromes: 5 cases with partial idiopathic epilepsy, 4 cases with partial symptomatic epilepsy, 6 cases with generalized idiopathic epilepsy and 1 case with generalized symptomatic epilepsy. The mean age of the patients was 36.2±9.9 years, with a large preponderance of females (13 out of 16 cases), with a ratio F:M=4.3:1. Three patients suffered from migraine with aura; in one of them the seizures occurred only during or immediately following migraine aura (1.5.5 Migraine-triggered seizures according to ICHD-II, in the past referred to as "migralepsy"). The remaining 13 subjects were affected by migraine without aura; one of them had also brief headaches synchronous with partial seizures (7.6.1 Hemicrania epileptica). Four patients complained of post-ictal headaches (7.6.2 Post-seizure headache), whose features were almost completely identical to those of their usual migraine headaches.

Discussion The prevalence of epilepsy in our population of migraineurs was 1.5%. This finding is in contrast with the data reported in previous studies, where a higher prevalence, ranging from 1% to 17%, was noted. A possible explanation for the low prevalence found in our study is that patients with seizure disorders may be more likely to contact specific centres for the study of epilepsy, even if they also suffer from disabling migraine headaches. Patients with both conditions could consider migraine less relevant to their health perception, as compared to epilepsy.

Conclusions The prevalence of epilepsy in migraineurs seems to be less prominent than reported in previous studies, even if methodologic problems make these studies difficult to interpret. Nonetheless, the prevalence of epilepsy in our migraine population was significantly higher than that found in the general population, which is approximately 0.5%. Our data support the hypothesis that the comorbidity of migraine and epilepsy may be explained by a state of neuronal hyperexcitability that increases the risk of both disorders.

ICHD-II: RE-EVALUATION AND INSTRUMENTS OF APPLICATION

REVISION OF THE ICHD-II CRITERIA FOR CHRONIC MIGRAINE

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Chronic headaches continue to be the most debated aspect of the International Classification of Headache Disorders. Following the introduction of the concept of chronic migraine in the second edition of the classification (ICHD-II), it has been found that the chronic migraine criteria proposed are, in fact, fulfilled by very few patients in clinical practice and clinical trials. To amend this situation, the Headache Classification Committee of the International Headache Society (IHS), which met during the International Headache Congress in Kyoto, decided to develop criteria that more accurately reflect the large majority of this population of patients.

The proposed version had already been distributed and through fruitful discussion, further amendments and improvements were made. It was decided to make the revised criteria available for future research, inserting them in the Appendix to ICHD-II. The Headache Classification Committee of the IHS invites the headache community to study these new criteria and to set up clinical trials for this severely affected population of headache patients.

The revised criteria for chronic migraine are: a) headache (migraine and/or tension-type) present for 15 or more days per month for at least three months; b) patients must have had five or more typical migraine attacks; c) typical migraine attacks must have been present on at least 8 days per month for no less than three months. An important additional criterion concerns the response to triptans or ergot treatment.

However, some important problems remain unsolved, including the threshold for considering a migraine "high frequency". In migraine prophylaxis clinical trials the threshold is from 2 to 6 attacks per month, but considering that an attack can last three days, a threshold of eighteen days per month for chronic migraine would seem to be more appropriate. Another question regards the need for at least two months' monitoring by diary card (as opposed to just one month). This would allow the inclusion, for female patients, of one or two menstrual cycles and make it possible to report different frequency of attacks or number of days of headache in different periods of observation. Furthermore, drug response could be extended to the NSAIDs. In addition, there is no consensus in treatment guidelines about the threshold at which prophylaxis is necessary, particularly with regard to additional clinical circumstances.

The Headache Classification Committee hopes that, with these revised criteria for chronic migraine, the majority of patients with this disorder seen in clinical practice can be correctly evaluated.

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LIMITS OF MEDICATION-OVERUSE HEADACHE CLASSIFICATION (CODE 8.2 ACCORDING TO ICHD-II)

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The classification of "Medication-Overuse Headache" (MOH) in chapter 8.2 of ICHD-II [1], although recently simplified to a list of drugs producing medication-overuse headache if overused [2], is still

ambiguous as far as combination analgesic-overuse headaches are concerned. Subforms 8.2.5 and 8.2.6 include drugs belonging to remarkably different classes, which can hinder and bias the comparative assessment of the clinical studies about medication-overuse headache. The same group of patients can include both patients taking combinations containing simple analgesics and caffeine and those taking combinations containing opioids and butalbital; but simple analgesics, even if associated to caffeine, do not have the same CNS effects as barbiturates and opioids. These central effects could influence the outcome of medication-overuse headache treatment differently from NSAIDs. We think that the classification of chapter 8.2 should be changed in order to be effectively used both in the clinical setting and in research. The classifying criteria should be the pharmacological class and the presence or absence of a dependence-producing property of the overused drugs. The same classification is also used by WHO ICD-10NA codes and aetiological ICD-10 code for secondary headache disorders and would simplify code transferability among classifications.

The major changes that we propose are: (i) classifying the drugs inducing MOH into two groups: drugs with psychotropic effects that produce tolerance, dependence, repetition of intake and, sometimes, abstinence symptoms after withdrawal; drugs related to non-dependence-producing substances; (ii) including in the first group also the combinations of analgesics and drugs with psychotropic effects, since we consider the latter as the most important component to maintain overuse.

The classification that we propose could contribute to a more precise assessment of the various drug classes in conditioning the evolution of primary headache syndromes, the outcome of withdrawal treatments and the short and long-term relapse rate. Finally, we believe that it would be useful, for clinical and research purposes, to know the dosages of overused drugs and the duration of overuse, in order to correctly assess the outcomes of medication-overuse headache treatments. In fact, the outcomes of the same medication-overuse headache treatment could be different, e.g., in a patient who has been taking 600 mg ibuprofen by mouth every other day for 4 months and in a patient who has been taking a combination containing 50 mg butalbital and/or 30 mg codeine on three days per week for two years.

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OSMOPHOBIA IN SECONDARY HEADACHES

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Introduction On the basis of our previous study [1], which highlights the specificity of osmophobia for migraine, in comparison to tension-type headache and other primary headaches, we started a clinical study to investigate the presence of this symptom in secondary headaches and to evaluate its relevance in the differential diagnosis between primary and secondary headaches.

Materials and methods The clinical study was conducted on a series of consecutive patients from the Neurological Clinic, the Operative Unit of Neurosurgery and the Neurotraumatological Clinic of the University of Padua, bearing pathological conditions potentially able to cause headache. Through a semistructured questionnaire we selected all patients suffering from secondary headache; the presence of a primary form of headache was also investigated (ICHD-II, 2004). A part of the questionnaire concerned the possible presence of osmophobia in the course of headache attack both in primary and secondary headaches. All the patients who presented alterations of their state of consciousness, who for any reason could not give reliable answers or who presented anatomic and/or functional alterations of olfactory function, were excluded.

Results We recruited 395 patients of whom 44 were excluded (according to the criteria previously reported). In the remaining 351, secondary headaches were referred in 36%; more specifically, of these, 39% had headache attributed to head and/or neck trauma (16/41), 34% to cranial or cervical vascular disorders (41/123), 36% to non-vascular intracranial disorders (65/179), and 25% had other secondary headaches (2/8). Among the group of patients who did not report secondary headache, 10% only had a preexisting primary headache; whereas, in the group with secondary headaches, 27% had a preexisting primary headache. Among these, only two migraineurs had osmophobia that was in connection with attacks of preexisting migraine without aura and not with secondary headache. None of the patients affected only by secondary headache reported osmophobia before or during the attacks.

Conclusions The presence of osmophobia is a relevant marker in favour of the diagnosis of migraine [1]. This study, which needs further confirmation with a larger survey, highlights how osmophobia presents a high specificity in the differential diagnosis between migraine vs tension-type headache and other primary headaches, even between migraine and the secondary headaches we considered.

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DEVELOPMENT OF A SOFTWARE PROGRAMME FOR THE DIAGNOSIS AND THERAPY OF PRIMARY HEADACHES FOR THE GENERAL PHYSICIAN

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Migraine is very frequently observed by general practitioners (GPs). Its clinical characteristics, which must fulfil the International Classification of Headache Disorders – 2nd edition (ICHD-II) criteria, along with a normal physical and neurological examination, are essential for the diagnosis; further investigations are usually requested only to exclude a possible secondary origin. GPs are largely the first medical figure that the migraine sufferers speak to; because of the workload of GPs, the traditional approach to the patient could be too time demanding.

We developed a computerized programme for use by GPs; the aim of the software is to give a simple, informative and timesaving support to GPs for the diagnosis of the principal forms of primary headaches (migraine, tension-type headache, cluster headache). It highlights the red flags of a possible secondary headache, and it lists, step by step and at the end of the process, the clinical features of the patient's headache which, previously inserted by the physician, led to the selection of a particular diagnosis, allowing a critical re-evaluation of the suggested diagnosis. With respect to a previous edition, we implemented the programme with the acute therapy options. In the case of a migraine diagnosis, the programme gives suggestions regarding the most appropriate choices, according to the category of drugs, to the comorbidity, and to the efficacy and tolerability of previous/actual drugs reported by the patient.

It is also possible to create a clinical sheet containing all the information regarding the first observation and the follow-up visits.

In conclusion, this software aims to represent a moment of educational growth, suggesting a practical clinical-therapeutic flowchart for migraine diagnosis, in accordance with ICHD-II criteria.

DEVELOPMENT OF A QUESTIONNAIRE FOR CLASSIFYING PRIMARY HEADACHES IN AN ELDERLY POPULATION SAMPLE ACCORDING TO THE ICHD-2

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Introduction Prior research shows that around 10% of women and 5% of men reported headache at the age of 70. However, the primary headaches (PHs) in the elderly are still poorly studied. To date, no studies that have used the International Classification of Headaches, 2nd edn (ICHD-2) to classify PHs in the elderly over 70 years old have been reported in the literature. This study had the objectives to classify the PHs in a USA and Italian elderly population (≥ 70 years old) according to the ICHD-2.
Methods Our cohort consisted of 426 elderly subjects without dementia (53% female, age range 70 to 94, mean=78.6 years). To assess the prevalence of PHs in this population we used a standardized questionnaire to prospectively survey participants of the Einstein Aging Study (EAS) and of the Rummo Aging Study (RAS). The EAS and RAS are a multidisciplinary project that follows a representative sample of seniors focusing on the description of cognitive pathways in the elderly. The questionnaire assessed current headache diagnoses (prior year), as well as prior headache diagnoses, according to the ICHD-2. All subjects participating in the EAS and RAS underwent neurologic examination, and most had neuroimaging. Consistently, we could confidently exclude secondary headache disorders.
Results One-year prevalence was 7.6% for migraine (migraine without aura 1.6%; migraine with aura 1.7%; probable migraine without aura 2.1%; probable migraine with aura 2.2%), 6.1% for episodic tension-type headache (ETTH) and 1.4% for chronic migraine. For those without headache in the past year a history of CDH was present in 3.1% of patients, a history of migraine in 4.7% and a history of ETTH in 6.9% of the sample. A remission of headache before age 50 was present in 50% while before age 65 in 81.2%. Around 15% of our sample had recurrent PHs in the past year, and 7.6% met ICHD-2 criteria for migraine. Most fulfilled a probable diagnosis rather than the full criteria.
Conclusions While 4.8% of patients had more than 15 days of headache per month at some point in their life, just 1.1% had it now. Headache remission prior to age 65 is common.
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APPLICATION OF THE ICHD-II DIAGNOSTIC CRITERIA FOR PAEDIATRIC HEADACHE USING A COMPUTERIZED STRUCTURED RECORD. A MULTICENTRE STUDY

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The actual application, by a computerized structured record, of the current International Headache Society (IHS) diagnostic criteria in clinical practice has been investigated in adults, while data in children are lacking. We tested the computerized record, based on ICHD-II criteria, by entering and analyzing data reported on the case sheets of 800 children (range 6–18 years) attending our paediatric headache centre.
Concordance between the clinical and computerized diagnoses was found in 70% of the cases examined. There was an absolute agreement of diagnosis (100%) in the subjects with chronic migraine (CM) and migraine with aura (MA) and almost complete in those with migraine without aura (MO) (99.1%). In episodic tension-type headache, concordance was reached in 50% of the cases and only in 9% with probable migraine. In the remaining types of headache, the computerized record showed, other than the diagnosis provided by the clinician, further probable alternatives.
In the types of headache with a large amount of information and typical accompanying symptoms, concordance was 100% and there were no diagnostic problems. In contrast, when we have headache types with intermediate characteristics and/or lack of accompanying symptoms, the software elaborates different diagnoses according to ICHD-II criteria.
The computerized structured record could be, in selected cases, an improvement for the specialist to orient the diagnosis. The clinician must make the diagnosis and consider the clinical and family history, the presence of trigger factors, and the psychological aspects in a holistic vision of the patient. Further studies are needed to improve the software in order to increase the diagnostic concordance.

CREATION AND PRELIMINARY VALIDATION OF A DIAGNOSTIC BASIC HEADACHE DIARY: THE EUROHEAD EXPERIENCE AND ITS POSSIBLE DEVELOPMENTS

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Migraine and tension-type headache represent the most common forms of primary headaches. In the absence of biological markers, the diagnosis of these forms of headache depends entirely on the information obtained from clinical interviews as well as from physical examination. Headache diaries make it possible to record prospectively the characteristics of every attack, and this may reduce the recall bias and increase accuracy in the description.
The advent of the International Classification of Headache in 1988, with its recent revision (2004), has greatly contributed to the definition of precise criteria for the diagnosis of migraine and tension-type headache across the world. Nonetheless, support is needed to facilitate the adoption of these criteria, especially in the non-specialized clinical settings.
We have recently developed a basic version of a diagnostic headache diary for migraine and tension-type headache. Our objective was to devise a tool for assisting the diagnosis of these two types of headache in headache centres, as well as in non-specialized practice. The diary had to satisfy two important requisites: 1) simplicity, and 2) completeness for ICHD-II based diagnosis.
A pilot study was performed in order to test the diary in the Headache Centres of Pavia and Copenhagen. The data obtained were presented and discussed in a Consensus meeting held in Valencia during the last European Headache Federation Congress (April 2006). The findings obtained showed that the use of the diary is suitable for naive (*de novo*) patients and provides complete information for diagnosis in a very high percentage of subjects. Comparison of the diagnoses based on history and physical examination (gold standard) with those obtained from the diary showed a satisfactory degree of concordance. Furthermore, the use of the basic headache diary allowed a more detailed diagnostic definition.
A second version of the diary, aimed at a more precise detection of aura symptoms, is under preparation and will be tested in several European

countries in the near future. Hopefully, this process will lead to the availability of a validated tool – common but at the same time country-specific – for the proper and homogeneous diagnosis of migraine and tension-type headache across Europe.
Future steps include: 1) the preparation of an electronic version with a software-assisted diagnostic process; and 2) the elaboration of targeted diaries (i.e., for menstrual related attacks, for cluster headache, for children, etc.).

CLINICAL ASPECTS OF HEADACHES I

SYNCOPE IN MIGRAINE

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Introduction Migraine is an episodic, multifactorial neurovascular disorder characterized by recurrent attacks of disabling headache and autonomic nervous system (ANS) dysfunction. Syncope is a paroxysmal symptom consisting of a brief, self-limiting transient loss of consciousness due to global cerebral hypoperfusion. Several reports suggest that there is comorbidity between the two conditions.
Case report We describe the case of a 53-year-old woman suffering from migraine without aura since the age of 20. The attacks were constantly characterized by severe intensity and remarkable autonomic disturbances, in particular, nausea, vomiting and photophobia. In association with the most disabling attacks, usually once a year, she suffered from typical syncopes, which never occurred outside the migraine attacks. The patient was otherwise healthy and did not need any pharmacologic treatment, other than the symptomatic drugs for migraine. After age 40, the syncopes occurred more frequently, on average 2–3 times a year, with the intensity and frequency of migraine remaining unchanged. The patient consequently underwent a cardiac electrophysiologic study that was normal. At the age of 51 she had an extremely severe migraine attack with prominent autonomic disturbances; she developed multiple brief syncopes and was thus referred to the Emergency Department. Immediately after her admission, she had a protracted loss of consciousness, and the ECG-monitoring showed a complete sinus arrest lasting 20 seconds and resolved by the precordial thump procedure. After sinus rhythm was restored, further brief episodes of sinus arrest were documented. It was therefore established, considering the previous history of frequent and recurring syncopes, to implant a permanent pacemaker. The cardiologic tests were normal, in particular, possible coronary heart disease was ruled out by performing a treadmill test and a myocardial scintiscan. The tilt table testing was positive for induced syncope. After her discharge, she was regularly followed-up for 2 years and no further syncope recurred, despite the persistency of severe migraine attacks.
Discussion A higher lifetime prevalence of syncope among migraineurs was reported in some studies and an autonomic dysregulation was suggested to be involved in the pathophysiologic mechanisms of migraine. A dysfunctional or unstable ANS might render an individual more susceptible to migraine by reacting to triggers at a lower threshold.
Conclusions Migraineurs with disabling attacks seem to be more prone to ANS dysfunction. To our knowledge, we report the first patient suffering from strictly and exclusively migraine-associated syncopes who required the implant of a permanent pacemaker.

ALTERATIONS IN GLUCOSE-INSULIN METABOLISM IN MIGRAINEURS: A POSSIBLE NEW ETIOPATHOGENIC FACTOR IN MIGRAINE

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Introduction Migraine is characterized by a complex biochemical dysfunction attributed to a disorder of the trigeminal and hypothalamic pathways. Impairment of glucose metabolism has been reported in migraine, but data are scarce and inconsistent [1].
Objective The main aim was to verify if migraineurs present alterations in glucose and insulin metabolism.
Patients and methods The study population included three groups of subjects: 1. Migraineurs (M) consecutively seen at the headache centre of our hospital; 2. Patients affected by headache other than migraine (O), consecutively seen at our headache centre; 3. Healthy volunteers (HV), recruited among colleagues, nurses and technicians from our hospital. All the recruited people underwent a general blood test and a standard oral glucose tolerance test after a 12-hour fasting period, measuring levels of glucose and insulin.
Results In a 6-month period we recruited 84 migraineurs (73 women, 11 men), 25 patients with non-migraine headache (20 women, 5 men), and 26 healthy controls (24 women, 2 men). Both headache groups presented blood glucose levels (mg/dL) higher than the healthy control group (fasting: M 96, O 98, HV 83, p=0.000; at 30 minutes: M 142, O 143, HV 114, p=0.001; at 60 minutes: M 122, O 117, HV 95, p=0.008; at 120 minutes: M 102, O 93, HV 93, p=0.139). Compared to the other groups, migraineurs presented significantly higher insulin levels at any time of the test, both fasting and after glucose loading (fasting: M 10, O 7, HV 6, p=0.001; at 30 minutes: M 86, O 47, HV 48, p=0.000; at 60 minutes: M 79, O 43, HV 35, p=0.000; at 120 minutes: M 51, O 28, HV 29, p=0.001).
Conclusions High blood glucose levels can be recorded in headache patients, but do not seem to be specific to migraineurs. High insulin levels are recorded in migraineurs, and these data seem to be specific to this group of patients [2]. These findings are in keeping with recent reports on the effects of insulin on brain functions and lend support to the possible involvement of insulin in the pathogenesis of migraine.
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CLINICAL PICTURE OF CLUSTER HEADACHE IS NOT RELATED TO SEVERITY OF PATENT FORAMEN OVALE

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Introduction Patent foramen ovale (PFO) recently has been implicated in several diseases such as cryptogenic stroke, Obstructive Sleep Apnea Syndrome (OSAS) and migraine with aura. The nature of the relationship between PFO and migraine has not been completely understood. Although migraine and cluster headache (CH) are separate entities, pathophysiology and treatment partially overlap between them; also, in CH some studies have documented that the prevalence of PFO is higher than in the general population [1]. No correlation has been found between the clinical picture of migraine and severity of PFO [2] and no data are available for CH.
Material and methods We studied 18 patients (15 males and 3 females) with episodic CH, according to ICHD-II criteria (2004), who resulted positive for the presence of PFO to evaluate a correlation

between the entity of PFO and clinical picture (duration, daytime recurrence of attacks and the age of onset of disease) of CH. PFO was assessed with transcranial Doppler contrast (detection of right-to-left shunt) and confirmed by transesophageal echocardiography. Clinical parameters were evaluated by means of the clinical chart of the patients.
Results and discussion The patients with CH had a mean age of 36±6 years and male/female ratio of 15/3. Eleven patients showed low-grade PFO, 2 medium-grade PFO and 5 high-grade PFO. The age of onset of CH was 35±6 years, duration of attacks was 96±16 minutes and the daily recurrence was 1.8±0.6. The correlation was analyzed with matrix of correlation (R^2). No relationship was found between clinical parameters and PFO entity – at least as evaluated by means of microbubble detection – suggesting that the extent of PFO does not affect the clinical parameters of headache. From a speculative point of view these data may support the hypothesis that a particular genetic substrate may determine the persistence of PFO and the presence of CH in absence of a clear pathogenic link.
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MYOFASCIAL TRIGGER POINTS IN MIGRAINE PATIENTS

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Introduction Previous studies have shown that migraine patients often present myofascial trigger points (TrPs) in the cervical muscles whose target areas coincide with the site of migraine pain and that TrP treatment (repeated injections) over two months significantly improves migraine symptoms during the same period.
Objective The aim of the present study was to evaluate, in this type of patients, the long-term effects of TrP treatment, and in particular, to assess if TrP extinction results in stable, beneficial effects on migraine symptoms.
Methods Thirty-five patients (30 women, 5 men, aged 23–47 years), affected with frontal and/or temporal migraine and TrPs in the sternocleidomastoid, splenius cervicis or semispinalis cervicis muscles (targets located in the same sites as the migraine attacks) were examined. All underwent measurement of electrical pain thresholds in skin, subcutis and muscle at TrP and target level at baseline, and after 60, 120 and 180 days. TrP infiltration with local anesthetic was performed on days 1, 3, 10, 30 and 60. Number and maximal intensity (VAS scale) of migraine attacks were recorded for 60 days before and 180 days after the start of treatment. All patients were free from any other pain medication during the study.
Results At baseline, pain thresholds of all three tissues at TrP and target level were significantly lower than those recorded in 20 healthy controls of comparable age, testifying to the state of hyperalgesia ($p<0.001$). After 60 days of treatment:– all thresholds were significantly increased in both TrP and target (ANOVA: $p<0.002$); number and intensity of migraine attacks decreased significantly compared to pretreatment ($p<0.001$). The threshold increase correlated significantly with the reduction of migraine pain ($p<0.01$). At 120 and 180 days, all thresholds did not change significantly with respect to day 60. Number and intensity of migraine attacks relative to the periods: days 60–120 and days 120–180 did not differ significantly from those of the period days 0–60 of treatment.
Conclusions Extinction of myofascial TrPs, whose targets coincide with the site of migraine pain, has beneficial effects on migraine symptoms, which go far beyond the treatment period. This procedure is therefore recommended as an integral part of migraine treatment in these cases.

STATIC AND DYNAMIC POSTURE OF HEAD AND NECK IN MIGRAINE PATIENTS

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Background Migraine attacks may be accompanied by tension headache-like symptoms, such as neck and shoulder pain with muscle contraction. Headache due to cervical dystonia has been recently recognised by the new IHS classification of headache disorders.
Objective The aim of this study was to assess the head-neck static posture and the range of head-neck motion in migraine patients without any disorders of the cervical spine or soft tissues of the neck.
Methods We studied the head-neck static posture and the range of head-neck motion in 70 headache-free migraine patients and 70 controls. Static posture was assessed with a photographic method. Dynamic posture was assessed with a specific computerized device that evaluated the following head-neck movements: right/left rotation, flexion/extension and right/left sidebending (while the patients were in the sitting position). The results were expressed as angles (in degrees).
Results Head-neck static posture was normal in migraine patients and controls. In motion testing, head rotation was decreased on one side and extension was less marked than flexion in migraine patients. Statistically significant differences between right versus left-side head rotation ($p<0.001$) and head flexion versus extension ($p<0.01$) were found in migraine patients, but not in controls.
Conclusions The results of this study suggest that, although the head-neck static posture was normal, head-neck motility may be abnormal in migraine patients. Muscle tenderness and contraction, as a possible consequence of pain, may be responsible for these abnormalities. Alternatively, more complex central mechanisms, such as sensitisation, may be evoked in the interpretation of our results.

HEADACHE IN THE EMERGENCY DEPARTMENT: CLINICAL AND DIAGNOSTIC ASPECTS IN A ONE-YEAR RETROSPECTIVE ANALYSIS

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Introduction Headache is one of the most frequent complaints in the population referring to an emergency department (ED): in previous studies it accounted for 1%–4% of all presenting symptoms. In Italian studies this percentage varied from 0.6% to 1.2%. Moreover, headache represents one of the most frequent reasons for neurological consultation (NC).
Methods By means of a computerized database, we retrospectively examined all clinical records of patients presenting to our ED during 2005, complaining of headache as the only or prevalent symptom.
Results A total of 69 441 patients were admitted to the ED during 2005. Among these, 1 009 (1.45%) complained of headache; 390 were males, 619 were females; mean age was 39.5 years (41.4 years for males, 37.6 years for females). In this period 2 437 NC were done in the ED (3.51% of all consultations) and 40.8% of them were requested because of headache. Two hundred and fifty-one (24.8%) headaches were diagnosed as primary headaches (PH) (belonging to the first 4 groups of the IHS classification) and 439 (43.5%) as secondary headaches (SH). Four hundred and thirty-two (42.8%) patients were coded as "headache not otherwise specified" (NOS) (code 784.0 of the International Classification of Diseases system (ICD)). As regards to diagnosis, 1 037 consults were requested; 418 (40.3%) were NC, followed by 50 (4.8%) neurosurgical, and 31 (3.0%) neuropaediatric visits. CT scan was performed in 341 patients (82.6%) requested mostly by the ED physician. Moreover, 5 perfusional SPECT (in migraine with aura), 3 lumbar

punctures and 2 MRI were carried out. Four hundred and eighty-four (47.9%) patients received post-discharge advice. Among these, 191 (39.4%) were referred to our headache centre, but only 48 (25.1%) attended it.

Discussion Our epidemiologic data are similar to those from international studies, but show a higher prevalence of headache, when compared to other Italian studies. This is probably because we considered all headaches, including traumatic and paediatric headaches.

The proportion between primary and secondary headaches (1/1.75) differs from that of other studies that show an equal prevalence for PH and SH or a higher prevalence of PH. We have indeed many NOS headaches, which could really be PH. In our opinion, PH are not easily diagnosed in an ED for many factors: 1) the IHS classification is too rigid to be used in this context; 2) the ICD system, to which ED physicians have to refer in the discharge form, is very limited and most headaches do not have a corresponding code; 3) the ED environment does not facilitate a differential diagnosis among headaches.

HANDEDNESS AND UNILATERAL HEADACHE IN MIGRAINE

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Introduction In april 2002, Lipscombe and Prior [1] published the results of a research inherent to "a possible relationship between handedness and unilateral headache in migraine".

The aim of the study was: "It seems surprising that if pain is related to vasodilation of the meningeal arteries that one side should be more painful than the other. Why should it be that vessels on one side dilate in preference to the other? One thought we had was the possibility that this could be linked to handedness".

The authors concluded that "The distribution of (patients) handedness was in accord with the expected 10:1 right-to-left-handedness. The identification of a unilateral location for two-thirds of the patients was interesting, though the variability of sides for a third of this subgroup (i.e., localized always to one side or the other but not predominantly one side) was higher than expected [1].

One-third of migraine patients who localized their headache did so to the left and one-third to the right. There was no correlation whatsoever with handedness" [1].

Objective The aim of the present study was to verify, through a wider patient sample size (502 v. 126, [1]), the relationship between handedness and unilateral headache in migraine.

Methods We administered a questionnaire, similar to the one used by Lipscombe and Prior, to migraine patients who presented to our Centre during a 6-month period and compared the results with a group of non-migraineurs, observed in the same period.

Results Of 2 395 neurologic non-migraine patients, 2 272 (94.86%) were right-handed and 123 (5.14%) left-handed, mean age: 60.25 years; F 1515, M 880. Of 502 migraine patients, 91.24% (458) were right-handed and 8.76%, (44) left-handed (more than expected), mean age: 35.19 years; F 394, M 108.

We found bilateral pain in 18.73% (94/502) of migraine patients and unilateral pain in 81.27% (408/502) (more than two-thirds of the patients of Lipscombe and Prior's study). Of these, 82.10% (376/458) right-handed and 72.73% (32/44) left-handed patients reported unilateral pain. Thus, the right-handed patients reported more often unilateral pain. Of all patients (502), 61.16% (307) identified recurrent headache occurring on the same side (right side or left side), but in the unilateral headache patient group (408) this recurrent headache occuring on the same side was referred by 75.24% (59.90%: right; 20.34%: left) and only 24.76% (101) referred pain changing sides.

Surprisingly, in the right-handed patients (74.76%) (209) with recurrent pain on the same side, it was referred to the right side, and only 25.36% (71) referred pain to the left side. In contrast, 55.56% (15/27) of the left-handed patients identified headache on the right side, and 44.44% (12/27) referred headache to the left side.

Discussion It is possible that unilateral right-handed headache sufferers might experience pain in their hand dominant hemisphere. Lipscombe and Prior's hypothesis of "a possible relationship between handedness and unilateral headache in migraine" [1] is confirmed, at least in right-handed patients, because our right-handed patients localized pain predominantly on one side; thus, a relationship between right-handedness and the dominant unilateral side of headache may be possible.

Why is the phenomenon predominant in right-handed patients and less so in left-handed patients? This is not a contradiction because unilateral headache sufferers might experience pain in their hand dominant hemisphere, while the left-handed patients, considering the possible variability of cortical centres [2] (for instance, speech centre), could report the pain in likewise varying manners.

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CLINICAL ASPECTS OF HEADACHES II

CHRONIC GASTRIC INFECTION BY HELICOBACTER PYLORI AND GASTROINTESTINAL SYMPTOMS DURING MIGRAINE ATTACKS

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Introduction In recent years *Helicobacter pylori* (*H. pylori*) infection has been supposed to play a role even in many extra-gastrointestinal illnesses [1], migraine among these [2].

Several mechanisms could link chronic *H. pylori* infection and vascular diseases including a low-grade acute phase response, free radical formation and immune-mediated mechanisms. However, the precise mechanism by which chronic *H. pylori* infection mediates these vascular effects remains unclear. Previous studies on seropositivity for *H. pylori* in migraine patients showed contradictory results.

Objective The purpose of this study was to investigate whether chronic gastric infection by *H. pylori* is in some way linked to the presence of gastrointestinal symptoms during migraine attacks.

Materials and methods A group of 104 patients (78 women and 26 men, age range 21–59 years, mean age±SD 39.70±12.41 years) attending the Headache Centre of the University of Turin, suffering from migraine without aura according to the International Headache Society criteria (ICHD-II), were studied.

H. pylori gastric infection was diagnosed by means of both the ^{13}C-urea breath test and the presence against *H. pylori* in serum. In accordance with previous published research guidelines, only patients with positive results for both tests were defined as infected by *H. pylori*.

The patients were divided into three groups, according to the presence of nausea (group A: 37 patients), both nausea and vomiting (group B: 54 patients) or the absence of both (group C: 13 patients) during the attacks.

Results In group A, 13 patients (35.1%) were positive and 24 (64.9%) negative to the infection; in group B, 20 (37%) were positive and 34 (63%) were negative to the infection; finally, in group C, 2 (15.4%)

were positive and 11 (84.6%) were negative to the infection (p=ns).
Discussion and conclusions On the basis of these data the presence of chronic gastric *H. pylori* infection does not seem to be related to gastrointestinal features during attacks, even though patients with gastrointestinal symptoms have a higher percentage infection than those without (36.3% *vs* 15.4%).
This observation could suggest the opportunity to ascertain the presence of infection particularly in this group of patients.
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HEADACHE PICTURES DURING THE COURSE OF CEREBRAL VENOUS THROMBOSIS

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Aim Description and classification of headache symptoms during the course of Cerebral Venous Thrombosis (CVT) in the acute-subacute phase (*group A*) and among headache patients with angiographic abnormalities suggesting previous CVT (*group B*).
Methods Headache classified according to ICHD-II; neurological deficits and outcome by National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS); seizures, intracranial hypertension, subacute encephalopathy and other syndromes by standard descriptive criteria. Neuroimaging: MRI and/or CT intracranial angiography and digital subtraction angiography (DSA). Clinical and neuroimaging follow-up: mean 19 months.
Patients Consecutive cases of acute CVT: n=40 (*group A*), 32 F (80%), mean age at onset 37.4 years; main risk factors: thrombophilic conditions in 28 patients (70%), oral contraceptives in 19 subjects (47.5%), overweight (BMI≥30) in 30%. Site of thrombosis: transverse sinuses (70%), superior sagittal (60%) and others (cortical veins/jugular/others) isolated or in combination (55%). Clinical pictures (acute-postacute phases): headache as presenting symptom in 25/40 (62.5%), during the entire course, 85%, isolated – as the only symptom – in 5/40 (12.5%); sensorimotor deficits 37.5%; seizures 30%; intracranial hypertension with or without papilledema 17.5%; other neurological syndromes 50%. Most frequent complications during follow-up: epilepsy (42%) and headaches (33%); neuroimaging evidence of partial or complete recanalization occurred in over 85% at different time intervals from the acute event.
A smaller group of headache patients – n=17 (group B) with disabling symptoms (either episodic or more or less continuous), poor response to treatments, with neuroimaging signs suggesting a previous/remote CVT: 12 F, 5 M, 39.2 years at observation and with concomitant neurological focal abnormalities (clinical/EEG, CT/MR) in 36%.
Results Headache (any new/sudden-onset) is confirmed as being the most frequent symptom during the acute phase of CVT (present in 85% of cases) and also the most frequent and significant inaugural symptom. Headaches attributed to CVT are more frequently characterized by hyperacute disabling symptoms mimicking primary thunderclap headache and headache during the course of CSF hypotension or subarachnoid haemorrhage – as underscored by ICHD-II. Less frequently, migraine-like attacks, cervicogenic headache and other headaches with less specific characteristics may be observed.
Migraine-like headaches and clinical pictures fitting the criteria for one of the complications of migraine are more often observed during the long-term follow-up of CVT as well as among those headache patients showing chronically recurring disabling symptoms coupled with evidence of possible-probable previous/remote CVT. Also for these cases, even in the absence of a close temporal relationship to the thrombotic event, the inclusion in the 6.6 diagnostic subgroup should be considered.

OSMOPHOBIA IN JUVENILE PATIENTS SUFFERING FROM MIGRAINE AND TENSION-TYPE HEADACHE

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Introduction The differential diagnosis between migraine (M) and tension-type headaches (TTH) is based on ICHD-II criteria (2004) including photophobia, phonophobia, nausea and vomiting as significantly associated symptoms. Osmophobia (O), i.e., altered odor perception, is reported in point D of the Appendix of this classification as a possible accompanying symptom of migraine without aura (MO); recently O has been found to be specific for the diagnosis of adult migraine [1]. In a pilot study we found that O was frequent in juvenile M, but it seems less specific than in adults [2].
Materials and methods Two hundred and seventy-five consecutive patients, referred to our Centre in 2005, were affected by M or TTH, according to ICHD-II criteria. Mean age was 11.4±3.0 (6–17 years), 158 females (57.5%) and 117 males (42.5%). One hundred and sixty–seven (60.8%) suffered from M (144 (52.4%) MO and 23 (8.4%) migraine with aura (MA)), and the remaining 108 (39.2%) from TTH (88 (32%) frequent TTH and 20 (7.2%) chronic TTH).
Results The prevalence of O during attacks in the study population was 18.5%, higher in M patients (25.1%) compared to those with TTH (8.3%). In particular, O was found in 27.1% of MO, 13% of MA, 8% of episodic TTH and 10% of chronic TTH. There was no correlation between O and age or gender. O was usually described as a very early onset symptom (mean age at the onset of O: 8.1± 3.3 years and of headache: 8.1±2.7 years). The offending odors were perfumes (63%), food-related smells (53%) and tobacco smoke (30%). The olfactory stimulus triggered the attack in 37.3% of osmophobic patients (26.2% with M).
In the differential diagnosis between MO and episodic TTH, O was a poorly sensitive symptom (27.1%) but rather specific (91.7%), and its specificity was greater than photophobia (61.4%) and phonophobia (45.5%). Regarding the positive predictive value, O had a greater value (82.3%) when compared to photophobia (74.1%) or phonophobia (65.5%), occupying third place after nausea (95.3%) and vomiting (100%).
Discussion In this sample of patients with juvenile primary headache, during M attacks, O was present in a smaller proportion (25.1%) than in adults reported in the literature (24.7–47.7%), and was observed less frequently in TTH. However, O represents a more specific factor for the diagnosis of migraine than photophobia and phonophobia.
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HEADACHE IN CHILDREN YOUNGER THAN 6 YEARS OF AGE

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Aim In order to study the clinical features of headache in pre-school-age children, we retrospectively reviewed records regarding subjects younger than 6 years observed in the Headache Centre of the Anna

Meyer Paediatric Hospital of Florence.
Methods We included in the study children who were evaluated during a period of five years (from 2001 to 2005), and were under 6 years of age at first observation. All the patients underwent a clinical evaluation/history and, if necessary, laboratory tests, radiological and other instrumental investigations. The headaches were classified according to the second edition of the International Classification of Headache Disorders (ICHD-II, 2004).
Results Of a total of 2 935 patients examined in the study period, 115 children (3.9%) were younger than 6 years, with a male/female distribution=68/47 (59.1% *vs.* 40.9%); mean age was 4.5 years, age range from 1.10–5.11 years. One hundred subjects (87%) had a positive family history for headache.
Thirty patients performed imaging tests: in 5 cases neuroimaging abnormalities were identified and led to the diagnosis: Arnold Chiari type 1 malformation in 1 case, sinusitis in 3 cases, and low CSF pressure in ventriculoperitoneal shunt in 1 case.
According to ICHD-II, 2004, we found 96 children at first observation with primary headaches (83.5%): 11 cases with migraine without aura (MO) (9.6%), 1 case with migraine with aura (MA) (0.86%), 2 cases with cyclical vomiting (1.7%), 6 cases with benign paroxysmal vertigo of childhood (5.2%), 69 cases with probable migraine (60%), 3 cases with infrequent tension-type headache (2.6%), 3 cases with probable tension-type headache (2.6%). Sixteen subjects had secondary headache (13.9%) (particularly systemic viral or bacterial infections and sinusitis); three children reported a mixed pattern.
A follow-up evaluation was possible in 57/115 cases (49.6%), 34 males (59.6%) and 23 females (40.4%); mean age of 4.5 years. Eighteen children (31.5%) were in "remission" and 39 patients (68.5%) showed recurrent symptoms: 12 cases with MO (21%), 1 case with cyclical vomiting (1.8%), 1 case with MO and cyclical vomiting (1.8%), 2 cases with benign paroxysmal vertigo of childhood (3.5%), 21 cases with probable migraine (36.8%), 2 cases with infrequent tension-type headache (13.5%). At follow-up only primary headaches were present.
Conclusions Our study shows male gender prevalence in pre-school age (male/female=1.44/1). Primary headaches were more frequent than secondary and post-traumatic headache; chronic daily headache and idiopathic stabbing headache were absent. Further follow-up studies are necessary to improve knowledge, treatment and outcome of headache in children younger than 6 years of age.

THUNDERCLAP HEADACHE CAUSED BY MINIMALLY INVASIVE MEDICAL PROCEDURES: DESCRIPTION OF TWO CASES

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Thunderclap headache, defined by IHS classification as a severe head pain of sudden onset, may raise the question of whether a subarachnoid hemorrhage has occurred.
We report two very unusual cases of thunderclap headache complicating minimally invasive medical procedures.
In the first case, headache developed as the consequence of a pneumocephalus caused by an inadvertent intrathecal puncture during oxygen-ozone therapy for lumbar disk herniation.
The headache of the second case was due to intracranial hypotension, caused by the persistence of the needle used for epidural anesthesia, which then penetrated into the subarachnoid space.

TREATMENT OF NONTRAUMATIC HEADACHE IN THE EMERGENCY DEPARTMENT

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Introduction Nontraumatic headache (NTH) is a common complaint in the Emergency Department (ED), accounting for 0.6%–4.5% of all visits. Guidelines for therapy of headache in the ED setting are lacking.
Objective The aim of the study was to analyse the therapies employed in patients presenting to the ED with a chief complaint of headache in order to provide therapeutic guidelines to ED physicians and improve the cost-to-benefit management of such patients.
Patients and methods A retrospective analysis of the records of all patients presenting in a six-month period (January 1, 2004 to June 30, 2004) with nontraumatic headache (NTH) to the ED of the University Hospital of Trieste was performed. Demographic and clinical information, therapies administered, and time spent in the ED were obtained. Data were analysed using the Statistical Package for the Social Sciences (SPSS 12.0).
Results We screened 300 NTH patients (0.8% of all ED visits), 61% F and 39% M with a mean age of 45 [SD 19] years. Diagnosis at discharge was secondary headache (41.3%), primary headache (24.3%), and headache "not otherwise specified" (NOS) (34.4%). One hundred and seventy patients (56.6%) were treated with mono- (86 patients, 50.6%) or poli-therapy (84 patients, 49.4%): 56.7% with NSAIDs, 13.4% with benzodiazepines, 10.7% with antiemetics, 6.2% with antihypertensives, 1.5% with triptans, and 11.5% with other drugs. Forty out of 50 patients with migraine received pharmacologic treatment, 90% with NSAIDs and 10% with triptans. The mean time spent in the ED was 225 [SD 285] minutes, with no differences between primary, secondary and NOS headaches (p=NS). The length of stay in the ED was similar in patients with primary headache treated with mono- (119 [SD 121] minutes) or poli-therapy (114 [SD 60] minutes) (p=NS). A significant difference in the length of stay in the ED between migraineurs who were administered triptans (112 minutes [SD 25]) and migraineurs treated with NSAIDs (265 minutes [SD 282], p=0.02) was found.
Conclusions Most used drugs were NSAIDs, first of all ketorolac and indomethacin. Patients with primary headache had the same outcome in terms of time spent in the ED when treated with mono- or poli-therapy. Only 10% of migraineurs received triptans, despite the recommendation to use triptans as first-line drugs for moderate and severe migraine attacks. The administration of triptans in patients with migraine significantly reduced the length of stay in the ED. Patients in whom triptans were used did not need other drugs. Therapeutic guidelines to ED physicians are needed to improve the cost-to-benefit management of such patients.

CHRONIC HEADACHES: NEW ACQUISITIONS

THE ROLE OF SENSITIZATION MECHANISMS IN CHRONIC HEADACHES

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The mechanism underlying the development of migraine attack as well as why episodic migraine becomes chronic over time in some patients, is still debated. It has been shown that sensitization of trigeminal peripheral nociceptors as well as the subsequent central sensitization of second and third order neurons play a critical role in migraine attack and cephalic and extracephalic cutaneous allodynia. In migraine it can be hypothesized that central sensitization is strictly dependent on incoming impulses from the meninges in the early phase of the attack, and later maintains

itself in the absence of such sensory inputs. This view is supported by evidence that early triptan treatment blocks the migraine attack and cutaneous allodynia in allodynic patients. It is reasonable that an activity-independent central sensitization can develop in patients with frequent attacks and long-lasting disease, leading to a chronic form of headache. This hypothesis could explain the high extracephalic sensitivity to electrical stimuli in chronic migraine with overuse of symptomatic drugs, to thermal and mechanical stimuli, observed in patients with migraine attacks and transformed migraine as well as the close association between chronic migraine and other chronic painful syndromes such as fibromyalgia, in which both a widespread central sensitization and a defective functioning of the supraspinal antinociceptive system, has been hypothesized.
Functional imaging studies in chronic headaches emphasized the involvement of modulatory nociceptive and antinociceptive brainstem and cortical structures. Such structures may contribute to the pathological changes in the physiological properties of trigeminal neurons and could explain the subsequent sensitization of the nociceptive pathways at several levels of the central nervous system during migraine attack. In this view, both an activity-dependent (sensitization of peripheral nociceptors) and an activity-independent (probably driven by a permanent dysfunction of descending modulatory pathways) central sensitization, may account not only for the transformation of episodic to chronic pain condition but also for a widespread abnormal nociceptive processing along the cephalic and extracephalic pain pathways, inducing a spreading process of central sensitization.

CURRENT VIEWS ON A NEW OPTION IN THE LONG-TERM PREVENTION OF CHRONIC DAILY HEADACHE

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The treatment of Chronic Daily Headache (CDH) is still inadequate. Effective, well-tolerated prevention represents the last goal for a complete rehabilitation of CDH patients. Medication-overuse headache (MOH) often overlaps CDH, causing the re-prophylaxis phase schedule after detoxification to be inadequate and providing only short-term relief. We presently reviewed studies concerning the efficacy of Botulinum Toxin Type A (BoNT-A) as preventative treatment for CDH. The 2004 IHS classification of CDH includes all chronic headaches lasting more than 15 days per month, for a period longer than 90 days. The clinical forms mentioned in this term are the following: Chronic Tension-Type Headache (CTTH), Chronic Migraine (CM), Transformed Migraine (TM), Hemicrania Continua (HC), and New Daily-Persistent Headache (NDPH). This large group of chronic headaches needs to be definitively recognized in the next revision of the IHS Classification.
The therapeutic armamentarium of CDH is based on old drugs, antidepressants (tricyclics) and NSAIDs. There is an evident paucity of evidence-based medicine current treatments used in the prevention of CDH. Both topiramate and BoNT-A seem to represent – in terms of efficacy – the most convincing options in the operational therapeutic scenario of CDH. Nevertheless, the presence of adverse events (AEs) should always be considered in the therapeutic choice of these chronic disorders.
A retrospective analysis of both open and double-blind studies on the efficacy of BoNT-A in CDH, with or without MOH, showed conflicting results. Some authors explained these results with a selection of CDH patients with and without MOH in the trials. BoNT-A prevention mechanisms for CDH are not completely known, and are probably not just based on acetylcholine inhibition of the neuromuscular junction. BoNT-A may have a distinct antinociceptive mechanism or inhibit calcitonin gene-related peptide release, substance P and other neuropeptides at the trigeminal level, as suggested by studies in animal models. Further larger studies are needed to confirm the efficacy of BoNT-A and therefore to provide a new effective, safe and widely accepted therapeutic option for CDH.

THE CHRONIC PATIENT AND DRUG ABUSE

MEDICATION-OVERUSE HEADACHE: FROM THEORY TO PRACTICE

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Medication-overuse headache (MOH) is a secondary headache coded in section 8.2 of the revised International Classification of Headache Disorders (ICHD-II) [1]; the diagnostic criteria for MOH defines the substance overused (ergotamines, triptans, analgesics, opioids, combinations), the duration of overuse (at least 3 months), and the days of intake per month. According to ICHD-II, the diagnosis of MOH can be assigned when, within two months of discontinuation of the overused medication, the following conditions are met: reversion of headache from a chronic to episodic pattern (<15 headache days/month) and discontinuation of overuse (<10–15 days/month).
MOH is a considerable health problem, reported by up to 10% of European Specialty Headache Clinics. The clear pathogenesis of MOH is unknown. Is the overuse a causative, aggravating or facilitating factor? Does the overuse depend on the drug type, the duration of exposure, or the habits of the patient? There is general agreement that the only treatment for MOH is withdrawal of the overused drug, but there are no guidelines or consensus recommendations on the management of this condition. There are some indications on withdrawal as outpatients or in-patients but very few prospective studies have investigated the course and outcome of MOH after withdrawal.
The main problem in the management of MOH is relapse into overuse after withdrawal. The management of these patients must therefore include, in addition to detoxification and drug therapies, an integrated programme of care covering the needs of the patient and family members, lifestyle indications, non-pharmacological therapy, interaction between patients (support groups), and planning for discharge.
In our Headache Centre a course of care (CARE) has been developed for the management of MOH patients [2]. In this prospective study inpatient detoxification was followed by scheduled visits for two years after discharge. Each subject underwent a baseline standard interview and a Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). After discharge the subjects returned for five scheduled visits (three in the first and two in the second year). We also conducted telephone follow-ups between visits. The management of these patients needs more than pharmacological treatment and must include non-pharmacological modalities and patient education. CARE is a model for the management of a chronic condition and it allows monitoring of the course of MOH with regard to relapses and predictors of outcome.

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COMPARISON BETWEEN PATIENTS WITH TRANSFORMED MIGRAINE AND MEDICATION OVERUSE AND PATIENTS WITH EPISODIC MIGRAINE AND OCCASIONAL MEDICATION USE

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Frequent use of symptomatic medication is considered one of the major factors able to transform an episodic headache into a chronic one. Migraine sufferers are most at risk of slipping into this complication. Our aim was to compare sociodemographic data, family history, physiological and medical history, health services utilized, drugs taken/prescribed and outcome of two groups of subjects: 1) transformed migraine patients with medication overuse, and 2) episodic migraine patients with only occasional analgesic use.

Methods We studied: – 150 patients, suffering from transformed migraine and probable medication-overuse headache (TM group), consecutively admitted during 2005 to the in-patient ward of the Headache Centre of the University Hospital of Modena and Reggio Emilia, Italy, to undergo withdrawal from their overused medications; – 100 patients suffering from episodic migraine, only occasionally using analgesics (EM group), consecutively referred to the outpatient wards of the Headache Centre during November and December 2005.

Results TM patients began to suffer from migraine earlier than EM patients. Drug and/or alcohol abuse was significantly higher among first-degree relatives of TM (19%) than of EM (6%) patients. The most frequent comorbid disorders were psychiatric (67%) and gastrointestinal diseases (43%) in TM patients, and allergies (31%) in EM patients. Seventy percent of TM patients and 42% of EM patients were taking daily at least another drug, besides those for headache treatment. TM patients were above all taking sedative-hypnotics (30%). Instead, EM patients were above all taking antiulcer agents (15%). Most overused medications in the TM group were triptans (43%); the EM group used primarily just NSAIDs (56%). After withdrawal of the overused medication, a prophylactic headache treatment was prescribed to each TM patient, antidepressants being the most prescribed drugs (59%). Prophylactic headache treatment was also prescribed to 86 of 100 EM patients, flunarizine being the most prescribed drug (58%). At 3 months follow-up, prophylactic treatments reduced at least by 50% the frequency of headache in around 75% of patients of both groups; however, headache remained significantly more frequent in TM than in EM patients: only a minority (15%) of TM patients reverted to a headache frequency comparable to that of EM patients.

Conclusions Most transformed migraine patients overusing medications had characteristics substantially different from those of episodic migraine patients. Transformed migraine, even after withdrawal from medication overuse, could not be completely reverted by current prophylactic treatments; therefore, a large number of patients with transformed migraine remain at risk of relapse.

MEDICATION-OVERUSE HEADACHE: CLINICAL ASPECTS AND PATHOPHYSIOLOGICAL IMPLICATIONS

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Medication-overuse headache (MOH) is a health problem widely recognized in the last few decades. Epidemiological data suggest that at least 1% of the general population have MOH. This pathological condition is associated with considerable long-term morbidity and disability. The substances associated with the overuse have dramatically changed over the past years. All symptomatic drugs, such as triptans, analgesics, ergots and opioids, along with the common combination substances currently on the pharmacological market are capable of inducing MOH. The delay between the beginning of symptomatic drug overuse and daily headache is shortest for triptans, longer for ergot alkaloids and longest for analgesics.

A linear relationship between analgesic use and headache frequency has been found. The disorder affects either adolescents or adults of various ages. MOH has been frequently associated with psychiatry comorbidity, behaviours of substance dependence, low socioeconomic status, metabolic and neuro-hormonal changes. The pathophysiology of MOH remains unclear. Among the suggested pathophysiological mechanisms underlying MOH are mechanisms of central sensitization as well as compulsive reward-seeking behaviour [1]. Medication-overuse headache has been recently found associated with reversible metabolic changes in some pain processing structures and with persistent orbitofrontal hypofunction even after withdrawal of analgesics [2]. Interestingly, this latter finding is known to occur in drug dependence and suggests similar pathophysiological pathways between MOH and some forms of drug addiction. Accordingly, preliminary results suggest an involvement of the endocannabinoid system in MOH. Recognition of MOH allows appropriate clinical intervention that includes drug withdrawal. Concerning the management of MOH, a combination of lifestyle modifications, behavioural therapy, and withdrawal of overused medications combined with preventive treatment are recommended. However, data from randomized clinical trials to guide the use of preventive treatment in patients with MOH are lacking.

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ONE-YEAR OUTCOME OF PROBABLE CHRONIC MIGRAINE+PROBABLE MEDICATION-OVERUSE HEADACHE AFTER AN OUTPATIENT REGIMEN OF ABRUPT WITHDRAWAL OF THE OVERUSED DRUG AND DETOXIFICATION REGIMEN: ANALYSIS OF THE NEED FOR OVERUSED DRUGS

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Introduction Successful detoxification is necessary to ensure improvement in the headache pattern when treating patients with chronic headaches who overuse acute medications. No rigorous prescribing guidelines are currently to facilitate the management of these patients. Little research has been conducted to investigate why the different proposed regimens failed, in particular, the aspects related to the need for analgesics/drugs overused by these patients [1].

Patients and methods A total of 120 patients, 82 females (68.3%) and 38 males (31.6%), mean age 48.6±10.4 years, affected by probable chronic migraine (PCM) and probable medication-overuse (PMOH) according to ICHD-II diagnostic criteria were admitted to the study.

Patients were treated in an outpatient regimen with abrupt discontinuation of the medication-overused, intravenous hydration and ademetionine, metoclopramide if necessary, and oral or intravenous administration of benzodiazepines for 7–10 days. Analgesics or triptans were used under medical supervision only in cases of severe rebound headache. Prophylactic medication was started immediately after admission.

The following outcomes at baseline and after one-year of follow-up were considered: number of days with headache per month; intensity of headache; duration of headache; headache scores (frequency x intensity), type of drugs abused and daily drug intake (DDI); and Leeds Dependence Questionnaire (LDQ) scores.

Results Before detoxification, 59% of patients overused more than one type of medication. Overused substances included: acetaminophen, 29.1%; nonsteroidal anti-inflammatory medications including aspirin, 65%; combination analgesics, 53%; triptans, 36.6%; and ergot derivatives, 7.5%.

Of 120 patients enrolled, 68 (56.7%) were successfully detoxified (group A), while 52 (43.3%) were not (group B). Comparison between groups A and B after one-year of follow-up showed a decrease in the

frequency of headache of 71.7% in group A and only 10.1% in group B (p<0.001). Similarly, the duration of head pain was reduced by 61.2% in group A and 15.6% in group B (p<0.0002). The headache score after one year was 17.7 in group A and 52.0 in group B (p<0.0001).
A total of 51 (42.5%) successfully detoxified subjects in group A returned to an episodic pattern of migraine, compared to 10 (8.3%) in group B (p<0.003).
The mean LDQ total score was higher in group B (11.10±6.35) than in group A (9.27±5.51) at baseline. Group B had the highest scores in item 9 (Z=-5.27, p<0.001) addressing the need for the continued administration of the drug to maintain well-being, and in item 3 (Z=-2.39, p<0.05), exploring compulsion to start the use of the drug. A significant reduction of LDQ scores was found at the one-year follow-up in group A (5.21±2.78) compared with group B (10.20±5.23) (p<0.001).
Discussion The results of the present study suggest that the abrupt withdrawal and detoxification regimen leds 56.7% of patients to discontinue the overused drugs and the majority of them within one year to return to a pattern of episodic migraine. The remaining patients did not discontinue the abused drugs and retained a chronic pattern of headache. They showed a behaviour of drug dependence similar to that found in the drug-addicted group. Patients who positively responded to the drug detoxification regimen had, in contrast, a drug dependence behaviour, which seemed to originate essentially from the necessity for the analgesic to cope with everyday life [2].
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ADVICE ALONE VERSUS STRUCTURED DETOXIFICATION PROGRAMMES FOR MEDICATION-OVERUSE HEADACHE: A 1-YEAR PROSPECTIVE, RANDOMIZED, OPEN-LABEL TRIAL IN TRANSFORMED MIGRAINE PATIENTS WITH LOW MEDICAL NEEDS

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The aim of this study was to compare the short- and long-term effectiveness of intensive advice to withdraw overused medication with the effectiveness of two structured, pharmacological detoxification strategies in a cohort of patients diagnosed with probable medication-overuse headache (MOH) plus migraine and presenting low medical needs. One hundred and twenty patients participated in the study. Exclusion criteria included: previous detoxification treatments, co-existent medical or psychiatric illnesses, and overuse of agents containing opioids, benzodiazepines, and barbiturates. Group A received only intensive advice to withdraw the overused medication. Group B underwent a standard outpatient detoxification programme (advice+prednisone+preventive treatment). Group C underwent a standard inpatient withdrawal programme (as in group B+ fluid replacement and antiemetics). Withdrawal therapy was considered successful if, after two months, the patient had reverted to an episodic pattern of headache and to an intake of symptomatic medication for fewer than 10 days/month. Relapse was defined as frequent use of any acute medication on more than 10 days/month for at least 3 months. After 2 months, we were able to detoxify 75.4% of the whole cohort, 77.5% of the patients in Group A, 71.7% of the patients in Group B, and 76.9% of those in Group C (p>0.05). At 1-year follow-up, the relapse rate was 22.2 % (15.3% of those in Group A, 26.9% of those in Group B, and 26.2% of those in Group C, p>0.05). In patients with migraine plus MOH and low medical needs, short- and long-term effective drug withdrawal may be obtained by just offering advice.

MEDICATION-OVERUSE HEADACHE: AN INTEGRATED PHARMACOLOGICAL AND BRIEF ANALYTIC PSYCHOTHERAPEUTIC APPROACH

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Introduction Chronic migraine (CM) with medication-overuse headache (MOH) is a very disabling condition, frequently associated with psychiatric comorbidity. At present, clear guidelines for the withdrawal of the overused drug and detoxification are lacking. In this regard, a role for psychological support has been hypothesized.
Objective We studied the efficacy of an integrated pharmacological and brief analytic psychotherapeutic approach in these patients.
Patients and methods We enrolled patients affected by probable CM and MOH (ICHD-II). They underwent a standardized neurological and psychiatric evaluation before and 6 months after medication withdrawal. Patients were randomly assigned to pharmacological treatment alone (group A), or associated with a brief analytic psychotherapy (group B). We applied the technique of Gillieron (1989), based on the principles of brief psychodynamic psychotherapy and mainly oriented toward assisting the patients with clarification and understanding of their disorder [1].
Results Twenty-one consecutive patients (M/F: 1/20, mean age 46±10 years) with probable CM and MOH were included. Headache frequency was 27.9±5.4 days/month, with a mean drug intake of 60.3±35.2 tablets (25.5% triptans, 13.1% ergotamine, 2.2% codeine, 32.4% NSAIDs, and 26.9% combined analgesics). The mean age of first attack was 19.6±7.8 years and mean duration of MOH was 7.6±9.4 years. Eleven patients were randomly assigned to group A and 10 to group B. About 70% of patients presented with psychiatric comorbidity, in particular, anxiety (42%) and depressive disturbances (32%). To date, 15 patients had completed the 6-month follow-up (A, 6; B, 9), showing a clinical improvement (headache frequency 16.7±11.4; days/month, drug intake 12.9±11.0 tablets/month). With respect to baseline, patients treated with the integrated approach showed a greater decrease of headache frequency (days/month: -48% *vs.* -32%) and drug intake (tablets/month: -87% *vs* -68%, p<0.04) than those only treated pharmacologically. In particular, they showed a lower relapse rate (10% *vs.* 36,4%).
Conclusions The integrated approach improved treatment efficacy in MOH patients, particularly decreasing drug overuse. This practical form of brief psychological support is effective and may help the patients in a shorter time and at a lower cost than long-term psychotherapeutic treatments.
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ALEXITHYMIC FEATURES AND PERCEIVED STRESS IN CHRONIC TENSION-TYPE HEADACHE AND MEDICATION-OVERUSE HEADACHE PATIENTS

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Introduction The definition of a personality profile in headache patients is no longer considered an attainable goal for empiric research, which has focused on specific psychological variables including coping mechanisms, emotional distress and alexithymia, conceived as difficulty in identifying and communicating emotions. Recent studies have found alexithymic features connected with anxiety and depression in headache patients [1, 2].
Objective The study intended to investigate the relationships between alexithymia and perceived stress in primary headaches, exploring pos-

sible differences between clinical subgroups of chronic tension-type headache (CTTH) and medication-overuse headache (MOH) patients.
Methods A sample of 104 outpatients (25 males, 79 females, mean age 46.1 years, age range 16–69 years), in treatment at the Headache Centre of the 2nd School of Medicine and Surgery, University of Rome "La Sapienza", composed of 70 patients with CTTH and 34 with MOH (primary headaches: 14 CTTH, 9 MO, 2 MA, 5 MO and CTTH, 3 MO and FTTH, 1 MO and ITTH), were administered:

a) the *Toronto Alexithymia Scale* (TAS-20), a paper and pencil questionnaire measuring 3 dimensions of the alexithymia construct: (F1) difficulties in identifying feelings; (F2) difficulties describing feelings; (F3) externally oriented thinking;
b) the *Rapid Stress Assessment* (RSA, by Tarsitani and Biondi, 1999), a perceived stress scale providing five clinical scores; Anxiety, Depression, Somatization, Anger, Lack of social support and a Total score.

Results and discussion According to the TAS-20 16.3% of the sample was classified as alexithymic, 20.2% as intermediate and 63.5% as non-alexithymic. RSA profile did not exceed the cut-off level for abnormal scores; Anxiety and Lack of social support showed higher values. Alexithymics scored higher than non-alexithymic and intermediate patients (One way-ANOVA) on all RSA scales (Lack of support: $F=8.2$, $p<0.001$; Total: $F=7.8$, $p<0.001$; Anxiety: $F=5.1$, $p<0.01$; Anger: $F=4.2$, $p<0.05$; Depression: $F=3.8$, $p<0.05$; Somatization: $F=2.4$, $p=.08$). Significant positive correlations (Pearson) were found among RSA scales, F1 and total TAS-20 scores, in both CTTH and MOH groups ($p<0.01$). No significant differences (unpaired t-test) were observed between CTTH and MOH groups on TAS-20 and RSA; however, MOH patients were more frequently classified as alexithymic (23.5% *vs.* 12.9%) and reported higher values on Anger scale ($p=.09$). MOH patients with primary diagnozsis of CTTH ($n=14$) were more frequently alexithymic (35% *vs.* 15%) and obtained higher values for Somatization ($p=.09$) than MOH patients with migraine.
Conclusions Findings supported the association between alexithymia and perceived stress as an index of psychological maladjustment. CTTH and MOH patients showed some distinctive features that require further research.

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PSYCHOPATHOLOGICAL FACTORS IN HEADACHES

SLEEP, SLEEPINESS AND FATIGUE IN MIGRAINE

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Introduction Several lines of evidence support the association between migraine on the one hand and sleep and sleep disorders on the other. Even though several pathogenic hypotheses have been postulated, the exact nature of this relationship remains enigmatic. Recently, interictal daily activities and functions were also examined in migraine sufferers. Low levels of realizable activity and of vigour were, indeed, documented, which could be conceptualised as the consequence of a migraine specific CNS functioning or alternatively as an acquired habit to anticipate and/or avoid a migraine attack. Moreover, limited data have suggested that daytime vigilance levels are impaired and that the complaint of chronic fatigue is greater in chronic migraine than in controls. The aim of this study was to verify sleep quality and daytime functioning parameters, such as sleepiness and fatigue, in episodic migraine.
Materials and methods One hundred patients diagnosed with migraine without aura, according to the second edition of the International Classification of Headaches (2004), were enrolled. Pittsburgh sleep quality index and Epworth Sleepiness Scale (ESS) were applied to all patients to evaluate sleep quality and "habitual" daytime sleepiness. In sixty patients, the Stanford Sleepiness Scale (SSS) was also administered in the prodromal phase (-24, -12 and -2 hours before attack onset) and during migraine attack, at onset and 1, 2, 4, 12 and 24 hours later to evaluate "critical" sleepiness. Patients were instructed to treat migraine attack with triptans in the early phase.
Results A total of 62% of migraineurs reported poor sleep quality and complained of chronic fatigue, while only 12% showed intercritical excessive daytime sleepiness according to ESS.
Evaluation of the time course of sleepiness by means of SSS confirmed significant impairment of vigilance levels in the prodromal phase, respectively, at –12 and –2 hours from the beginning of the episode. Significant differences in SSS scores were also documented at attack onset and 1 and 2 hours later compared with interictal values.
At four hours, mean SSS scores did not differ from their interictal values in the whole group and in patient responders to the treatment (pain free at 2 hours from drug intake), whereas non responders were sleepier than in intercritical conditions.
Discussion These data confirm the occurrence of sleepiness in the prodromal phase, possibly related to hypothalamic involvement and orexin neurotransmission impairment. The evidence that drowsiness, evident at the start of the attack, is resolved after migraine specific treatment, when efficacious, suggests that critical sleepiness might also be related to pathogenic mechanisms of migraine, whereas the role of triptans might be absent or minimal.

SLEEP AND HEADACHE DISORDERS: THE INTERNATIONAL CLASSIFICATION OF SLEEP DISORDERS, 2ND EDITION (ICSD-2) VERSUS THE INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS, 2ND EDITION (ICHD-II)

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In clinical practice and in the literature the co-occurrence of sleep disorders and headache is well known. Conversely, the intimate mechanisms of this association are not quite known. Surely, in the so-called sleep-related headaches, a causal and/or temporal relationship is admitted and both the International Classification of Headache Disorders, 2nd Edition (ICHD-II) [1] and the International Classification of Sleep Disorders, 2nd Edition (ICSD-2) [2] provide diagnostic criteria for these cases.
The ICHD-II includes two provisions for sleep-related headaches. Sleep apnea headache is a subclassification of headaches attributed to hypoxia and/or hypercapnia under the major code heading 10; it had the same code 10.1.3 in the previous classification but the diagnostic criteria are well defined only in this edition. According to the comment, it is unclear whether the mechanism of the headache is related to hypoxia, hypercapnia, or the disturbance in sleep. Hypnic headache is a new entry in the classification of headaches and is coded 4.5 within "Other primary headaches": it is characterized by attacks of dull pain that may be unilateral or bilateral and always occurs after falling asleep with no autonomic symptoms. No pathophysiological mechanisms are purposed.
In the first edition of ICSD, sleep-related headaches were included in the secondary sleep disorders, within those due to neurologic disorders. In ICSD-2, the secondary sleep disorders are not included: "following ICD rules, as soon as the underlying disorder is diagnosed, it becomes the primary diagnosis, and the previous sleep-related diagnosis is usually dropped because it is seen as a symptom of the underlying disorder". Thus, the sleep-related disorders are listed in Appendix A within the sleep disorders associated with conditions classifiable elsewhere.

The group includes "a heterogeneous group of different headache entities with the common feature of occurrence during sleep" (during REM sleep or 3–4 non-REM sleep) or upon awakening.
A singular sleep disorder, listed under "Other Parasomnias", is the Exploding Head Syndrome, which consists of the perception of a sudden sense of explosion in the head either at the wake-sleep transition or upon waking during the night followed by sudden arousal with a sense of fright. Although this experience is typically painless, the possible simultaneous occurrence of a stabbing pain raises the problem of a differential diagnosis from sudden-onset headache syndromes.
Knowledge of the diagnostic criteria of sleep-related headaches allows the headache specialist to better recognize the co-occurrence of the two disorders, resulting in a clear advantage for the management of the patient.

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PSYCHIATRIC DISORDERS IN MOTHERS OF HEADACHE AND EPILEPTIC CHILDREN: A CONTROLLED STUDY BY THE MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW (MINI)

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Introduction Headache and epilepsy are disabling conditions affecting the life of the patients and their families.
Studies showed a high rate of anxiety and mood disorders in both conditions, but we do not know the direction of influence and the aetiological mechanisms. We know that both disorders may run in families, as psychiatric disorders do.
The main aim of this study was to examine the psychiatric situations of the mothers of headache or epileptic patients, compared to the mothers of healthy children.
Material and methods Sixty-five (37%) (mean age 39.05 years) mothers of headache sufferers, 50 (29%) of epileptic children (mean age 38.8 years) and 60 (34%) mothers of healthy children (mean age 40.07 years) were interviewed using the MINI to make diagnoses according to DSM-IV criteria. The ICHD-II (2004) was used to make the headache diagnoses and the classification of the International League against Epilepsy (1989) to classify seizures. All statistical analyses were carried out using the χ^2 test.
Results Comparing data with the healthy sample, both headache and epileptic samples showed higher numbers of psychiatric disorders than controls (p<0.05). Among the 65 mothers of headache patients, 25 (38.4%) had at least one anxiety and/or mood disorder, of the 50 mothers of epileptic children, 28 (56%) had at least one anxiety and/or mood disorder (p=n.s.).
In the group of 65 mothers of children with headache, a subgroup exists from the 38.4% of mothers who showed at least one anxiety or mood disorder with 9 (13.85%) showing mood comorbid with an anxiety disorder.
In this sample of 25 mothers with a psychiatric disorder, we found that mothers with an anxiety disorder have a higher percentage of migrainous *vs* non migrainous children (24% *vs* 16%); mothers with mood disorders have children who suffer from tension-type headaches, mainly the episodic type (12%); mothers with an anxiety disorder comorbid with a mood disorder have the same number of children with migraine without aura (3) and chronic tension-type headache (3).
Discussion and conclusions Very few studies have investigated the psychiatric situation of the mothers of children with epilepsy or headache, while there are many concerning the psychological profile of children or adolescents with these disorders. Mothers of epileptic children showed a greater number of psychological disorders compared to mothers of headache sufferers, even without a statistical difference. The meaning of the high prevalence of psychiatric disorders needs further study to understand the direction of influence, the etiological mechanisms and the diagnostic implications.

EFFICACY OF A WORKPLACE COGNITIVE AND PHYSICAL PROGRAMME ON HEADACHE, NECK AND SHOULDER PAIN: A LONGITUDINAL COMMUNITY-CONTROLLED STUDY

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Objective Our purpose was to examine the effects of a cognitive and exercise instruction programme on frequency of headache, neck and shoulder pain in a working community.
Materials and methods Three hundred and forty-three employees of the city of Turin, whose working activities involved public contact (registry and tax office), were distributed into two groups: study group (n=169) and controls (n=175). In all subjects data were collected on headache, and facial, neck and shoulder pain, if present. They were then given a diary in which to record, on a daily basis, frequency, severity and duration of the headache and facial, neck and shoulder pain episodes from March to October 2005. At month 3, an instruction programme was administered to the study group: it consisted of brief shoulder and neck exercises to be performed several times a day, a relaxation exercise and instructions on how to reduce hyperfunction of the craniofacial and cervical muscles during the day. Both groups kept the diary for a further six months (months 3–8). For each subject, the difference in symptom frequency between each month and months 1–2 (baseline) was calculated, and the mean differences between the two groups compared with parametric and nonparametric tests.
Results The monthly frequency of headache significantly decreased over time in the study group compared to controls; the same pattern was observed for the frequency of facial pain, neck and shoulder pain (p<0.001 at month 8). Moreover, the monthly frequency of drug intake significantly decreased in the study group (p< 0.05 at month 8). The data were confirmed in a multiple regression analysis adjusted for gender and age. The relative benefit at month 8 was: 35% for headache frequency, 38% for frequency of neck and shoulder pain and 35% for drug usage.
Discussion To the best of our knowledge, this is the first, longitudinal controlled study of this kind, carried out on a relatively extensive working community. The results demonstrate that the administration of a simple instruction programme can significantly decrease the prevalence of headache, facial and cervical pain in large population samples.
Conclusions The intervention programme employed in this trial is a powerful and economical instrument to reduce head and cervical pain, along with drug intake, in an extensive working community.

ANXIETY, DEPRESSION AND HEADACHE: CLINICAL AND THERAPEUTIC ADVANCES

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Introduction Several studies on the general population and in the clin-

ical setting have confirmed the clinical impression that depressive and anxious symptoms or disorders are common in headache patients [1, 2]. Breslau et al. showed that over a 2-year period, having baseline depression increased the risk of incident migraine but not the risk of other severe headaches; in addition, the risk of incident depression was higher in those with baseline migraine [1]. Merikangas et al. [2] suggested that anxiety might precede headache onset and that headache in turn might be followed by depression.

Objective The aim of this study was to verify the possibility of a preferential order of onset of psychiatric disorders in relation to headache. Moreover, several therapeutic options among antidepressant and antiepileptic drugs were compared.

Patients and methods A broad sample of primary headache sufferers consecutively referring to the Headache Disorders Centre of Bari and receiving a diagnosis of primary headache according to diagnostic criteria of the International Classification of Headache Disorders (ICHD-II) were included. Detailed personal and familial medical histories were collected. Patients' psychopathological profiles were evaluated by means of SCL-90R. Data concerning the natural history of headache, possible psychopathologic features and therapies were collected at baseline and after a three-month treatment period with antidepressant or antiepileptic drugs.

Results No differences were found either in headache onset, age, or attack frequency between headache patients with and without depression symptoms. In the same way, anxious patients did not show any differences between headache onset, age, and frequency when compared with non anxious patients. In about 75% of cases with psychiatric comorbidity, headache onset preceded the occurrence of psychological symptoms. In less than 10%, headache, anxiety and depression onset were concurrent. In the remaining cases the psychopathological symptoms occurred before headache. Both antidepressants and antiepileptic drugs showed good efficacy and tolerability in the therapy of chronic headache patients with and without anxiety and depression irrespectively of symptomatic drug overuse.

Discussion and conclusions The results of this study confirm the high prevalence of psychopathology in chronic headache even though the mechanisms underlying these associations remain poorly understood. Among the possible therapeutic options, antidepressants remain the gold standard in the treatment of headache associated with psychiatric symptoms or disorders. The question of comorbidity between headache and substance-related disorders remains a priority for future research.

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STRATEGIES IN TRIPTAN USE

TRIPTANOGENOMICS

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Completion of the human genome sequence has opened up new prospects as far as pharmacological research is concerned. There is great variability in the way patients affected by the same disorder respond to medications. This variability results in total or partial inefficacy of the therapy and side effects. Pharmacogenetics deals with the discovery of genes involved in drug metabolism, whereas pharmacogenomics studies the relationship between DNA and administered active principles. Both disciplines help discover which drug, among the different ones used for treating a disease, will be the most effective for a certain individual.

It is well known that migraine has a strong genetic component, although the type and number of genes involved remains unclear.

In view of the treatment options available in migraine, the studies most relevant here seem to be those analysing the role of genetic variations in genes involved in the metabolism of dopamine and serotonin (5-HT), catecholamines both thought to underlie at least part of the mechanisms of migraine.

There is evidence to suggest that serotonin-related genes may be involved in the pathogenesis of migraine. To investigate whether the 5-HT_{1A} receptor gene contributes to the risk of migraine, Yang et al. performed an association study of C-1019G promoter polymorphism of the gene in 102 migraineurs and 93 controls [1]. Two functional polymorphisms of the serotonin transporter gene (5-HTTLPR and STin2) were analyzed to assess whether these variants are associated with migraine. No significant differences in allele (p=0.82) or genotype frequencies (p=0.71) were seen in migraineurs compared with controls. These results suggest that C-1019G in 5-HT_{1A} is not a major genetic risk factor for migraine [1]. Similar results were found studying the Val158Met variant of the COMT gene. In contrast, two functional polymorphisms of the serotonin transporter gene (5-HTTLPR and STin2) were studied, and results confirm the association between the STin2 polymorphism of the 5-HTT gene and migraine with aura using paediatric probands.

Triptans are commonly used anti-migraine drugs and show agonist action mainly at serotonin 5-$HT_{1B/1D/1F}$ receptors. It is not known whether frequent or long-term treatment with these drugs would alter 5-HT receptor function. The effects of protracted (14–18 days) sumatriptan and zolmitriptan treatment in rats on 5-HT(1) receptor mRNA expression and function in tissues could be related to migraine treatment results. RT-PCR analysis revealed that 5-$HT_{1B/1D/1F}$ receptor mRNA was reduced in the trigeminal ganglion after treatment with either triptan (reduction by: sumatriptan 39% and zolmitriptan 61% for 5-HT_{1B}; 60% *vs.* 41% for 5-HT_{1D}; 32% *vs.* 68% for 5-HT_{1F}). Chronic triptan treatment had no effect in two functional assays [sumatriptan mediated inhibition (50 mg/kg, i.p.) of electrically induced plasma protein extravasation in dura mater and 5-nonyloxytryptamine-stimulated [(35)S]guanosine-5'-O-(3-thio)triphosphate binding in substantia nigra]. Furthermore, vasoconstriction to 5-HT in isolated basilar artery was not affected by chronic triptan treatment, while it was slightly reduced in coronary artery. The authors concluded that, although their treatment protocol altered mRNA receptor expression in several tissues relevant to migraine pathophysiology, it did not attenuate 5-HT(1) receptor-dependent functions in rats.

Other genes have been studied to outline differences, if any, between migraneurs and "controls".

It seems that genomic profiles for human peripheral blood T cells, B cells, natural killer cells, monocytes, and polymorphonuclear cells can be involved, because a number of the major genes previously reported to be regulated in ischemic stroke, migraine, and Tourette syndrome were shown to be associated with distinct cell populations in blood.

Another field explored in migraine pathogenesis was the increased expression of platelet genes in patients with migraine and chronic migraine (CM), which suggests similar underlying pathophysiology. The differences seen between migraine and CM in other genes suggest an overlapping but not identical pathophysiology.

Recently, the response properties of dural nociceptors in relation to headache have been reviewed by Strassman and Levy [2]. In exploring the aspects linked to the presence/absence of allodynia, lack of response to sumatriptan and other clinical features, the Authors concluded that studies of meningeal sensory neurons have not found evidence of unique properties or qualitative differences that distinguish them from nociceptive neurons in other tissues.

In addition to the properties of chemosensitivity and sensitization, dural afferents also exhibit resistance to tetrodotoxin, indicating that they possess a class of voltage-gated sodium channels that are characteristic of nociceptors in other tissues and that are not found in any

other type of neurons in the peripheral or central nervous systems. Meningeal sensory neurons also express the same constellation of neuropeptides that are found in other sensory innervations. Although 5-HT_{1D} receptors are not unique to meningeal sensory innervation, studies have not yet investigated the possibility of quantitative differences in the level (density) of expression.

These results suggest that pharmacogenomics, by studying the primary differences in number and/or affinity of 5-HT receptors, could play a significant role in the development of new targeting drugs.

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RESPONDERS AND NON-RESPONDERS TO TRIPTANS: BIOLOGICAL CORRELATES

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Background Although triptans are the first-choice drugs for the treatment of migraine attack, a percentage of patients ranging from 25% to 35% had a poor, lacking or inconsistent response to triptan treatment. Few studies have focused on the clinical characteristics of attacks in responders and non-responders to triptans. Recent research has suggested that the occurrence of unilateral cranial autonomic symptoms in migraineurs may predict a better response to triptans [1]. This clinical observation suggests the potential large-scale recruitment of the trigeminovascular system and/or peripheral neurovascular 5-$HT_{1B/1D}$ receptors, the target of the acute antimigraine drugs, in such patients. No studies have been carried out until now on the clinical and biochemical phenotype of migraine patients responders and non-responders to triptans.

Objective We tried therefore to verify markers of trigeminal and parasympathetic systems activation in responders and non-responders to one new generation triptan after administration of the drug during a migraine attack.

Patients and methods Ten migraine without aura patients responders to rizatriptan and 10 migraine without aura patients non-responders to the same triptan were studied. Patients were admitted to our Clinic to be assessed when they presented a migraine attack. Its characteristics as well as the presence of unilateral autonomic signs were recorded at baseline, before rizatriptan administration, and at 1, 2, 4, 6, and 12 hours after rizatriptan administration. Serial external jugular venous blood samples were also collected at the same times. Calcitonin gene-related peptide (CGRP), neurokinin A (NKA), and vasoactive intestinal peptide (VIP) were determined by RIA methods.

Results In all patients, responders to rizatriptan, the attacks were unilateral, severe, and pulsating, and in 5 of them at least one sign suggestive of activation of the parasympathetic system was recorded. Five non-responders to rizatriptan had a bilateral location and a non pulsating quality of pain, even though it was of severe intensity in the majority of them. Levels of CGRP and NKA measured in the external jugular venous blood before rizatriptan administration were significantly higher in responders than in non-responders ($p<0.0001$ and $p< 0.002$, respectively). In the 5 patients with autonomic signs among rizatriptan responders, detectable levels of VIP were found at baseline in jugular venous blood. One hour after rizatriptan administration, a drop in CGRP and NKA was evident in the internal jugular venous blood of rizatriptan responders, and this corresponded to a significant pain relief or alleviation of accompanying symptoms. VIP levels were also significantly reduced one hour after administration in the 5 patients with autonomic signs. After rizatriptan administration, CGRP and NKA levels in non-responder patients showed less significant variations at all time points compared with rizatriptan responders.

Conclusions The present study, although carried out in a limited number of patients, supports recent clinical evidence of increased trigeminal activation associated with better response to rizatriptan in migraine patients. This was accompanied by parasympathetic activation in a subgroup of patients.

In contrast, the poor response to rizatriptan seems to be correlated with a lesser degree of trigeminal and parasympathetic activation, which is confirmed by reduced levels of markers of the trigeminal system and undetectable levels of VIP in the external jugular venous blood [2].

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ALLODYNIA AND EARLY TREATMENT OF MIGRAINE ATTACKS WITH TRIPTANS

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Migraine is a neurovascular disorder that involves meningeal blood vessels as well as trigeminal C fibres that provide innervation to the vasculature. Sensory nerves originating from the trigeminal and upper cervical ganglia follow meningeal blood vessels but not nonvascular areas of the dura. C fibres and A-delta fibres originating from the trigeminal ganglion and C2-C3 dorsal root ganglia contain vasoactive peptides that are responsible for vasodilatation and plasma protein extravasation [1]. This complex response has been studied in animal models and challenged with drugs that provide relief to migraine and cluster headache attacks. The observation that prolonged or chronic pain is associated with long-lasting activation and sensitization of peripheral nociceptors and/or central nociceptive neurons in the dorsal horn has led to an animal model for long-lasting headache, consisting in prolonged activation and subsequent sensitization of the trigeminovascular system by substances that activate and sensitize somatic visceral nociceptors. Those substances, including serotonin, bradykinin, prostaglandins and histamine, are also capable of inducing pain in humans, and also headache. Meningeal nociceptors are activated and sensitized over a long period of time and become responsible for throbbing pain and its aggravation during physical activities. Cutaneous allodynia develops in the early phase of a migraine attack, and its recognition has become important to achieve benefit when treating an attack. Central sensitization is strictly dependent upon impulses from the meninges during the early phase of a migraine attack. However, it is also maintained later in the absence of meningeal sensory input. The antimigraine drugs, the triptans, are effective in blocking neuronal hyper-responsiveness in animal models. In humans, early treatment (within one hour after the onset of a migraine attack) inhibits the development of cutaneous allodynia [2]. Patients who do not develop cutaneous allodynia benefit from triptan administration at any time during the attack. This is possibly due to an action of those molecules on the dorsal horn, i.e., they block transmission of nociceptive signals between first- and second-order trigeminovascular neurons. Triptans are not effective in blocking second-order neuron, i.e., established allodynia. Inhibition of cyclooxygenase (COX) production may help to treat a migraine attack with allodynia. The best treatment option would therefore be a combination of a triptan + COX inhibitor to act at the first-order neuron level, on transmission as well as at the spinal trigem-

inal nucleus.

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PRE-HYPERTENSION IN MIGRAINE PATIENTS REDUCES THE EFFICACY OF ORAL TRIPTANS: AN OPEN CLINICAL STUDY

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Introduction Meta-analysis on the efficacy of oral triptans has demonstrated that only 18%–27% of migraineurs have obtained the goal of sustained pain-free state. In the patients observed at our Headache Centre, we noted a higher frequency of non-responders to triptans in those affected by pre-hypertension. The aim of the study was to assess the efficacy of oral triptans in 12 migraineurs without aura affected by pre-hypertension before and after antihypertensive treatment

Materials and methods The sample included 12 migraineurs without aura, diagnosed according to IHS criteria [1] and affected by pre-hypertension (defined as systolic blood pressure (SBP): 120≤SBP≤139 mm Hg and diastolic blood pressure (DBP): 80≤DBP≤89 mmHg) before and after antihypertensive treatment (oral terazosin, 2 mg daily). Mean age (SD) was 38.25±4.75 years, number of migraine attacks per month (SD) 4±1.04. Patients were invited to take oral triptans (rizatriptan RPD 10 mg and sumatriptan tablet 100 mg, in casual order) two consecutive attacks before and after antihypertensive therapy.

Results At baseline, triptans had no efficacy in 7/12 patients, efficacy in one attack in 4/12 patients, and efficacy in two attacks in only 1 patient. After antihypertensive treatment, triptans had no efficacy in 0/12 patients, efficacy in one attack in 3/12 patients, and efficacy in two attacks in 9/12 patients.

Conclusions These data point out the possible role of pre-hypertension as a possible cause of inefficacy of triptan administration in the treatment of migraine attacks, especially in sustained pain-free state.

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AUTONOMIC SYSTEM ACTIVATION AS A PREDICTOR OF REDUCED RESPONSE TO TRIPTANS IN MIGRAINE ATTACKS

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Background and objective To test the hypothesis that the existence of allodynia and the activation of the autonomic nervous system influence the response to triptans during acute attacks of migraine without aura (MO).

Patients and methods The presence of severe autonomic symptoms during migraine attacks was carefully evaluated in 76 consecutive subjects (M/F 27/49; mean age 36.2±6.4 years) with history of MO by both a structured interview and telethermographic investigation. Based on these findings, the entire group was dichotomized into a subgroup with severe autonomic symptoms (42 patients, migraine with aura (MA)) and a subgroup without (34 patients, MO). The two subgroups were comparable for demographic characteristics and other clinical variables, including pain severity. Clinical response to triptans (eletriptan 40-mg tablets) during 3 consecutive migraine attacks was recorded in each subject. End points were pain-relief and pain-free response at 1 and 2 hours.

Results Pain relief was reported in 58.2% of migraine attacks at 1 hour and in 75.8% at 2 hours, while pain free was observed in 27.3% at 1 hour and 28.0% at 2 hours in MA patients. Pain relief in MO patients occurred in 75% at 1 hour and 83% after 2 hours, while pain free was observed in 38% and 42% at 1 and 2 hours, respectively. Response to treatment was related to the co-existence and complexity of autonomic symptoms. In particular, the more complex the autonomic activation, the less evident the benefit of treatment.

Conclusions Since the autonomic system contributes to the sensitization of nociceptors with consequent peripheral and central allodynia, and the progressive occurrence of allodynia is supposed to be one of the most relevant contributors to inefficacy of triptans, our findings support the assumption that activation of the autonomic nervous system plays a pathogenic role in the clinical response to these drugs in migraine. The degree of activation of the autonomic system might be used as a marker to predict the clinical outcome to triptan therapy.

TRIPTAN UTILIZATION PATTERNS: A STUDY BASED ON PATIENTS PRESCRIPTION RECORDS OF AN ITALIAN HEALTH AUTHORITY IN TUSCANY, ITALY

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Introduction At least 50% of migraine patients are undiagnosed or undertreated. Studies performed in selected populations show that triptan use for migraine is low in Italy (3%–4% of migraine patients) as well as in other developed countries. This study was aimed at establishing the patterns of triptan prescription in a large community by using the drug prescription database of a Health Authority of Tuscany, Italy.

Materials and methods Because of the reimbursement system of the Italian National Health Service, all prescribed drugs included within the essential level of assistance (LEA) are recorded by Regional Health Authorities in association with the demographic characteristics of patients. Therefore, medication records of individual patients are quite complete in drug prescription databases. This allows accurate investigations on drug utilization in a given community. The patterns of triptan prescription in the population of Health Authority no. 11 of Tuscany were investigated. We analysed prescription databases by using the ATC classification (Anatomical Therapeutic Chemical classification, NO2CC: triptans) dispensed during 2005.

Results Of a total population of 224 065 residents of Health Authority no. 11, the total number of triptan prescriptions was 8 982. Oral tablets accounted for 5 954 prescriptions (66.3%), soluble oral tablets for [2486 (27.7%), subcutaneous injection for 316 (3.5%), nasal sprays for 147 (1.6%), and rectal suppositories for 79 (0.9%). In the prescription database, 455 (5%) prescriptions presented incomplete demographic data and were excluded from this study. Thus, the following analyses were conducted on 8 527 prescriptions. We found that 6.9 packages on average were prescribed per patient. At least one prescription of one triptan package was dispensed to 1 238 (0.55%) individuals in the study period. Of these patients, 964 were females (77.9%) and 274 were males (22.1%). The patients over 65 years of age received 14% of the overall number of dispensed packages. Up to 2 packages per year were dispensed to 714 patients (57.7%), and up to 6 were dispensed to 920 (74%). Forty patients received more than 120 dosage units (>10 single doses/month). It is remarkable that 5.7% of the patients received 38% of the overall number of packages.

Discussion In our evaluation we found that 0.55% of the residents in

our district received at least one prescription of a triptan in one year. Assuming that the migraine prevalence in Italy is reported to be 12%, only 6% of our patients received specific triptan antimigraine drugs. About 60% received only one prescription in one year, supporting a very low utilization of triptans. Oddly, we found that 14% of the prescriptions were filled for subjects over 65 years old, a population with higher risk of hypertension and cardiovascular diseases. Oral formulations accounted for the most prescribed route (94%), probably reflecting patients' and/or physicians' preferences for the oral route of administration and better compliance. At least 3.2% of patients could be triptan abusers (>10 dosage units/month).
Conclusions This study shows a very low triptan utilization in the studied population. These data may imply that most migraine patients do not achieve adequate relief because of undertreatment and have need of more effective strategies. Another point to mention regards the considerable amount of prescriptions in the elderly and the high dosages utilized by a small cohort of subjects (triptan abusers).

PERSPECTIVES ON PROPHYLAXIS IN HEADACHES

LONG-TERM ECONOMIC ESTIMATION OF BOTULINUM TOXIN TYPE A USE IN CHRONIC TENSION HEADACHE

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Objective To analyze the efficacy of botulinum toxin type A (BTX-A) preventive treatment of chronic tension-type headache (CTTH) and the impact on headache pharmaceutical utilization and cost.
Design/Methods A retrospective chart review of the efficacy of BTX-A preventive treatment of 100 CTTH patients, diagnosed according to International Headache Society criteria, was followed by a one-year prospective analysis of headache pharmaceutical utilization and costs before and after BTX-A treatment. A direct survey of per patient pharmaceutical consumption was obtained through appropriate questionnaires [1]. Pharmaceutical average cost and incremental (additional) average cost criteria were utilized for the periods before and after BTX-A treatment.
Results The retrospective chart review revealed that BTX-A treatment resulted in 26 patients reporting a total absence of pain and substantial reduction in pharmaceutical use; 37 patients reported significant pain reduction and significant reduction in pharmaceutical use; 22 patients reported some pain reduction and a slight reduction in pharmaceutical use; 15 patients reported no effect or "possible" worsening of pain and no reduction in pharmaceutical use. The one-year prospective analysis revealed that after BTX-A treatment, there was a 45% of reduction in the use of analgesics/antimigraine drugs, a 35% reduction of nonsteroidal anti-inflammatory drugs and a 100% reduction in the use of calcium channel blockers. The average cost of pharmaceuticals was reduced from € 853,43 before BTX-A treatment to € 450,47 after BTX-A treatment.
Conclusions BTX-A was an effective preventive treatment of CTTH resulting in a substantial reduction of headache medication utilization and cost as emerged by previous studies by our group [2].
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PREGABALIN: BEYOND NEUROPATHIC PAIN

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Objective This was an open label study aimed at evaluating the efficacy of pregabalin in reducing the number of days with headache and the amount of acute medication taken monthly in patients with chronic headache with medication overuse.
Methods The studied sample consisted of 20 subjects. Pregabalin was administered at 75 mg a day for 7 days and at 75 mg in two daily administrations. The study consisted of a titration phase (1 week) and of a maintenance phase (8 weeks).
Outcome measures
- Reduction in the number of days with headache/28days
- Reduction in the amount of acute medication taken/28 days
- Number of patients who were pain-free at two hours after triptan intake and headache recurrence rate in the 22 hours following the pain-free condition
- Tolerability profile

Results The group treated with pregabalin had a significant reduction in the number of days with headache and in the mean amount of acute medication taken.
Conclusions Pregabalin proved to be well tolerated and effective in reversing chronic migraine with medication overuse to episodic migraine.

HYPOSTIMULATION OF EPICRANIAL NERVES IN THE PROPHYLACTIC TREATMENT OF MIGRAINE

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Objective A disorder in the head region can provoke pain in the areas innervated by the trigeminal and upper cervical nerves due to convergence of the afferent fibers of the three superior cervical roots on the neurones of the spinal nucleus of the trigeminal nerve. The therapeutic effectiveness of greater occipital and supraorbital nerve blockade in 262 patients with migraine (ICHD-II classification: migraine without aura, 230; migraine with aura, 19; and cervicogenic headache, 13) unresponsive to conventional therapy was investigated.
Methods and results Patients were given repeated daily anesthetic blocks (range 5–10). Perineural injections of 0.5 to 1.0 mL of 0.5% bupivacaine were given at the epicranial emergence points of the nerves in relation to the distribution of the cephalic pain only if the nerves were conspicuously pain sensitive to pressure. Clinical evaluation was based on a monthly Pain Total Index and recording of the monthly number of migraine attacks and analgesic consumption. Patients were considered responsive when the Pain Total Index decreased by ≥50% in the first month after treatment.
Two hundred and fifteen patients (82%) responded well and maintained a favourable response over the 6-month period of observation. The treatment was considered to be of long-lasting effectiveness and without side effects. Method and evaluation criteria are exhaustively described in a previous study carried out by our group [1].
Discussion and conclusions Therapeutic blockade of the greater occipital and supraorbital nerves may have resulted in inhibition of the constant trigeminal hyperexcitability, which characterizes headache, not only by blocking the conduction of noxious stimuli but also by blocking the antidromic flow of substance P and calcitonin gene-related peptide (CGRP), mediators of the axonal reflexes that underlie perivascular neurogenic inflammation. The consequent

vasodilatation and extravasation of these peptides, local reinforcing factors of the algogenic stimulation, may have been interrupted by the anesthetic, resulting in normalization of the response threshold to the nociceptive stimuli.
Inhibition of axonal transport by local anesthetic is well documented [2]. Repeated anesthetic blocks could produce a long-lasting hypostimulation of the peripheral nociceptors, rebalancing their activation threshold and consequently arresting induction of the neuroplastic mechanism of central hypersensitization that may clinically produce chronic pain.
Repeated anesthetic nerve blockade, albeit not influencing the underlying cause, would interfere in the central pathogenic mechanism of formation and transmission of trigeminal nociceptive stimulation of the migraine crisis.
The treatment appeared to be effective in these forms of unresponsive migraine and in the chronicized form with drug abuse. We hope that this clinical experience, together with a correct neurophysiological study, may prove useful in clarifying the pathogenic aspects of migraine.

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LANGUAGE DISTURBANCES AS A SIDE EFFECT OF PROPHYLACTIC TREATMENT OF MIGRAINE

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The present study was aimed at verifying the occurrence of language disturbances as a side effect of topiramate treatment for at least 3 months in 30 migraine patients (86.7% in the chronic form). Twenty migraine patients treated with other prophylactic drugs, but not antiepileptic drugs, for at least three months and 20 migraine patients without prophylactic treatment, with similar characteristics of headache and distribution of migraine subtype and subform diagnoses, were used as control groups. Language functions were explored with neuropsychological tests, including the Trail Making Test, a test of Phonemic and Semantic Verbal Fluency, and a Denomination test.
Language disturbances were referred by 26.7% (n=8) of patients under topiramate treatment but by none of the patients of the two control groups. The majority of patients were accompanied by other side effects. In only one case they were moderate in intensity, but mild in the other cases.
Regarding neuropsychological testing, a significant difference between the topiramate group and the two control groups emerged for the TMT-B subtest of TMT and two of the three categories of semantic verbal fluency (flowers and cities) with the worst scores for the topiramate group. When patients with referred language disturbances in the topiramate patient group were compared with those without, the former had scores indicative of a worse performance for all neuropsychological test variables, and a statistically significant difference was reached for TMT-A, TMT-B and denomination test. Patients without referred language disturbances in the topiramate group showed, in all cases, a worse performance on all tests compared to patients in other prophylactic treatments or untreated migraine patients.
It can be hypothesized that a disorder such as migraine, which involves numerous cortical and subcortical circuits implicated in pain processing as well as behavioural and emotional processing of pain, represents a facilitated substrate for the occurrence of language disturbances due to topiramate [1, 2]. This can be the expression of a more generalized impairment of cognitive processing. These aspects should be investigated in prospective studies involving larger migraine patient samples, and research should not be limited to topiramate prophylactic treatment but should also extend to prophylactic treatment with other antiepileptic drugs.

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TOPIRAMATE VS. AMITRIPTYLINE IN THE THERAPY OF CHRONIC PRIMARY HEADACHE

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Background and aims The revised edition of the International Headache Classification (ICHD-II) seems to have resolved most of the diagnostic controversy concerning chronic headaches: migraine is considered chronic if attacks occur at least 15 days a month for at least 3 months as well as the criteria already stated for tension-type headache [1]. Amitriptyline has been extensively studied and can be considered as the gold standard in the preventive treatment of chronic headache. Contemporary concepts of headache pathogenesis provide an account for the use of antiepileptic drugs as preventive drugs [2]. Therapeutic indication for topiramate is limited to migraine preventive therapy. The aim of this study was to compare amitriptyline and topiramate in the preventive therapy of chronic headache.
Methods A sample of 110 adult subjects consecutively referred to the Headache Disorder Centre, Department of Neurological and Psychiatric Sciences, University of Bari were included. All of them were affected by chronic migraine or tension-type headache according to ICHD-II criteria. The Symptom Check List 90R was administered to all of them for possible psychopathological disorders. Patients were randomly assigned a therapy of amitriptyline, 20 mg or topiramate 50 mg. The two groups were age- and sex-matched. Drug efficacy and tolerability were assessed after a three-month therapy period.
Results A ≥50% decrease in attack frequency was shown in 63% of cases after topiramate and in 65% after amitriptyline treatment, without significant difference between drugs. No significant difference was found between amitriptyline and topiramate efficacy both in the sample of chronic tension-type headache and in the sample of chronic migraine. No difference was found between the two drugs in patients with and without symptomatic abuse. Patients with anxiety and depressive symptoms showed a greater improvement when treated with amitriptyline. Both drugs were well tolerated.
Discussion and conclusions These results suggest that topiramate as well as amitriptyline can be effective and tolerated in chronic headache. Although the exact mechanism of action of this drug in headache prevention is still unclear, it might act by means of the modulation of the nociceptive system preventing both peripheral and central sensitization, which predisposes to attack recurrence [2]. Amitriptyline should be the first choice drug in the case of headache comorbidity with psychopathological symptoms.

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EFFECTS OF PHOSPHODIESTERASE INHIBITORS ON MIGRAINE AND CLUSTER HEADACHE

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Introduction In the 2nd edition of the International Classification of Headache Disorders [1] we find at chapter 8.1.2 the "Phosphodiesterase (PDE) inhibitor – induced headache". The diagnostic criteria are A) Headache with at least one of the following characteristics and fulfilling criteria C and D: 1 bilateral, 2 frontotemporal location, 3 pulsating quality, 4 aggravated by physical activity; B) A single dose of a phosphodiesterase inhibitor has been given; C) Headache develops within 5 hours of PDE inhibitor intake; D) Headache resolves within 72 hours. PDEs are a large family of enzymes (11 types) that break down cAMP and cGMP; the inhibition of PDEs raises intracellular levels of cAMP and cGMP. Sildenafil, the most widely known PDE-5 inhibitor, seems to determine headache through other mechanisms in addition to arterial dilatation, such as stimulation of perivascular pain sensitive fibers or central neurons of pain-pathways. We report on the effect of PDE-5 inhibitors in four patients (suffering from impotence), three affected by migraine and one by cluster headache.
Materials and methods Of three migraine patients (mean age 39 years) suffering from impotence, two were treated with vardenafil 10 mg, one with sildenafil 50 mg. One patient, affected by cluster headache (CH), was treated with sildenafil 50 mg. All patients were asked to refer the possible effect of PDE inhibition on their headache.
Results and discussion Two of the three migraine patients, one treated with vardenafil and one with sildenafil, referred headache similar to their usual migraine attacks within 5 hours from ingestion of the drug. The third patient, referred within 5 hours from taking vardenafil 10 mg a "cluster-like" attack, of less than one hour duration. The CH patient, after taking sildenafil 50 mg, referred headache similar to his usual cluster attacks.
Conclusions Whereas in two of three migraineurs the headache that followed consumption of a PDE inhibitor was like their usual headache, the symptoms of the third migraine patient were novel, in that he developed a "cluster-like" headache. Also remarkable was the headache of the patient affected by CH, who referred after taking the drug, a typical cluster attack. Thus both migraineurs [2] and CH patients should be informed of PDE-5 inhibitor-induced headache.
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PLACEBO AS A PROBLEM OR A RESOURCE?

PLACEBO AND ANALGESIA: FROM THE LABORATORY TO CLINICAL PRACTICE

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The placebo effect has long been a source of debate in order to identify its nature and real power. The effect that follows the administration of an inert treatment, pharmacological or not, is the consequence of several endogenous mechanisms, including conditioning and expectation of clinical benefit.
Electrophysiological studies in humans have highlighted the role of opioids and non-opioid systems in placebo analgesia. Several studies show that placebo analgesia is antagonized by the opioid antagonist, naloxone, suggesting a role for the endogenous opioids, but the role of opiates is still far from clear. The use of different methodologies for exploring pain perception, including intense and prolonged stimulation (i.e., for ischaemic pain) instead of strong painful phasic electrical stimulation (i.e., nociceptive withdrawal reflex) seems to play a different role in inducing the activation of the opioids system and analgesia.
Anticipation of pain and prolonged intense stimulation seem to be necessary in producing the so-called "stress-induced analgesia", which is typically opiate-mediated and naloxone-reversible; in contrast, the placebo effect generated by expectation of analgesia is absolutely irrelevant on the excitability of the nociceptive withdrawal reflex or plasma endogenous opioids system.
The mechanisms of the placebo response carry significant implications for clinical trial designs and thus clinical practice. The importance of the expectation of a benefit in the treatment outcome has been emphasized in several reports in recent years, and it could represent a significant limitation during placebo-controlled trials.
The utilisation of a hidden injection coupled with standard administration is known as the open-hidden paradigm, a paradigm that may provide an excellent alternative to placebo-controlled trials.
These considerations are particularly relevant in the headache field, where the placebo effect in the treatment of the attacks has been estimated to be from 6% to 47%.
Further research identifying and quantifying the factors involved in the mechanisms of the placebo response can increase the outcomes of the treatment and enhance our knowledge of the mind-brain-body interaction.

PREVALENCE OF THE PLACEBO AND NOCEBO RESPONSES IN PATIENTS WITH MIGRAINE AND TENSION-TYPE HEADACHE

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Introduction Placebo and nocebo responses have not been adequately investigated in patients with primary headaches. In randomized clinical trials of analgesic, approximately 30% of the patients with migraine showed a placebo effect. However, a tremendous variation among the different studies was observed. The purpose of this study was to evaluate the prevalence of placebo and nocebo responses in a large group of patients with migraine or tension-type headache recruited from a university-based Headache Centre.
Methods A total of 726 consecutive patients (208 men, 518 women; mean age±SD=41.9±16.0 years), attending the Headache Centre of the University of Turin (Italy), were involved in the study. The diagnosis of migraine was made according to ICHD-II criteria. The patients underwent an extensive physical and neurological examination. Psychological evaluation was performed using the BDI, the STAI X-1 and STAI X-2 tests. A standardized record of all the clinical and psychological characteristics of headache was obtained. Patients were divided into three groups: A) migraine (with and without aura): 258 patients; B) tension-type headache (episodic and chronic): 137 patients, and C) mixed headaches (migraine and tension-type headache): 331 patients. Patients received a tablet containing talcum powder and were told, according to the presence or absence of pain, that the pill was able to produce a pain decrease or increase (extinction or induction of pain). Three hundred and twenty-five patients performed the placebo test and 401 the nocebo test. Patients recorded on the headache diary the presence or absence of headache in the 4 hours following the test.
Results A placebo response was observed in 31.1% of migraine patients, in 38.7% of patients with tension-type headache and in

34.0% of patients with mixed headache. A nocebo effect was reported by 12.% of migraine patients, 22.7% of patients with tension-type headache and 19.7% of patients with mixed headache. Placebo and nocebo effects were not influenced by age, gender or headache diagnosis. Nocebo responders had a longer duration of the disease than non-responders.

Discussion Our study showed that approximately one-third of patients with migraine or tension-type headache presented a placebo response. The nocebo effect was reported by 15% of the patients. The placebo and nocebo responses were not influenced by age, gender or disease diagnosis. Duration of the disease may influence the nocebo response.

LESSONS FROM PLACEBO EFFECTS IN MIGRAINE TREATMENT

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The word "placebo" is derived from Latin, meaning "I please". Although placebo is regarded as an "inactive" substance, its impact can be profound, such that if the effects of placebo are not measured in clinical trials, placebo response may obscure a true pharmacological effect of an active comparator. It is well reported that the variability of placebo response in clinical trials of acute migraine can be high, ranging between 6% and 47% of patients, and this has led to the recommendations that active drugs for migraine must be shown to be significantly superior to placebo. Bendtsen et al. (2003) [1] evaluated the placebo response in placebo-controlled randomised clinical trials of analgesics in migraine attacks that met International Headache Society criteria (ICHD-II). Eleven studies qualified for inclusion in their review. For "headache response", a placebo response occurred in 30% (mean) of migraineurs, although the range (variability) was large (7%–50%). Even though the placebo effects on 2-hour pain-free rates were lower (mean 9%), variability ranged between 7% and 17%, indicating that this is a more robust outcome measure. A review of the literature of placebo-controlled trials with triptans in acute migraine has been reported by Loder et al. (2005) [2] with 31 trials meeting their criteria for inclusion. The mean standard deviation (SD) proportion of patients with a headache response to placebo at 2 hours was 28.5±8.7% (range 15%–50%), while the mean (SD) proportion of patients with a pain-free response to placebo at 2 hours was 6.1%±4.4% (range 5%–17%). Placebo response in children and adolescents with migraine represents a particular challenge not least because placebo effects appear to be enhanced in this young group. Other authors have reviewed the limited data on the use of analgesics and triptans in placebo-controlled trials of migraine in children and adolescents and found a large variability in placebo response: 37%–53% of patients treated with placebo analgesics/non-steroidal anti-inflammatory drugs (NSAIDs) and 28%–65% of patients treated with placebo triptans. Alongside placebo response for efficacy outcomes, placebo is associated with a spectrum of adverse events (AEs) reported across placebo-controlled clinical trials – the "nocebo" effect. This underscores the need to attempt to disentangle AEs associated with placebo from those associated with active medications to enable a more accurate profile of the tolerability and safety of the active medication. In placebo-controlled trials of migraine, AEs may occur with placebo in >30% of patients and in triptan trials the mean (SD) proportion of patients reporting an AE to placebo was 23.4±14.1% (range 5%–74%). As placebo-response rates in clinical trials in migraine may be affected by many variables, placebo-subtracted outcome data may facilitate a more accurate picture of the profile of active medication. In summary, although Medical Ethics Committees are becoming increasingly resistant to the use of placebo in acute migraine trials, placebo remains the pivotal comparator in trials of migraine medications.

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THE "PLACEBO" EFFECT IN CHILDREN AND ADOLESCENTS

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There is no unique definition of placebo (or placebo effect), and the most common is "any effect attributable to a pill, potion, or procedure, but not to its pharmacodynamic or specific properties". The mechanisms of the placebo effect have not been definitively understood; we are dealing with the intriguing field of mind/brain relationship, psychology and biology. The mechanisms of placebo are related to psychological aspects, as "desire", "expectation", or "conditioning". Of note, recent studies showed that placebo has implications also in the biological field; antidepressants influence both brain structure and function. Placebo is a significant issue in headache disorders. Studies on triptans showed a placebo response from 18% to 35% in adults and from 25% to 61% in children and adolescents [1]. In preventive therapy, response to placebo has been estimated as high as 40%–50% in children [2]; in adults, the placebo effect in preventive therapy is about 50% [3]. While the high placebo response in headache trials is an obstacle, it may yield new insights into understanding the mechanisms involved in triggering and relieving headache.

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SOCIO-ECONOMIC ASPECTS OF HEADACHES

HEADACHE MANAGEMENT IN A DIFFERENT TERRITORY OF SOUTHERN ITALY: PROPOSAL FOR A NEW OPERATIONAL MODEL

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In this new operational model of headache management, its practice means integrating individual clinical expertise with clinical evidence from systematic research, and its main principle is that clinical decision should be based on the best available scientific evidence from previous experience and the conclusion based on such evidence should stimulate quality improvements in patient care. The impact of migraine headaches is one of the major public health problems in several industrialized countries, with many patients reporting frequent and significant disability. In order to effectively and efficiently support the medical-clinical management of the patients affected by headache disorders, we propose to devise, develop and validate an innovative web-based platform of services, which is able to optimally support physicians in all the

processes related to diagnosis, prognosis and treatment of headache disorders. This general goal can be achieved by providing the technological platform of a suitable set of functionalities that are able to:

1. integrate biomedical data within electronic health record systems, for easy and ubiquitous access to heterogeneous patients' data;
2. provide services for both healthcare professionals and patients, including education and learning, knowledge and support for specific actions, teleconsulting;
3. support clinical decisions in the medical domain, based on pattern recognition in historical data, knowledge discovery analysis and inferences on patients' clinical data.

Moreover, the real application of the platform could bring a substantial increase in the quality of treatment of the individual patient, by ensuring the possibility to personalize the therapy and provide continuous assistance to the same patient. On the other hand, optimisation of the therapeutic processes will assure control and reduction of the overall economic and social costs of medical care, by decreasing the frequency of hospital admissions and healthcare migration. In Calabria, the majority of drug expenditures is partly or wholly borne by the patient, and the costs of hospitalisation and working days lost are significant. Therapeutic control, based not only on pharmacological therapy but also on the integrated assistance of headache sufferers would dramatically reduce social costs while improving the quality of life of these individuals. Patients, clinicians, and the healthcare system influence different types of barriers to migraineurs who receive early intervention with triptan therapy.

THE MEDICALLY UNRECOGNIZED MIGRAINE: LONG-TERM EFFECTS OF A SENSITIZATION CAMPAIGN ON BOTH GENERAL PRACTITIONERS AND THE POPULATION

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Introduction Migraine disorders are, despite the heavy burden they impose on individuals and society in general, largely unrecognised and untreated. In general practice, few patients consult a physician for headache. In this view, we investigated the impact of a sensitization campaign on migraine in a large cohort of patients, living in a district of Rome.
Objectives The aim of the present study was to evaluate the long-term effects on migraineurs of this sensitization campaign. Three-years later, patients were re-investigated by means of a semi-structured telephone interview.
Patients and methods The initial study had involved the "Cooperativa dei Medici per il Territorio" (10 general practitioners (GPs)) and a population of about 12 000 people, who had been contacted by mail and posters located in the clinics of the GPs. The study recruited 195 patients, of whom 92% (n=179) were migraineurs, according to the IHS criteria (1988). A total of 73% of the patients were diagnosed for the first time.
Results Out of 179 migraineurs, 90% (162 cases, mean age 40.7±15 years, 139 females) underwent follow-up study. Migraine with aura was present in 25% (n=41) of the cases. At follow-up, a significant improvement was observed in the mean pain intensity (on a scale 0–10) (8.6±1.5 *vs.* 7.4±2.1; p<0.0001), the mean headache duration (37.1±24.9 *vs.* 33.7±24.5 hours: p<0.006) and the mean HIT-6 score (61.3±7.6 *vs.* 57.4±10.9; p<0.0001). About 70% of the patients considered the sensitization campaign useful and 58% reported an improvement of their clinical status. Comparison between improved versus worsened or unchanged migraineurs showed a significant decrease in the mean pain intensity (-33%; p<0.0001), mean headache duration (-24%; p<0.001), mean days of headache per month (-72%; p<0.0001), and mean HIT-6 score (-14%; p<0.0001).
Conclusions Our data indicate that a simple awareness campaign is likely to identify a high percentage of previously undiagnosed migraineurs, who could thus receive more appropriate acute care and prophylactic treatment than that offered by uncontrolled self-medication. This positive effect persists for a long time after the sensitization campaign and stresses the crucial role of patient education to medical and non-medical management of migraine. This study further supports the need for development of new interventions or educational strategies aimed at reducing the burden of migraine.

INCREASING PATIENT INFORMATION TO REDUCE THE BURDEN OF MIGRAINE: A NEW PROJECT: "THE HEADACHE DAYS"

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Despite the prevalence, disability and burden of migraine, many patients (30%–70%) have never seen a doctor and only 4% of headache sufferers are referred to a pain specialist for their problem [1]. Possible causes may be unsatisfactory patient - physician relationships, lack of information and the insufficient ability to recognize migraine in primary care. Last year we held free meetings for a week in a Headache Centre: "The Headache Week Project" (La Settimana delle Cefalee) to understand patients' requests about their headache. This initiative was very useful for enlightening migraineurs who do not refer to physicians for their headache ("invisible migraineurs") and pointing to the lack of patient information about headache. Of the 180 participating subjects, with severe headache, 78% had never visited a headache centre nor a specialist and had never taken preventive drugs and their major request was which headache centre or pain specialist to refer to to improve their headache [2]. These results highlighted the need to extend and give continuity to initiatives for patient information, by increasing the number of sites (more headache centres) and their overall period of activity. To favour the participation of as many headache centres as possible, we have now reduced the duration of activity of each information site to one or two days, calling the initiative "The Headache Days" (Le Giornate delle Cefalee).
Nine headache centres are now scheduled to participate in the "The Headache Days Project" in the city and province of Palermo, covering a period of about two months (May - June 2006). The initiative has been advertised in local newspapers and television programmes and the list of centres involved can be found on the national website www.cefalea.it.
Participating patients will receive informative material about headache (including headache diaries and a list of the headache centres in the city and province of Palermo); moreover, they will complete a questionnaire concerning their headache, physician and specialists visited, knowledge and usage of symptomatic (triptans) and preventive treatments; they will also undergo the ID Migraine questionnaire to screen for migraine.
We hope that this will increase patients' knowledge about headache, and also provide more insight about "invisible migraineurs" with the final goal (through more appropriate diagnosis and treatment) to reduce the disability and burden of migraine.
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HEALTHCARE RESOURCES AND MANAGEMENT OF HEADACHE IN PATIENTS REFERRED TO A REGIONAL HEADACHE CENTRE

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Objectives Primary headaches are a public health problem with socio-economic burden and related disability. Despite impairing quality of life, headaches remain underdiagnosed and undertreated with a low healthcare utilization rate. We investigated the use of healthcare resources and the management of headache in patients referred to a headache centre.
Methods All consecutive patients referred for a first visit to our Headache Centre in 2000 and 2005 were considered. We investigated the primary headaches classified according to the International Classification of Headache Disorders, the management of the headache pain before access to the Headache Centre, and causes of delay in seeking a specialist medical referral.
Results We enrolled 533 patients (316 women and 217 men; mean age 45±31 years) from 2000 and 624 patients (423 women and 201 men; mean age 42±28 years) from 2005. Patients with migraine were 336 (63%) in 2000 and 443 (71%) in 2005 (p<0.05); those with tension-type headache were 192 (36%) and 175 (28%) (p <0.05); while those with cluster headache were 5 (1%) and 6 (1%) (p=0.79), respectively. Before referring to the Headache Centre, patients who had never consulted a physician were 320 (60%) in 2000 and 281 (45%) in 2005 (p<0.005); patients who consulted a general practitioner were 160 (30%) and 237 (38%) (p<0.005); patients who asked for a neurologist were 53 (10%) and 106 (17%) (p<0.05). Reasons discouraging patients from referring to a headache centre were: lack of information about specialist centres in 53 (10%) patients in 2000 and in 38 (6%) in 2005 (p<0.05); self-management of pain with over-the-counter medication in 160 (30%) and in 243 (39%) (p<0.05); and the attempt to live with the pain in 320 (60%) and in 343 (55%) (p<0.05), respectively.
Conclusions In 2005, the diagnosis of migraine was more frequent than that of tension-type headache in 2000 showing a trend in patients with more severe headaches to search for a specialist consultation. The increased proportion of patients consulting a neurologist in 2005 and the reduced proportion of those who did not refer to a headache centre because of a lack of information suggests that a better understanding of the opportunity to refer to a headache centre represents the proper approach in headache management. These results were achieved by improving communication between general practitioners and neurologists, and explaining to patients that a specific approach to headache may improve their quality of life, and reduce the frequency and severity of the headaches.

IMPROVED PRESCRIBING IN PRIMARY CARE OF MIGRAINE THERAPY IN THE CALABRIA REGION

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Introduction Most people with headache in the Calabria Region are treated at the primary care level. General practitioners (GPs) play a substantial role in the detection and management of headache and it is of primary importance to investigate their clinical practice.
Materials and methods A random sample of 500 GPs from the list of GPs in Calabria, received a questionnaire by mail. The questionnaire consisted of four sections focusing on: demographic and practice characteristics; knowledge about the role of studies aimed at testing effectiveness and cost-effectiveness of alternative treatments of headache; and sources of information for headache management and educational needs perceived in this field.
Results A total of 453 (91%) completed and returned the questionnaire. Data from the questionnaire were collected, analysed and produced in tabular form. The study of almost 450 headache patients consulting their primary care physician indicated that only 9% were referred to a neurologist as part of their migraine management. In the study, the pattern of referral was not dissimilar, despite the notable differences between these healthcare systems, with only 15% of migraine patients being referred to a neurologist and only 2% seen by a headache specialist.
Discussion This pattern reflects three important and persistent barriers to improved migraine care: failure to consult, failure to diagnosis, and failure to appreciate disease severity, by not recognizing and assessing the impact of migraine on the sufferers' quality of life. Approximately 50% of people with migraine consult a physician about their headaches. Of these patients, only 21% continue under a physician's care with the majority of patients who do consult quitting after just a single consultation. The quality of migraine diagnostic skills at the primary care level may be compared with other conditions such as asthma, which has a similar occurrence, and like migraine, is managed almost exclusively at the primary care level. Physicians may be overly concerned with excluding secondary headache, at the expense of effectively managing primary headache syndromes.
Conclusions Despite the major advances achieved in migraine diagnosis and treatment, primary care physicians still face major challenges in making the correct diagnosis and selecting the most appropriate treatment for this common disabling condition.

HEADACHE AS AN EMERGENCY IN CHILDREN

HEADACHE AND CRANIAL TRAUMAS

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Children's head traumas represent one of the most widespread causes of mortality and morbidity in childhood. Cranial trauma is a functional or structural injury, which affects the central nervous system caused by physical mechanical forces. The trauma may be open or closed, in relation to the presence or not of a communication between the CSF and external spaces.
Various types of traumas may cause different types of damage: concussion, contusion, oedema, herniation, (subdural or epidural) haematoma, haemorrhages, diffuse axonal injury and cranial fractures [1].
The criteria of the ICHD-II do not focus on the characteristics of the pain but concern above all the temporal and pathogenic relationships with the traumatic event. It is possible that a trauma worsens, in terms of frequency and intensity, a pre-existing primary headache (ICHD-II, 2004).
Given the high frequency of mild cranial traumas, we shall focus our attention on these forms.
Because posttraumatic headache (PTH) follows moderate cranial trauma, the question is whether this headache is truly secondary to the trauma or is only the trigger factor. This has already been doubted by several authors, starting with Bille, Sinlappa, Raskin, Haas, Lanzi and Russell. The indications that summarize all these doubts are reviewed by Linder [2].

1. CPT may develop after light, moderate or severe trauma.
2. Often the symptoms appear more severe than the trauma itself.
3. Even though these headaches resemble migraine, they do not respond to migraine relieving/pain killing drugs.

4. It is just as important to treat comorbidity problems such as anxiety and depression.

All the above data have led us to evaluating the real incidence of PTH secondary to moderate cranial trauma in the population of certain Italian headache centres. The data on more than 2 000 patients (4–18 years) have given an incidence of PTH of approximately 3%. We confirm that the first cause of PTH are the falls when playing, followed by traffic accidents. Also, in this case there is no direct relationship between the intensity and type of trauma and the onset of headache. PTH is more frequent in the age range of 6–12 years. The more frequent type of headache is migraine without aura.

In the period close to the trauma there are more anxiety manifestations, such as sleep disturbances and panic crises; this may be due to the same traumatic event as well as to possible axonal micro-damage. It is also true that after some months these disturbances diminish, due to a reassurance mechanism and also due to restoration of the axonal damage.

The poor evidence of headache after moderate cranial trauma leads us to actually doubt the existence of this classifying diagnosis. It leads us, conversely, to confirm this event as a triggering moment of the headache.

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HEADACHE AND PSYCHIATRIC EMERGENCY IN CHILDREN AND ADOLESCENTS

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Clinical experience suggests that headache occurring in children and adolescents may be related to the presence of psychological triggering factors, as major or minor life events. Parents, sometimes, may feel more confident in asking for help for a "neurological" problem than a "psychiatric" one. From a psychiatric point of view, we know that young patients also exhibit a lot of physical disorders: Livingston et al. (1990) found that between 25% and 30% of children admitted to a psychiatric hospital had physical symptoms, including headache, food intolerance, abdominal pain, nausea and dizziness [1].

These aspects have clinical and research implications. On the one hand, we should be able to recognise factors (from headache characteristics to psychological triggers), which suggest that facing the psychiatric problem is compelling. On the other hand, we are dealing with the subtle link where mind interacts with body, a field whose comprehension may also furnish elements for understanding the pathophysiology of headache.

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CLUSTER HEADACHE AND PAROXYSMAL HEMICRANIA IN CHILDHOOD

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Cluster Headache Cluster headache (CH) is infrequent and is one of the most painful primary headaches. Its prevalence in the general population is 0.1%, and it begins after the age of 20. Onset in adolescence is rare and its observation under 10 years of age is quite singular; despite the typical clinical features, it is not ever correctly diagnosed, especially in young patients. Children affected by CH have a bizarre behaviour and frequently are excited, typical characteristics of this headache, and they are often considered affected by a psychiatric headache. According to the 2nd edition of the International Classification of Headache Disorders [1], CH crises in childhood have a short duration (15–180 minutes); they may repeat several times in a period of 10–20 days ("minicluster") and pain has a severe intensity, strictly unilateral, in orbital, temporal or zygomatic sites. Autonomic signs, homolateral to the pain, are also present (lacrimation, conjunctival hyperemia, nasal obstruction or rhinorrhoea, miosis, eyelid oedema). In the following years, the autonomic signs increase in intensity and the cluster periods are longer (1–3 months). Scientific evidence and our personal experience suggest that clinical features of juvenile CH remain until adolescence, especially for site and type of pain.

Paroxysmal Hemicrania In chapter 3 of the International Headache Classification, we also find Episodic and Chronic Paroxysmal Hemicrania (EP): the attacks are shorter (2–45 minutes) and their number is higher (4–20/day) than CH. It occurs frequently in females and responds well to indomethacin, but this last characteristic is less observed in young patients. Like CH, pain has a severe intensity, strictly unilateral, in orbital, temporal or zygomatic regions. One of the autonomic signs on the pain side has to be present (lacrimation, conjunctival hyperemia, nasal obstruction or rhinorrhoea, miosis, eyelid oedema). The rarity of this headache in childhood is confirmed by the lack of articles in the scientific literature; from 2000 to 2005, according to MEDLINE, we can find only two case reports, both primary, one in a boy of 6 years [2] and the other in a girl of 10 years.

Conclusions When a strictly unilateral headache of severe intensity accompanied by autonomic signs is observed in a child, the possibility of CH or EP (or another trigeminal autonomic cephalalgia - TAC) has to be considered, for providing the best symptomatic and/or prophylactic therapy.

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BRAIN TUMOURS AND HEADACHES IN CHILDREN

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Headaches are initially present in 20% of patients with brain tumours and increase to about 60% during the disease. They are a more common symptom of brain tumours in children (90%) than in adults (60%). The overall incidence of headaches was 62%, ranging from 70% with infratentorial lesions to 58% with supratentorial tumours, to 35% in patients with spinal canal tumours [1]. Headache is a rare initial symptom in patients with pituitary tumours, craniopharyngiomas, or cerebellopontine angle tumours. It is a very common initial symptom in infratentorial tumours, occurring in 80% to 85% of patients. Headache can occur intermittently and mimic migraine. Paroxysmal headaches are a unique feature of some patients who have a colloid cyst of the third ventricle or other tumours that may obstruct CSF flow. They may be a cause of brief losses of consciousness or "drop attacks". Headache was typically associated with other signs or symptoms and was rarely an isolated symptom (<1%). Battistella et al. (1998) [2] showed that in 10% of children with tumours, headache is the only symptom, and occurs at presentation with others symptoms in a further 17%.

Wilne et al. (2006) reported that headache is the first symptom in 41% of patients with tumour more than in seizures (9%), and vomiting (12%) [3].

We report 2 cases. Case 1: 3-year-old male, suffering from a daily global pounding headache and sleep disorders. These had begun 3 months previously and ataxia started during the last week. MRI showed deformity, displacement and partial obstruction of the right ventricle by mass with characteristics of supratentorial primitive neuroectodermal tumours. Case 2: 11-year-old male, presenting at the hospital because of a seizure during sleep, followed by severe headache. Headache in the last year mimicked migraine. MRI showed an intracortical occipital cystic lesion (dysembryoplastic neuroepithelial tumour).

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HEADACHES IN THE PAEDIATRIC EMERGENCY DEPARTMENT

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Headache is a common presenting complaint to the Paediatric Emergency Department (about 1%–2%) and although the majority of headaches are benign and self-limited, it may be the initial symptom of life-threatening disorders. It is therefore essential for physicians to have a rational approach in the evaluation of a child or adolescent with headache who presents to the Emergency Department, because the headache may be the presenting complaint of serious diagnoses such as meningitis, brain tumour, cerebrovascular diseases or other dangerous illness. The majority of headaches in the Paediatric Emergency Department are secondary to concurrent diseases like viral illness, sinusitis and minor head trauma, while primary headaches (migraine and tension headache) are less frequent compared to those in adult studies where they are the most common. The prevalence of serious neurological diseases is about 5%–7% and the most reported causes are meningitis, brain tumour, ventriculoperitoneal shunt malfunctions, subdural hematoma and intracranial haemorrhage. The cause or type of most headaches can be determined by a careful clinical history supplemented by a general and neurological examination. The first important step is to identify the temporal pattern of the headache, acute, acute-recurrent, chronic-progressive, chronic-nonprogressive or mixed. The general physical examination must include blood pressure and temperature and a detailed neurological examination is essential. Several "red flags" in the patient's clinical history and general and neurological examination should lead to more attention and further important diagnostic testing. Special attention is warranted if the acute headache is occipital in location, or if papilloedema, ataxia, paresis or altered levels of consciousness are present. Also, a history of (i) increase in intensity and frequency of headache; (ii) abrupt onset of headache; (iii) persistence of headache despite analgesics; (iv) alteration of the characteristics of headache should lead to suspicion of a serious illness, also in the presence of a negative neurological examination. The American Academy of Neurology [1] formulated evidence-based recommendations regarding the evaluation of children and adolescents with recurrent headaches suggesting that EEG and neuroimaging are not indicated in children with recurrent headaches and a normal neurological examination.

The majority of headaches in the Paediatric Emergency Department can require only treatment for the secondary illness, no pharmacological treatment or simple treatment with minor analgesics. However, sometimes it may be necessary to manage the paediatric headache in the Emergency Department and most available acute treatments are extrapolated from adult studies. Recently, in Italy the use of sumatriptan nasal spray has been approved, and it has shown to be effective in the treatment of acute migraine in children over 12 years.

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MIGRAINE AND JUVENILE STROKE

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Objective In Western Europe less than 5% of strokes occur in subjects under 45 years. In Italy, a recent study reported only a 2% incidence of young stroke cases.

Subarachnoid haemorrhage prevails in young cases and in the subgroup of patients with cerebral infarction, interatrial septum defects and inherited thrombophilic disorders seem to play an important role. Risk factors for stroke in older patients, e.g. blood hypertension, hypercholesterolemia, diabetes, smoking, can be significant also in younger patients. Moreover, in this age group the association of migraine with aura and the use of oral contraceptives seem to amplify the impact of these risk factors, especially in women younger than 45 years of age.

As illustrated in a recent study of our group, the recurrence of acute cerebrovascular and cardiovascular events is higher in first degree relatives of migraine patients then controls [1]. This link could be explained considering stroke and migraine as two possible phenotypic manifestations of a common genetic background as clearly demonstrated in CADASIL and MELAS. Moreover, it is known that migraine can be characterized by stroke-like episodes and that it can also be a direct cause of ictus (i.e., migraine infarction). Finally, recent studies have hypothesized that the link between migraine and stroke could be the patent foramen ovale [2]. In children and adolescents, migraine is a frequent disorder and rarely could be the presenting symptom of stroke.

Material, methods and results Two patients came to our clinic presenting symptomatology of migraine diagnosed according to ICHD-II criteria. In one case, a patient was admitted to our clinic for migraine without aura attack that started in relationship with a first episode of substance abuse. Neuroimaging revealed the presence of a stroke. The second case was diagnosed as affected by basilar-type migraine. Neuroimaging showed the presence of a stroke involving the basilar artery territory.

Discussion and conclusions Headache is a frequent disorder in childhood and adolescence. Occasionally it could be the presenting symptom of a stroke. The relationship between these two entities is still controversial due to its complexity under clinical, epidemiological and genetic points of view.

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PROS & CONS: HEADACHE PROPHYLACTIC THERAPY IN CHILDHOOD AND ADOLESCENCE

PROS: IS PROPHYLACTIC DRUG THERAPY USEFUL IN

CHILDREN WITH MIGRAINE?

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Introduction The treatment of paediatric migraine requires a balance between non-pharmacological and pharmacological measures. This includes acute symptomatic treatment and more rarely a judicious use of prophylactic agents.
Acute treatment The most rigorously studied agents for symptomatic treatment of juvenile migraine are acetaminophen, ibuprofen and sumatriptan nasal spray, all of which have shown efficacy and safety in controlled trials. However, no differences in efficacy were found between oral triptans and placebo, probably because of shorter duration of attacks and migraine associated gastric stasis.
Preventive treatment Prophylactic drug therapy is indicated only for children with severe and frequent attacks (about 30%). However, the results of daily preventive medication of paediatric migraine is more controversial. Older drugs, i.e., antihypertensive agents (propranolol and clonidine), antidepressants (amitriptyline and trazodone), serotonin modulators (pizotifen and cyproheptadine), have shown insufficient or conflicting data. In the calcium channel blockers class, only flunarizine resulted effective and superior to placebo. There is not yet sufficient evidence for the emergent class of antiepileptic drugs (i.e., divalproex sodium and topiramate). Two open trials, using levetiracetam and gabapentin, have given encouraging results, even with the bias due to the open design and the small sample. Most of these drugs were well tolerated, but clinical efficacy in children and adolescents may differ from that in adults.
Two recent reviews summarized all the criticism on the present data in the literature [1, 2]. The major cause of negative results in controlled trials must be attributed to the elevated percentage of placebo-responders migrainous children both in the prophylactic (from 16% to 55%), and symptomatic (from 20% to 60%) approach.
Conclusions Future trials must take into account: a) larger multicentric sample sizes, patients recruited from primary care centres, and IHS criteria for diagnosis; b) some methodological suggestions: migraine for at least one year, three-month retrospective history, one-month prospective baseline period, randomised, double-blinded placebo-controlled trials of at least three-months' duration; c) expanded measures for efficacy of treatment: clinical improvement in headache, quality of life, lack of attendance at school, satisfaction of child and parents; d) new primary end-points incorporating both "pain" and "disability", and "migraine-free" as an important measure of efficacy; and e) new scales with a broader range of measures of pain, and lower age of children (six to twelve years).

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CONS: IS PROPHYLACTIC DRUG TREATMENT USEFUL IN CHILDREN'S MIGRAINE?

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The management of paediatric migraine requires an individually tailored regimen of both pharmacologic and psychological treatment, which is based on individual and integrative approaches using symptomatic and preventive measures.
Prophylactic medication is not indicated in all cases. In published statistics, less than about 30% of children require daily preventive agents, because of high frequency and/or significant disability due to headaches. Follow-up studies demonstrated that the spontaneous outcome of headache in children is the complete remission in many cases. Moreover, we know that family and environmental interventions often reduce headache frequency. Psychiatric comorbidity and family dysfunctioning are to be evaluated in all our patients because they are often part of the clinical picture and may play a critical role in the prognosis of headache. Recently, a Cochrane review summarized the evidence about the effectiveness of different psychotherapeutic approaches for migraine and tension-type headache.
With reference to prophylactic drug treatment, there is a paucity of controlled clinical research. Older therapies (ß-blockers, antidepressants, serotonin modulators and calcium channel blockers) have shown conflicting results or furnished insufficient data, and the more recent therapies (antiepileptic drugs), generally well tolerated in paediatric epilepsy, are in need of placebo controlled trials.
In conclusion, tension-type headache and migraine treatments need an integrative approach, where pharmacological therapy is to be considered only one of the different options for the care of children and adolescents.

PROS & CONS: ANTIEPILETICS

ANTICONVULSANT DRUGS IN MIGRAINE PROPHYLAXIS: USES AND LIMITATIONS

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A variety of clinical trials have consistently shown the benefits of antiepileptic drugs (AEDs) in improving migraine [1]. Prophylactic treatment is often necessary, not only to improve the quality of life but also to avoid the development of analgesic abuse. AEDs could have benefits in migraine prophylaxis because of specific neuromodulation in the pain pathways and, more specifically, in the trigeminal system. AEDs could have a role not only in reducing cortex excitability but also, probably, on the neurotransmitters implicated in the transmission of sensory information in the trigeminovascular system, such as glutamate, calcitonin gene-related peptide, nitric oxide, and 5-HT. These increase GABA-A modulation on nociceptive afferent traffic or regulate the descending anti-nociceptive system from peri-acqueductal grey, which suggests, in this case, that AEDs could act at a distant site from the trigeminovascular system. Pappagallo [2], suggests seven mechanisms of action, which are shared by one or more of the newer AEDs that relate directly to the pathophysiology of migraine, any or all of which may account for its effectiveness. Moreover, there are other possible mechanisms that may be important for migraine but do not seem to be important in epilepsy, such as inhibition of the trigemino-cervical complex directly, or by influencing the neural network that controls sensory inputs, elevation of the cortical threshold for spreading depression propagation, attenuation of glutamate release and others. A recent Cochrane review for use of AEDs in migraine prophylaxis showed that AEDs are efficacious for the prophylaxis of migraine. The mean frequency was significantly reduced with AEDs as compared to placebo and patients were more than twice as likely to have a 50% or greater reduction in the number of migraine attack with AEDs than with placebo. AEDs do not appear to give rise to an unexpectedly high rate of adverse events when used for migraine prophylaxis, although clearly nausea is a problem with the use of valproate and

paraesthesia with topiramate. Moreover, valproate is known to be teratogenic. Gabapentin has beneficial effects but this drug needs further evaluation. In conclusion, valproate, topiramate and, to a lesser extent, gabapentin, have demonstrated efficacy in randomized, placebo-controlled trials. Lamotrigine may be effective at controlling migraine aura, but has not demonstrated effectiveness at controlling migraine headache.

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ANTIEPILEPTIC DRUGS: CONS

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Until a few years ago, the prophylactic treatment of migraine relied mainly on two classes of drugs: beta-blockers and calcium channel antagonists. Recently, there has been great interest in the use of antiepileptic drugs (AEDs) in preventing migraine. The use of AEDs, however, must be carefully evaluated, balancing pros and cons. AEDs employed in migraine prophylaxis can be divided into three groups: group 1, includes drugs (e.g., valproic acid and topiramate) highly effective but with several side effects that can affect compliance and quality of life; group 2, contains drugs (e.g., gabapentin) which are well tolerated but with marginal efficacy; and group 3, consists of drugs (e.g., levetiracetam, oxcarbazepine, zonisamide) for which only anecdotal experience and case series are available or drugs (e.g., lamotrigine) effective only in certain migraine subtypes. So far, only group 1 drugs are a real option for migraine prophylaxis, but, in our opinion, they should not be used as first choice drugs. Their side effects, such as nausea, asthenia, fatigue, memory complaints, weight gain or loss, tremor, dizziness, vertigo, depression etc., limit their use to cases resistant to other, better tolerated, drugs or to difficult-to-treat patients, such as those with chronic migraine.

ROMAN JUNIOR MEMBERS MEETING

IS DEFICIENT HABITUATION OF THE NOCICEPTION-SPECIFIC BLINK REFLEX A TRAIT OR A STATE MARKER IN MIGRAINE?

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Background and objective The nociception-specific blink reflex (nBR) [1] explores the trigeminal nociceptive system, which is pivotal in migraine pathophysiology. Migraine without aura patients (MO) are characterized interictally by a deficient nBR habituation [2]. This could be related to the habituation deficit of evoked cortical responses, which has a familial character, or to central trigeminal sensitisation due to repeated attacks.

We have compared nBR habituation in healthy volunteers (HV) devoid of personal or family history of migraine, and in MO patients and in HV with a family history of migraine in first degree relatives (HV-F).

Subjects and methods We elicited the nBR by stimulating the right supraorbital region with a custom-built electrode in 16 MO patients between attacks, 15 HV and 14 HV-F. Only the responses obtained in the ipsilateral orbicularis oculi will be considered here. Habituation was measured as the % area-under-the-curve (AUC) decrease in 10 consecutive blocks of 5 averaged, rectified EMG responses.

Results nBR habituation was clearly reduced in MO and HV-F compared to HV. AUC decreased between the 1st and 10th block by 55% in HV, by 25.7% in MO (p=0.001 *vs* HV) and by 26.7% in HV-F (p=0.04 *vs* HV). HV-F had an abnormal response more pronounced than MO in the 1st four blocks where they showed potentiation instead of habituation.

We found a positive intraindividual correlation between attack frequency and habituation in MO (r=0.621; p=0.01).

Conclusions Migraine patients have interictally a deficient habituation of the nBR, which is inversely related to attack frequency, as shown here, and normalizes during the attack [2], suggesting that it is not due to central trigeminal sensitisation. Surprisingly, a pronounced habituation deficit is found in asymptomatic individuals with a family history of migraine. Deficient nBR habituation could thus be a trait marker for the genetic predisposition to migraine.

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ELECTROPHYSIOLOGICAL ANALYSIS OF THE TRIGEMINAL SYSTEM IN MIGRAINE

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There is a general consensus on the crucial role played by activation of the trigeminovascular system in the genesis of migraine attack.

The presence of cutaneous allodynia and of decreased pain thresholds in the first trigeminal division (V_1) on the headache side, as well as the electrophysiological finding of an increased area of the nociception specific blink reflex R2 (nBR) during migraine attacks suggest temporary sensitization in the spinal trigeminal pain system.

Recently, an interictal habituation deficit of the nBR was demonstrated in migraineurs with a custom-built electrode preferentially activating nociceptive Aδ fibres. This habituation deficit is in line with similar findings described for cortical evoked potentials.

Numerous migraine patients complained of cervical tenderness and many of them also complained of the neck as the starting point of their headache. In these cases, the headache surpassed the trigeminal level and involved the first cervical innervations.

In the last decade a functional and anatomical connection between trigeminal pathways and both motor neurons in the neck and upper limb muscles was revealed.

It is well known that the trigemino-cervical reflex allows exploration of the activity of the neck muscles innervated by the great occipital nerve (GON), and that the blink reflex explores the activity of the first trigeminal division.

Therefore, the aim of our electrophysiological investigation was to study the activity of the trigemino-cervical complex in migraine and in a group of healthy volunteers, through the simultaneous recordings of the blink and trigemino-cervical reflexes. The latter are elicited by a nociception specific electrode, which preferentially stimulated the Aδ fibres. The area under the curve of the first 5 rectified responses, as well as the time course of the 3 blocks of 5 responses in a habituation

paradigm, were considered as parameters of investigation.

MIGRAINE, CRANIOMANDIBULAR SYSTEM AND CERVICAL SPINE: A CLINICAL STUDY BASED ON A MULTIDISCIPLINARY APPROACH

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Background It has been shown that migraine and temporomandibular disorders (TMDs) share several epidemiological and clinical features. Nevertheless, a pathophysiological link between diseases of the craniomandibular system and cervical spine as well as between the cervical spine and migraine has been discussed.
Objective The aim of this study was: 1) to compare the clinical aspects of migraine of patients who referred to the Odontostomatological Department for their TMDs with those observed in patients who referred to our Pain Centre for migraine; 2) to perform a multidisciplinary approach in both groups of migraine patients to better understand the potential pathophysiological link between migraine, craniomandibular system and cervical spine.
Materials and methods According to IHS criteria (2004), we consecutively enrolled migraineurs with TMDs and migraineurs without TMDs with the following inclusion criteria: 1) age between 18 and 55 years; 2) patients with no preventive therapy; and 3) patients studied during the interictal phase. A control group composed of healthy subjects was also recruited. All subjects of the study underwent the following clinical evaluations: 1) a clinical investigation of pericranial muscle tenderness according to "Tenderness Total Score" (TTS); 2) a clinical investigation of the temporomandibular system according to "Craniomandibular Index" (CMI); and 3) physical examination of the cervical spine (PECS) by also using a chiropractic approach.
Results We enrolled 35 migraine patients with TMDs (mean age 35±10 years), 32 migraine patients without TMDs (mean age 34±11 years) and 25 healthy controls (mean age 32±12 years). All migraine patients showed significantly higher scores in TTS, CMI and PECS than healthy controls ($p<0.05$). When we considered separately the three groups of subjects, we found that those with TMDs showed higher scores in TTS, CMI and PECS scales than both those without TMDs and healthy controls ($p<0.05$). Similar differences were observed when we compared migraineurs without TMDs and healthy subjects ($p<0.05$). Duration of illness, frequency of attacks as well as MIDAS and HIT-6 scores were higher in migraineurs with TMDs than those without ($p<0.05$).
Conclusions Our data suggest that TMDs and cervical spine disorders are present in all migraineurs and that TMDs may represent a consequence of "migraine pathology" and at the same time a risk factor for high migraine disability. It may be important to pick out these clinical features in a multidisciplinary manner for therapeutic implications and to better understand the comorbidity and the pathophysiological link between migraine, masticatory system disorders and cervical spine dysfunctions.

GENETIC BASIS OF THE VARIABILITY OF CLINICAL FEATURES IN MEDICATION-OVERUSE HEADACHE

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Introduction A chronic pain condition due to analgesic drug overuse is more likely developed by migrainous than other headache patients: about 10% of migrainous patients will develop as a complication of their clinical picture a chronic form of headache sustained by medication-overuse (MOH). The biological basis of this difference could be genetically determined. For instance, polymorphisms in genes regulating dopaminergic transmission were found associated with migraine, alcoholism and drug abuse. It is also well known that psychiatric comorbidity is more prevalent in MOH than migrainous patients. Many studies, with contrasting results, were conducted in the past to explore the association of MOH with the same genes known to be involved in abuse behaviour or psychiatric disorders, comparing migrainous to MOH patients. Here we propose a different approach to the problem, looking for the clinical variability in MOH related to genetic variability. If the commonly used approach is considered a categorical one (comparing two different diseases), the one we propose is a dimensional approach (observing the variation of degree of a clinical parameter).
Materials and methods Seventeen MOH patients were recruited, and diagnosis was confirmed after 2 months of drug discontinuation. All the patients, after a complete headache history, were interviewed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), to obtain a categorical psychiatric diagnosis and completed the Beck Depression Inventory (BDI), and the Cloninger's Tridimensional Personality Questionnaire (TPQ). After obtaining the patients' written informed consent, the genotype was determined for the DRD4 120bp tandem repeat polymorphism, the wolframin His611Arg polymorphism, the BDNF G196A, and the 5HTTPLR polymorphism.
Results A linear logistic regression indicated that the examined polymorphisms are predictors of a high monthly consumption of analgesic drugs. ANOVA analysis showed that the DRD4 polymorphism is related to TPQ novelty seeking (NS) and BDI score, 5HTTPLR to TPQ harm avoidance (HA) and BDI score, and wolframin His611Arg to monthly number of analgesics and BDI.
Discussion Until now, all genetic research in MOH was based on genotype–phenotype association studies, looking for genetic differences between migrainous and MOH patients. Some of these studies have not been able to verify a genetic influence in MOH. We used a different quantitative approach, preferred to the categorical one, to scan the influence of genetic variability on MOH clinical features, which yielded promising results.
Conclusions The clinical picture of MOH is influenced by the studied genes. This evidence confirms the usefulness of dimensional tools when seeking to associate biological markers with clinical disorders.

JOINT MEETING WITH THE ITALIAN ASSOCIATION OF AMBULATORIAL AND TERRITORIAL NEUROLOGISTS

TACs AND SHORT-LASTING NEURALGIAS

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Trigeminal Autonomic Cephalalgias (TACs) are a group of primary headache syndromes including cluster headache (CH), paroxysmal hemicrania (PH) and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). These forms are clinically recognized on the basis of their strictly unilateral, orbital or temporal, severe stabbing pain, associated with one or more homolateral autonomic symptoms and signs. Differential diagnosis is based on frequency and duration of attacks, quality of pain and temporary pattern of attacks. CH is more frequently found in males and is characterized by attacks of strictly unilateral excruciating pain, lasting 15–180 minutes, with a frequency between 1 every other day and 8 daily and grouped in cluster periods followed by remissions. Attacks are accompanied by at least one of the following: lacrimation, conjunctival injection, nasal congestion, forehead and facial sweating, miosis, ptosis, rhinorrhoea or eyelid oedema on the side of the pain; moreover, during the attack the patient is restless and "paces the floor". PH is similar to CH, but more prevalent among females, with shorter (2–30 min) and more frequent attacks (more than 5 daily). SUNCT is a male preponderance headache form with short (5–240 seconds) but very frequent (up to 200 daily) attacks. Chronic PH and all forms of SUNCT can be precipitated by mechanical triggers. When dealing with short-lasting headache forms, primary and secondary neuralgias form part of the differential diagnosis. Trigeminal neuralgia can be differentiated on the basis of lack of autonomic signs and very short duration of pain (less than 2 minutes), precipitated from trigger areas or by trigger factors. CH attacks can be treated with sumatriptan 6 mg s.c., and a lower percentage of patients respond to oxygen 100% at 7 l/min for 15–20 minutes. When required, verapamil, lithium or valproate can be used for preventive treatment of acute and chronic CH. PH responds completely to indomethacin 100 mg daily (range 25–300 mg), which can be used as a diagnostic test. Antiepileptic drugs (i.e., lamotrigine and topiramate) have shown efficacy on SUNCT. Trigeminal neuralgia typically responds to carbamazepine and other antiepileptics. Therapeutic guidelines represent a useful tool for the routine treatment of TACs and short-lasting neuralgias.

RELATION BETWEEN PATENT FORAMEN OVALE (PFO) AND MIGRAINE

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A potential relationship between patent foramen ovale (PFO) and migraine, in particular with migraine with aura (MA), has been recently suggested, based on the results of scarce epidemiological studies, which demonstrated two to three times higher prevalence of this interatrial abnormality in patients with MA than in controls. These observations support the hypothesis that PFO closure might be an alternative and effective treatment option for patients with migraine, and in several recent studies, a decrease in migraine attacks has been observed. However, these data must be interpreted with caution because of several methodological shortcomings and potential biases, including recall bias, use of anti-platelet drugs, and also the placebo effect of any migraine treatment, in particular, those treatments that are invasive. A large double-blind randomised trial on PFO closure in MA prophylaxis is underway in the United Kingdom. At present, whether the association is a mere comorbidity or there is a cause-effect relation remains to be determined. Furthermore, the possibility that the PFO related MA might be another example of symptomatic migraine having little to do with migraine as a primary disorder (i.e., migraine without aura) cannot be ruled out *a priori*. The available evidence suggesting that PFO closure could be a treatment for migraine seems to be very simplistic.

WARNING HEADACHES

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Headache is a syndrome due to various etiologies. Most of the patients usually suffer from migraine or other primary headaches. However, headache can also be an early symptom of a life-threatening condition.

Subarachnoid haemorrhage (SAH) is a condition associated with high morbidity and mortality. The cardinal symptom is headache (severe, sudden, and occipital), which is present in nearly all patients; frequently, motor deficits, altered consciousness and meningeal signs are symptoms associated with headache. When bleeding is of minor entity, thunderclap-like headache could be the only symptom. This clinical scenario needs to be evaluated with brain CT and CSF evaluation.

Spontaneous dissection of carotid and vertebral arteries preferentially affects the fifth decade of life and accounts for 20% of all early onset strokes. The typical patient presents with one-sided pain of the face, head or neck (ipsilateral to dissection) followed hours or days later by neurological motor deficits. Magnetic resonance imaging (MRI) angiography can show the intramural hematoma and is replacing conventional angiography as the diagnostic gold standard [1].

Cerebral venous thrombosis (CVT) is a vascular disorder that affects young female adults. A prothrombotic risk factor is identified in about 85% of patients with CVT. Headache is the most frequent but non-specific symptom. Usually, focal neurological signs, seizures and intracranial hypertension develop in one-half of patients. The diagnosis should be considered in a young woman with recent unusual headache or with stroke-like symptoms. The most sensitive technique is MRI venography.

Giant-cell arteritis is an inflammatory vasculopathy that affects patients usually older than 50 years of age. Headache is frequent but non-specific. Typical symptoms include ocular disturbances, jaw claudication and scalp tenderness. Evidence of systemic inflammation is essential for the diagnosis. Temporal artery biopsy is the diagnostic gold standard, and corticosteroid therapy induces dramatic improvement.

Early recognition of meningitis is imperative for appropriate therapy. The classic clinical presentation of fever, neck stiffness and altered mental status has a low sensitivity. However, almost all patients present with at least two of the four symptoms of headache, fever, neck stiffness and altered mental status. CSF examination is mandatory to confirm the clinical suspicion.

Idiopathic intracranial hypertension (IIH) is a condition of increased intracranial pressure without clinical, laboratory or radiological evidence of intracranial pathology [2]. The syndrome is typical of obese women in childbearing age. The more frequent symptoms are attributable to raised CSF pressure (headache, transitory visual deficits, diplopia, and papilloedema). Cerebral MRI is the technique of choice, followed by measurement of CSF pressure.

Headache can be a late or early symptom of brain tumour. Traditional features of brain tumour are present in a minority of patients. Headache is non-specific and tension-type-like. Long-lasting isolated headache as the presenting symptom of a brain tumour is uncommon. The features of headache suggestive of a space-occupying lesion are recent and/or progressive course, nocturnal occurrence, worsening by postural changes and any abnormal neurological sign.

Hypertensive encephalopathy represents an acute organic brain syndrome resulting from failure of cerebral vascular autoregulation. These patients require emergency blood pressure reduction. Clinically this condition is characterised by acute onset of confusion, headache, visual disturbances and seizures.

Because of the wide differential diagnosis, the physician must be prepared to perform a meticulous patient work-up, with thorough clinical history and examination.

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MIGRAINE PREVALENCE AND CARDIOVASCULAR RISK FACTORS: FIRST DATA OF THE TERRITORIAL NETWORK IN CAMPANIA, ITALY

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Introduction Migraine and headache have been linked, mainly in retrospective case-control studies, in general to a subsequent risk of cerebrovascular stroke. Limited data from prospective studies have evaluated the real association among various forms of headache and increased risk of cerebro- and cardiovascular pathologies.
Materials and methods The AINAT (Italian Association of Ambulatorial and Territorial Neurologists) boasts in Campania a vast network of neurologists that have been involved in the management of an epidemiological study in which the various forms of headache are compared with cerebrovascular risk factors.
They have recruited about 100 (the study is still ongoing) subjects affected by various forms of migraine. The risk factors considered were: hypertension, diabetes mellitus, smoking, atrial fibrillation, familiarity, left ventricular hypertrophy, carotid stenosis (>70%), hypercholesterolemia, hypercysteinemia, and oral contraceptives.
Results Preliminary results seem to confirm, in agreement with the limited data present in the literature, that migraine patients and, in particular, an elevated percentage of those affected by migraine with aura, show a higher association with cardiovascular risk factors.
Discussion This study confirms that patients affected by migraine, particularly with aura, have a higher cardiovascular risk compared with subjects without a history of migraine.
Conclusions Our data could offer a possible biological explanation for the increased risk of ischemic stroke among subjects affected by migraine. However, since the presence of these cardiovascular risk factors alone cannot fully explain the link between migraine and early stroke and coronary heart disease, it seems clear that other etiological factors must be involved.

ESTABLISHMENT OF A TERRITORIAL NETWORK FOR THE STUDY OF MIGRAINE HEADACHE IN THE CAMPANIA REGION

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In the Health Programme for 2003–2005, the Minister of Health, Dr. Sirchia, introduced the so-called "devolution" plan. This has led to a more rational and economic use of the health services offered with better utilization of human resources and available funds, and has also led to the search for new models and diagnosis assistance programmes differing from those available at the national level.
One of the characteristics of the Campania Region has been to significantly increase, in recent years, its specialized assistance throughout the territory, so as to have a more capillary presence of ambulatory neurological services throughout the Region.
Based on these considerations, it has been decided, together with the Regional Coordination of the Italian Society for the Study of Headaches (SISC) of the Campania Region, to create a regional network of first level ambulatory structures dedicated to migraine and headaches, by using the neurologists working in the territory.
The first phase consisted of these specialists attending an educational course organized together with the SISC Regional Section Campania and the Italian Association of Ambulatorial and Territorial Neurologists. The course had a basic didactic scope and served to standardize current methods such as patient charts.
The second phase, which is still ongoing, foresees that every local health organization will activate an automatic system whereby each patient requiring treatment for migraine headache will be sent to the nearest specialist adhering to this network.
The third phase, which has not yet been implemented, will have each ambulatory dedicated to the treatment of migraine headaches connected to a 2nd and 3rd level centre for further diagnostic therapeutic problems.
It is worthy to note that the practical outcome of this type of organization is zero management costs, while, at the same time, guaranteeing:
- a uniform and codified diagnostic system throughout the territory;
- improvement in the diagnostic treatment offered;
- an efficient filter for the Headache Centres which will be freed from routine work that engulfs current waiting lists;
- and also the economic aspect.

HEADACHE ACCORDING TO SCIENTIFIC TRADITIONS OF THE SALERNO MEDICAL SCHOOL

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The origins of the Salerno Medical School go back to the beginning of the Medieval Age. Legend attributes its foundation to four doctors, the Hebrew Helinus, the Greek Pontus, the Arab Adela and the Latin Salernus, epitomizing that the *Ars Medica* of Salerno was born from the confluence of these four cultures.
In the scientific world of the 12th century – corresponding to the "golden period" – various personalities stand out: Masters as Bartolomeo, Ferrario, Salerno and Nicolò Salernitano wrote a series of exhaustive books on general pathology, diagnosis and pharmacological therapy widely used at the School.
Master Salerno, in his work *Catholica*, distinguishes severe headache, in which the pain is "total" from migraine, which only affects one half of the head [1].
Master Bartolomeo, in his manual *Pratica*, defines migraine as "passio capitis in media parte aut in destra aut in sinistra" [2].
Pathogenesis can always be explained by the humoral theory: various external and internal factors are quoted, which can affect and change the organic humours. The qualitative distinction of pain was given attention: acute, periodic, irregular, persistent, continuous and grave. The distinctive characteristics for the "blood headache" were: sensation of burning in the head, heaviness of the forehead, pulsation of the temples and dilatation of the veins.
The diagnosis was aided by a rich urinary semeiology.
One of the therapies for the "blood headache" was bleeding or application of blood-sucking leeches in different parts of the head. The use of purging agents, in particular, diets and remedies (such as coffee) were also advised, according to the type of headache.
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JOINT SYMPOSIUM WITH THE ITALIAN SOCIETY OF INTERNAL MEDICINE

HEADACHE IN CONNECTIVE TISSUE DISEASES

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Introduction Headache is frequently reported by patients affected by connective tissue diseases (CTDs), especially patients with Systemic Lupus Erythematosus (SLE) or Behcet's disease (BD). Virtually all kinds of headaches ranging from migraine to tension-type are represented. Establishing whether a headache has a specific link with the underlying disease is often a difficult clinical challenge, because headache can have a number of causes other than CTDs. For instance, it may be a pre-existing condition or may be the consequence of a psychological reaction to a chronic, disabling disease.
Matherials and methods Migraine of SLE patients is still a debated entity and evidence of brain impairment is controversial. SLE-migraine has been investigated as a prototype of headache complicating CTDs. Perfusion SPECT was performed to investigate brain impairment in SLE patients with migraine-like headache either since diagnosis or later in the course of the disease. Eighteen SLE patients (mean age: 40.8±13.6 years) matching these requisites underwent brain SPECT with ^{99m}Tc-HMPAO in the interictal period. EEG and MRI were performed in twelve and ten patients, respectively. SPECT was analyzed through visual and asymmetry combined analysis as well as by voxel-based statistical analysis (Statistical Parametric Mapping, SPM99) *versus* a control group of matched normal subjects (height threshold: p=0.01).
Results Fifteen (83%) patients disclosed focal hypoperfusion, often in keeping with the main side of pain location, whereas both EEG and MRI gave a positive result in 50% of cases. By voxel-based analysis, significant hypoperfusion was found in 8 (44%) patients, either lateralized to one side or localized to the anterior cingulate cortex (ACC), independent of pain location.
Conclusions Brain perfusion SPECT is a sensitive tool to disclose brain impairment in SLE-related migraine, although the mechanisms of brain damage remain to be elucidated. Besides confirming focal hypoperfusion in a part of the patients, statistical analysis highlighted in four patients interictal hypofunction of ACC, a key structure in the midline network for the cortical elaboration of pain. An integrated neuroimaging and neurophysiological approach is required to disclose the pathophysiological correlates of headaches during CTDs.

CARDIOVASCULAR DISEASES AND HEADACHE

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A complex relationship exists between cardiovascular diseases and headache. In particular, stroke has been associated with both migraine and nonmigraine headache [1].
It has long been debated whether migraine might be considered a possible risk factor for cerebral ischemia. To describe this association, a clearly clinically defined stroke syndrome must occur remotely in time from a typical attack of migraine [1]. A history of migraine may contribute to the risk of stroke through the presence of activation of the clotting system and/or cerebral vasospasm. Several case-control studies investigated the relationship between migraine and stroke and showed that migraine was an independent risk factor for stroke with odds ratios ranging from 2.8 to 4.3 [2]. The association between migraine and cerebral ischemia was limited to women below the age of 35 years, and odds ratios were higher in patients with a history of migraine with aura than in patients with a history of migraine without aura. Other risk factors for stroke might interact with the migraine-induced pathogenesis. Concurrent use of oral contraceptives, high blood pressure, or smoking had more than multiplicative effects on odds ratios for ischemic stroke associated with migraine. Moreover, migraineurs, particularly with aura, have a higher cardiovascular risk profile than individuals without migraine [1]. In fact, compared to controls, migraineurs were more likely to smoke, less likely to consume alcohol, and more likely to report a parental history of early myocardial infarction [1].
Another condition that might help explain and contribute to the association of migraine and stroke is patent foramen ovale (PFO) [1]. PFO has been associated with cryptogenic stroke episodes caused by paradoxical embolism. Moreover, PFO is over represented in migraineurs, and conversely, the frequency of migraine in PFO-associated cryptogenic stroke is twice than expected. Therefore, the excess stroke risk of migraine could result from the association with PFO through paradoxical embolism. Closure of the patent foramen has been associated with suppression of migraine attacks, possibly because a venous to arterial passage of activated platelets or chemical substances may trigger headache by overwhelming the filtering capacity of the lung.
Recognition of the interaction between migraine and cardiovascular disorders as well as comorbid vascular risk factors in migraineurs is important since it may impose therapeutic challenges, life-style modifications, and further investigation to reduce the global vascular risk.
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ENDOCRINE DISEASES AND HEADACHE

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Headache is the most common neurological symptom presenting to family physicians, neurologists, and to the Emergency Department. Some endocrinological disturbances can be associated with headache. Recently, in chronic migraine patients with medication-overuse, a reduction of growth hormone (GH) and TSH responses after GHRH and THRH as well as an increase of ACTH and cortisol levels after hCRH have been described. In contrast, headache can be an important symptom of disease of the endocrine system.
Pituitary tumours are often associated with troublesome headache, both chronic and episodic. Although dural stretch and cavernous sinus invasion are widely considered the mechanism responsible for pain, evidence demonstrates that headache is a recognized feature of small, non invasive functional tumours, and pituitary size itself is unrelated to headache, suggesting that tumour activity may be important in some forms of pituitary tumour-associated headache. The commonest tumours are prolactinomas, which are microadenomas in 52% of cases, and GH-secreting pituitary tumours, which are 68% macroadenomas. Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) has been found only in these kinds of pituitary tumours, and primary stabbing headache is also more common in these two groups. In acromegaly, headache may occur in 55%–85% of presentations as well as in about 60%–70% of prolactinomas.
The mechanism of pituitary tumour-associated headache is currently unknown, and also, the involvement of some neuropeptides as in primary headache is not supported.
Headaches due to endocrine diseases in childhood are rare, but any child with chronic headaches should be given serious consideration. The most serious etiology is a tumour of the hypothalamic-pituitary region such as craniopharyngioma, characterized by headache, visual disturbances, GH and gonadotropin failure.
The role of thyroid dysfunction in headache remains uncertain. In 102 hypothyroid patients, approximately 30% had bilateral, continuous, non pulsatile headache, which disappeared with hormone therapy. In contrast, a larger population-based study reported that TSH

was lower amongst headache sufferers than in those without headache complaints.
The association between hypertension, including endocrine hypertension, and headache has been a contentious issue. Recently, it has been found that headache and hypertension classified at moderate to severe stage were not associated. On the other hand, pheochromocytoma is related to a paroxysmal catecholamine release from the tumour, and headache occurs in more than 80% of patients: it may be severe, frontal or occipital and throbbing or steady.

CHRONIC PAIN AND HEADACHE

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Introduction Epidemiological studies show that a number of chronic/recurrent pain conditions, both somatic (fibromyalgia-FMS) and visceral (dysmenorrhea-DYS, Irritable Bowel Syndrome-IBS) are significantly more frequent among headache sufferers than in the general population. Conversely, the percentage of FMS patients, as well as of DYS and IBS patients who also suffer from headache is significantly higher than that of headache patients in the population not affected with these diseases. These data support the notion of some common underlying mechanism for the pain of all these conditions, at least in subsets of patients. Based on these premises, the aim of the present study was to evaluate and compare the state of general sensitivity to painful stimuli in different groups of headache patients concomitantly affected or not with one or more of the chronic/recurrent pain conditions described above.
Methods Four groups of headache patients (H) were considered: 1) without concomitant FMS/DYS/IBS; 2) with FMS; 3) with DYS or IBS; 4) with FMS + DYS and/or IBS. All groups were age- and sex-matched. Patients of the various groups did not differ significantly regarding the number of years they had been suffering from headache (tension-type or migraine) and mean number of monthly attacks. Patients of the FMS groups did not differ significantly regarding the number of years they had been suffering from diffuse chronic musculoskeletal pain. In all groups, pain thresholds to electrical stimulation in skin, subcutis and muscle were measured in multiple body sites (deltoid, trapezius and quadriceps) not coinciding with the areas of spontaneous pain from any disease. Measurement was made in the pain-free interval and with a wash-out of at least 72 hours from any drug potentially interfering with pain sensitivity.
Results The lowest electrical thresholds at all body sites and all tissues were found in group 4 (H+FMS+DYS/IBS), followed by group 2 (H+FMS), group 3 (H+DYS/IBS) and group 1 (H), in that order. The trend for variation among groups was significant ($p<0.01$).
Conclusions The results indicate a progressively higher state of generalized hypersensitivity towards painful stimuli in headache patients when concomitant chronic/recurrent pain conditions are present. They suggest different levels of central sensitization in subgroups of headache patients, which are expressed clinically with progressively higher manifestations of chronic/recurrent pain conditions, both somatic and visceral, but all typically characterized by the lack of any identifiable organic cause, such as FMS, DYS or IBS.

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HEADACHES: PATHOGENETIC ASPECTS

EFFECT OF NITROGLYCERIN ON TEMPORAL SUMMATION THRESHOLD OF NOCICEPTIVE FLEXION REFLEX IN MIGRAINE PATIENTS

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Background and aims In migraineurs, nitroglycerin (NTG) induces severe delayed headache, resembling spontaneous migraine attacks. The temporal summation threshold (TST) of the nociceptive flexion reflex (NFR) is considered an objective method that offers the potential to examine pain processing in the central nervous system. The aim of the present study was to evaluate the NFR-TST during NTG-induced migraine.
Methods Twenty-nine patients (19 females and 10 males, mean age 36.2±7.67, range 18–55 years), suffering from migraine without aura (1.1 ICHD-II, 2004) were selected. Headache was induced by sublingual administration of 0.9 mg of NTG. NFR-TST and the subjective painful sensation were measured before and 30, 60, 120 and 240 min after drug administration.
Results All patients exhibited a significant ($p<0.01$) reduction of the NFR-TST 120 min after drug administration. In particular, a sub-group of patients experiencing severe attack showed a significant ($p<0.01$) reduction of NFR-TST at both 60 and 120 minutes.
Conclusions NTG appears to support a reliable experimental model of migraine, based on the neuronal effects on the integrative-nociceptive structures. The NFR-TST facilitation during NTG-induced attack reflects an extracephalic generalized hypersensitivity of pain pathways during migraine attack that provides the susceptibility for triggering migraine attack and probably its persistence.

CAN HIGH-FREQUENCY rTMS RESTORE NORMAL INTRACORTICAL EXCITABILITY IN MIGRAINE WITH AURA? EFFECTS OF PRIMING STIMULATION ON 1 HZ rTMS

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Introduction We showed that motor intracortical inhibition (ICI) is reduced in patients affected by migraine with aura. Consequently, 1 Hz rTMS-induced paradoxical effects increase motor intracortical facilitation (ICF) in these patients. In conditions of enhanced excitability due to reduced inhibition, high frequency rTMS acts by potentiating intracortical inhibition [1, 2].
On this basis, we used high frequency priming stimulation of the motor cortex to enhance intracortical inhibition and reverse paradoxical facilitation induced by 1 Hz rTMS in migraine with aura patients. To differentiate the possible different effects on ICF or ICI, we applied the double-pulse TMS technique that allows evaluation of the intracortical circuits.
Methods Seven patients with migraine with aura and six controls underwent a paired-pulse TMS paradigm to evaluate ICI and ICF of the motor cortex before and after a conditioning high frequency rTMS followed by 1 Hz rTMS train. Patients were examined interictally at least 48 h before or after an attack. The hot-spot for the right abductor pollicis brevis (ABP) was checked by mean of a figure-of-eight coil and motor threshold (MT) on this recorded point. ICI and ICF were assessed by means of a conditioning stimulus (CS) at 80% MT followed by a test stimulus (TS) at 120% MT, with two different interstimulus intervals: inhibitory: 2 msec and facilitatory 10 msec. Priming rTMS (900 stimuli at 10 Hz frequency, in trains of 50 stimuli separated by 45 s intervals) was followed by a single 15-min-long train (900 stimuli) at 1 Hz rTMS. rTMS was delivered at 90% of MT over the hot-spot. Motor evoked potential (MEP) amplitude of TS post-rTMS was expressed as percentage of baseline MEP. Amplitude of MEPs recorded at 2 and 10 ms ISIs before and after rTMS were expressed as percentage of change from the respective mean TS alone.
Results At baseline, ICI was significantly lower in migraineurs with respect to controls. In healthy controls, MEP amplitude and ICF were significantly reduced by priming 1 Hz treatment with respect to baseline values. In contrast, the priming stimulation significantly increased ICI in migraineurs, leaving quite unchanged MEP amplitude and ICF values with respect to baseline.
Conclusions In migraineurs, rTMS-priming potentiates intracortical inhibition and reverses the paradoxical increase in ICF observed with 1 Hz rTMS [1]. These findings strengthen the hypothesis of reduced inhibition in migraine with aura and might open perspectives for new treatment strategies.
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EFFECTS OF REMOTE CUTANEOUS PAIN ON TRIGEMINAL LASER EVOKED POTENTIALS IN NORMAL SUBJECTS AND MIGRAINE PATIENTS

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Introduction In a previous study a different modulation of trigeminal laser evoked potentials (LEPs) was detected in migraine patients *vs* controls during topical application of capsaicin on the supraorbital skin. The inhibiting central effect exerted in controls by capsaicin on trigeminal LEPs was less evident in migraine, suggesting a disturbed pattern of pain modulation at the cortical level, which may subtend the onset and persistence of migraine [1].
Objective The aim of the present study was to detect the functional changes of trigeminal LEPs during topical application of capsaicin over a remote site of the body in migraine patients outside the attacks *vs.* non migraine healthy controls.
Methods Ten patients suffering from migraine without aura (ICHD-II, 2004), free from pain and symptomatic drugs for at least 72 hours and not taking preventive treatment for migraine were selected for the study. Eight age- and sex-matched healthy controls were also examined. LEPs were recorded by 31 scalp electrodes, referred to the nasion, stimulating the dorsum of the right hand and the right supraorbital zone in basal conditions and 30 minutes after application of 3 mL of 3% capsaicin in a cream base (Teofarma), which was applied topically on the entire surface of the dorsum of the left hand, within an area

of at least 6 cm^2. The subjective pain induced by both laser stimulus and capsaicin was rated by a 0–100 visual analogue scale (VAS).
Results In normal subjects, the N2-P2 vertex complex showed 32.3%±3.4% rate of amplitude reduction at the trigeminal level and 30.2%±7.8% at the hand level, caused by remote capsaicin application. In migraine, the rate of N2-P2 amplitude reduction at the hand level was similar to controls (31.3±9.8; F=0.67, n.s), while it was significantly lower at the face level (2.1%±4.5% F=16.5, $p<0.001$). The N1 amplitude was not significantly modified by capsaicin, when both the face and the hand were stimulated. N2-P2 amplitude modifications were reversed after capsaicin removal in both patients and controls.
Discussion The N2-P2 amplitude reduction induced in normal subjects at both the hand and face levels could be due to a diffuse noxious inhibitory control and to the distraction induced on LEPs by concurrent capsaicin-induced pain. Both the pain-inhibiting mechanisms appeared inadequate in reducing experimental trigeminal pain in migraine patients.
Conclusions In migraine patients trigeminal pain is not inhibited by the anti-nociceptive endogenous control system.
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SLEEP STUDIES IN PRIMARY HEADACHES

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Introduction Primary headaches have an intimate relationship with sleep. Although strictly sleep-related headaches, such as hypoxemia-related headache, cluster headache (CH) and hypnic headache (HH) are less prevalent and more easily recognized, other primary headaches are often impacted to some degree by sleep.
Objective The aim of the study was to describe the results of sleep studies performed in different forms of primary headache and their pathophysiological correlates.
Methods Patients underwent a full-night laboratory nocturnal video-polysomnography following adaptation. Patients slept in a sound-proof room. A wrist actigraphic study was also performed in patients with HH and CH.
Results *Hypnic Headache*: The most relevant finding regarding sleep structure was the quantitative reduction of rapid eye movement (REM) sleep. Actigraphic recordings showed that the index of motor activity was consistently increased following the start of effective drug treatment. This might constitute further support for the hypothesis of hypoarousal as a pathogenic mechanism for HH.
Cluster Headache: No modifications of polysomnographic arousal parameters across the recordings were observed in the acute phase, when compared with the interictal phase, except for the arousal index in REM sleep. At a microstructural level, the arousal index calculated in REM was much lower in the nights in which attacks occurred. Actigraphic recordings revealed, moreover, that the patient's sleep-wake schedule was irregular during the CH period and progressively modified, becoming more regular after remission. All the observed modifications are consistent with an abnormal function of the posterior hypothalamus.
Sleep-related migraine: Evaluation of the pattern of arousal from sleep in a group of patients affected by sleep-related migraine showed a lower continuous airway pressure (CAP) rate in non REM sleep and, in particular, a lower number of A1 phases (low-frequency, high-amplitude EEG bursts) compared with controls. Migraineurs also showed a lower index of high-frequency EEG arousals during REM sleep. Reduction in the CAP rate indicates a lower level of arousal fluctuation in non REM sleep. The reduced arousal index in REM sleep suggests a dysfunction in neural structures involved in both the control of REM sleep and the pathophysiology of migraine, such as the hypothalamus and the brainstem.
Conclusions We believe that sleep studies, including both macro- and microstrucural analysis of sleep and actigraphy, may be useful in clarifying the pathogenic mechanisms of primary headaches.

DESTABILIZING CONDITIONS IN MIGRAINE PATIENTS EVALUATED BY COMPUTERIZED STATIC STABILOMETRY

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Objective The aim of this study was to assess the presence of destabilizing inputs that, by acting on vestibulospinal pathways, are able to induce postural changes and imbalance conditions in migraine patients during the interictal period, by computerized static stabilometry.
Material and methods Twenty patients were studied (14 F and 6 M; mean age 32.6 years) affected by migraine without aura (MO) according to ICHD-II, 2004 criteria and were compared with 35 controls. The stabilometric parameters considered were: statokinesigram surface (S) in eyes open (EO) and closed (EC) conditions, EC with head retroflexion (ECR), EC condition with occlusal bite, and optokinetic stimulation (OKN). Regarding the OKN condition, we used two different kinds of stimulation: the "look" (active) type, in which the patient must follow with the eyes the visual stimulation running through the monitor, and the "stare" (passive) type, in which the patient must look at a fixed point on the monitor and not the visual stimulation crossing the monitor.
Results We found a significant statistical difference ($p<0.045$) between patients and controls in only one stabilometric condition, the OKN stimulation. In particular, the OKN "stare" stimulation was more destabilizing for migraine patients than for controls, inducing conditions of imbalance.
Conclusions In MO patients, the alterations appear under optokinetic stimulation and support a control impairment in involuntary oculomotility of central origin. This is suggested by recent stabilometric findings of our group [1].
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AUTONOMIC DYSFUNCTION IN MIGRAINE WITH AURA

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Introduction Some studies suggested that migraine is associated with an impaired activity of the autonomic nervous system [1]. It is known that the subject with migraine has a reduction in R-R intervals and a reduction in the increase of the heart rate during "handgrip" in comparison with the control group [2].
Objective The objective of our study was to analyse in subjects with migraine with aura the heart rate variability (HRV), evaluated in time and frequency domains by means of ECG holter during 24 hours.
Patients and methods We recruited subjects with migraine with aura during headache-free periods, without treatment. The control group consisted of age- and sex-matched healthy control subjects. Autonomic nervous system function was evaluated by HRV analysis during 24-hour ECG recording, SDNN (millisec, total autonomic

activity), RMS-SD (millisec parasympathetic component), low frequency (LF, modulated by the sympathetic system) and high frequency (HF, mediated by the parasympathetic system) were calculated. The day was divided into two periods: diurnal (7–12 a.m.) and nocturnal (0–6 a.m.).

Results Autonomic function measures: SDNN day (millisec): migraine 146.16±28.41, control 175.92±30.13, p=0.38; SDNN night: migraine 116.26±22.23, control 121.98±26.59, p=0.63; RMS-SD day: 121.98±26.59, control 121.98±26.59, p<0.001; RSM-SD night: migraine 48.19±15.28, control 48.19±15.28, p=0.75; LF day (normalized unit): migraine 61.20±2.27, control 69.90±8.34, p=0.003; HF day: migraine 38.80±2.27, control 22.95±7.31, p=0.002; LF night: migraine 55.13±10.72, control 34.92±5.99, p=0.03; HF night: migraine 44.95±10.69, control 58.62±6.77, p=0.03.

Conclusions In subjects with migraine, the data showed the increase of parasympathetic activity during the day and the predominance of the sympathetic component at night with loss of circadian rhythms. It remains unclear if the alteration of the autonomic nervous system is a risk factor for migraine, or instead, is a consequence of the pathology.

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HIGH-FREQUENCY OSCILLATION SOMATOSENSORY EVOKED POTENTIALS: EVIDENCE OF A REDUCED THALAMO-CORTICAL ACTIVATION IN MEDICATION-OVERUSE HEADACHE

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Background Recently, studies using FDG-PET techniques have reported hypoactivation of nuclei belonging to the "pain network" in patients with medication-overuse headache (MOH). In particular, it has been shown that the ventral posteromedial thalamic nuclei were hypometabolic in migraineurs suffering from MOH [1]. Since the high-frequency oscillations (HFOs) embedded in the common somatosensory evoked potentials (SSEPs) recording reflect spike activity in thalamo-cortical cholinergic fibers (early HFOs phase) and cortical inhibitory GABA-ergic interneurons (late HFOs phase), we studied a group of MOH patients with this neurophysiological approach.

Materials and methods Right median nerve SSEPs were recorded from the contralateral parietal area in 9 patients affected by medication-overuse headache (MOH, ICHD-II 8.2) and in 9 healthy volunteers (HV). Digital off-line filtration (band-pass between 450 and 750 Hz) was employed in order to extract the high frequency (600 Hz) oscillations embedded in the broad-band SSEPs.

Results The amplitudes and latencies of conventional broad-band SSEPs showed no between-group differences. After applying the digital filter, we found a significant decrease of maximal amplitude (p=0.030) and area under the rectified curve (p=0.038) of the early SSEP HFO component in patients compared to HV. By contrast, no difference was found for the late SSEP HFO component.

Discussion These results show thalamo-cortical hypoactivity in patients with MOH. This is in line with the previous FDG-PET study showing thalamic hypometabolism. The absence of SSEP HFO late component changes suggests normal intracortical inhibition at the level of the somatosensory cortex in this patient group.

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INCREASED CEREBROSPINAL FLUID LEVELS OF NERVE GROWTH FACTOR AND BRAIN-DERIVED NEUROTROPHIC FACTOR ARE NOT SPECIFIC FOR CHRONIC MIGRAINE: COMPARISON WITH FIBROMYALGIA

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Background Experimental findings from animal pain models support the role of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) as putative candidates intervening in the pathogenesis of chronic pain. Few studies have been carried out to establish their role in maintaining the pain states in humans and their involvement in chronic migraine (CM) and fibromyalgia [1, 2].

Objective The present study was aimed at investigating cerebrospinal fluid (CSF) levels of NGF and glutamate measured by sensitive immunoassay and by HPLC respectively in CM patients and patients affected by primary fibromyalgia syndrome (PFMS), comparing values with those of 20 age-matched control subjects.

Material and methods Twenty consecutive patients suffering from CM according to ICHD-II classification and attending the Headache Centre of the Neurologic Clinic of the University of Perugia were admitted to the study.

A further patient group included 20 patients affected by PFMS. Diagnosis of PFMS was made according to the American College of Rheumatology Criteria (1990).

All patients were admitted to the Neurologic Clinic to undergo lumbar puncture. Control CSF specimens were obtained from 20 age-matched subjects who underwent lumbar puncture for diagnostic purposes. In all subjects CSF and blood tests excluded CNS or systemic diseases. All control subjects were drug-free for at least two months and none of them were taking any medication at the time of CSF sampling nor had a personal or family history of migraine nor suffered from tension-type headache. None of the above controls developed post-lumbar puncture headache.

Results Significantly higher levels of both neurotrophins were found both in patients with CM (p<0.0001, p<0.0005) and PFMS (p<0.001 and p<0.001) compared with control subjects, without significant differences between the two patient groups. Both patient groups had significantly higher CSF levels of glutamate than controls (p<0.001 and p<0.003, respectively). A significantly positive correlation emerged between CSF values of BDNF and those of NGF (r=0.61, p<0.001; r=0.53, p<0.01) and glutamate (r=0.44, p<0.02; r=0.51, p<0.01) in both CM and PFMS patients, respectively.

Conclusions These findings suggest the possibility of an NGF-mediated up-regulation of BDNF in central sites involved in long-term sensitization, which plays a key role in persistent, chronic painful conditions, such as CM and fibromyalgia. NGF might indirectly exert its effect through enhancement of glutamatergic transmission via BDNF. The above mechanisms could account for sustained central sensitization in both chronic pain states but cannot be considered specific for just one of these two disorders. They may rather be considered expression of the pathogenic mechanisms underlying chronic pain per se.

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ENDOCANNABINOIDS IN PLATELETS OF MEDICATION-OVERUSE HEADACHE PATIENTS AND CHRONIC MIGRAINE PATIENTS: CORRELATION WITH SEROTONIN LEVELS

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Background Based on experimental evidence of the antinociceptive action of endocannabinoids [1], we hypothesized a dysfunction of this system in medication-overuse headache (MOH) and chronic migraine (CM).
Objective To test this hypothesis, we determined the levels of the endogenous cannabinoid 2-arachidonoylglycerol (2-AG) and arachidonoylethanolamide (anandamide, AEA) in platelets of 15 patients affected by MOH according to ICHD-II and 15 patients with CM without medication overuse, as well in 15 age-matched control subjects. We also investigated the intra-platelet levels of serotonin.
Methods Endogenous cannabinoids were purified from platelet pellets by high-performance liquid chromatography (HPLC), and quantified by isotope dilution gas-chromatography/mass-spectrometry. Serotonin levels were also measured by HPLC.
Results In both patients and controls levels of 2-AG were about 20-fold greater than that of AEA. 2-AG and AEA levels were significantly lower in medication overuse and CM patients than in controls ($p<0.02$ and $p<0.04$, respectively), without significant differences between the two groups. Serotonin levels were strongly reduced in both patient groups ($p<0.001$ and $p<0.002$, respectively) and were significantly correlated with 2-AG and serotonin levels ($r=0.48$, $p<0.01$ and $r=0.46$, $p<0.02$).
Conclusions The finding of reduced 2-AG and AEA in platelets correlated with reduced serotonin levels may reflect an imbalance in the endocannabinoid system, which occurs in parallel with serotonergic dysfunction in these two chronic head pain conditions. The parallelism in the failure of these two systems is in line with experimental findings of mutual interaction of 2-AG and 5-HT in modulating different signalling pathways, which can also be relevant for pain control. Variations in activity of AEA transporter and AEA hydrolase in peripheral platelets, as recently shown in female but not male migraineurs [2], remain to be established in MOH and CM.
This study has been partially supported by the Lega Italiana Cefalalgici.
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THE WOLFRAMIN HIS611ARG POLYMORPHISM INFLUENCES MEDICATION-OVERUSE HEADACHE

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Introduction The wolframin gene (WFS1) is mentioned as being possibly responsible for a heterogeneous combination of psychiatric disorders; in a number of studies it has been suggested that common variants in *WFS1* are associated with psychiatric illnesses. For instance, homozygous carriers of the His611Arg polymorphism (R/R genotype) are at increased risk of attempted suicide and generally score higher than non-R/R individuals on both novelty seeking (NS), impulsivity and depression scales. It is well known that psychiatric comorbidity is widely represented in medication-overuse headache (MOH). In the present study we investigated the wolframin His611Arg polymorphism in a sample of MOH patients who submitted to psychiatric, psychometric and clinical assessment.
Materials and methods Fifty-two consecutive, unrelated MOH patients (42 women and 10 men) were recruited. Mean age was 46.37±11.35 years; mean analgesic-drug consumption was 44.81±28.24 doses/month. All the patients were interviewed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), to obtain a categorical psychiatric diagnosis, and completed the Beck Depression Inventory (BDI), a self-reported questionnaire for a dimensional assessment of depressive symptoms. The BDI mean score was 13.15±10.01. Thirty-seven lifetime and 36 current psychiatric disorders were diagnosed. After obtaining the patients' written informed consent, the genotype for the wolframin His611Arg polymorphism was determined.
Results R/R genotype carriers (10 patients) showed significantly higher drug consumption (62.3±35.35 *vs.* 40.64±25.00 doses/month; t=2.266, $p=0.028$) and more severe depressive symptoms on the BDI questionnaire (19.40±10.57 *vs.* 11.66±9.40; t=2.285, $p=0.026$) than non-R/R individuals (42 patients). No significant correlation was found between monthly drug consumption and depression score in our MOH patients ($r=0.137$, $p=0.334$), even when their genotype was considered (R/R $r=0.172$, $p=0.635$; non-R/R $r=0.004$, $p=0.979$).
Discussion Even if it has been reported that depression predicts disability and increased drug consumption in headache patients, in our MOH patients we found no direct correlation between depression scores and monthly intake of analgesic drugs. We believe that the increased drug consumption observed in R/R carriers is a consequence of increased impulsivity and NS traits, irrespective of depression.
Conclusions WFS1 R/R genotype appears to be an aggravating factor in drug overuse in MOH patients.

HEADACHES: CLINICAL ASPECTS

ANALYSIS OF PATIENTS ATTENDING A SPECIALIZED HEADACHE CENTRE OF THE CALABRIA REGION OVER A ONE-YEAR PERIOD

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Objective Our aim was to analyse the diagnosis, prescribed medications and examinations conducted on patients attending a specialized Headache Centre of the Calabria Region over a one-year period.
Methods An audit of clinical records of patients attending the Headache Centre of the "Pugliese-Ciaccio" Hospital in Catanzaro, from January 2005 to January 2006, was conducted. Data regarding diagnosis, current medications, prescribed medications, and examinations conducted were collected.
Results Four hundred and fifteen patients attended the clinic during the audit period. Two hundred (48%) of them were diagnosed with chronic daily headache (CDH), 160 (39%) with migraine, 32 (8%) with cluster headache, and 19 (5%) with neuralgia headache TACs. All other diagnoses involved only one patient (<1%) in each case. Most common medications used by patients with CDH at the time of initial consulta-

tion were: analgesics (64%), prophylactic drugs (17%), triptans (14%), and diazepam (3%). Following the consultation, prophylaxis was prescribed for 51% of patients while triptans for only 1%. At the time of initial consultation, patients with migraine were taking: analgesics (59%), triptans (26%), prophylactic drugs (19%), and ergotamine (2%). Following the consultation, prophylactic drugs was recommended for 75% of patients, triptans for 49%, manipulation for 13%, and analgesics for only 10%. Examinations were arranged for 19 patients (9%) and were negative in all cases.
Conclusions Most patients attending our headache centre were suffering from CDH or migraine. Cluster headache was rarely diagnosed. Despite this being a secondary care clinic, most patients were taking analgesics and relatively few specific acute therapies or prophylactic drugs. In contrast, triptan consumption markedly increased following consultation. In all clinical cases, further examinations were negative and were primarily conducted to reassure the patients.

A VALIDATION STUDY OF AN ITALIAN VERSION OF THE "ID MIGRAINE"

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Introduction Migraine is a highly prevalent and disabling disease that is substantially underdiagnosed in primary care. Recently, the ID Migraine, a self-administered questionnaire, consisting of only three items, was shown to be a valid and reliable screening instrument for migraine in primary care in the U.S.A. The aim of the present study was to validate an Italian version of the "ID Migraine" questionnaire.
Methods A total of 222 consecutive headache patients referring to eight headache centres in Sicily (Italy) completed an Italian version of the ID Migraine. The responses to the questionnaire were compared with the diagnosis of headache made by a headache specialist who did not know the results of the questionnaire. Sensitivity, specificity, positive and negative predictive value and accuracy level for migraine were calculated.
Results The statistical analysis on 222 patients examined showed a very good performance of the ID Migraine with high sensitivity: 0.95 (95% CI, 0.91–0.98), specificity: 0.72 (95% CI, 0.62–0.82) and positive predictive value: 0.88 (95% CI, 0.82–0.93). ID migraine also showed a very good accuracy level: 0.87 (95% CI, 0.83–0.92).
Conclusions This study demonstrated "ID Migraine" to be a valid tool for migraine screening also in Italian patients referring to headache centres. If confirmed in a primary care setting, these results would establish the "ID Migraine" as a valid screening instrument for migraine in the Italian population.

PATIENT COMPLIANCE TO COMPILATION OF THE HEADACHE DIARY

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Introduction One of the most important tools in the approach to a headache patient is the headache diary, whose compilation is a fundamental step in the formulation of the definitive diagnosis and in the organization of a therapy, which must be appropriate to the individual patient. The Headache Centre of the University of Turin began many years ago to use such a diary which, though modified and improved in the course of time, is still fundamentally the same.
Objective The purpose of this study was to evaluate the patient compliance to the compilation of the headache diary.
Materials and methods A total of 575 patients (133 males and 442 females, age range 18–85 years) attending for the first time the Headache Centre of the University of Turin in the period January 1 - December 31, 2004, were enrolled in the study. They all suffered from various kinds of primary headache diagnosed according to the International Headache Society criteria (ICHD-II).
The usual diagnostic approach to the patients at the Headache Centre of the University of Turin starts with a first visit, in the course of which as much information as possible is collected from the patient's interview, and a symptomatic therapy is suggested. This is followed after three months by a second visit, when a more definitive diagnosis is formulated and, if it is deemed necessary, prophylactic therapy is suggested to the patient.
The patients are given the headache diary at the first visit. They are instructed how to complete it and are asked to be as careful as possible in its compilation.
They have to record many different characteristics of their headache (pain, duration, intensity, localization, aggravation by routine physical activity, presence of other symptoms, and drugs used).
It was evaluated how the diary had been filled in by all the patients who came to the second visit, considering their age, level of instruction, type of work, and comprehension of the language.
Results After the first visit 393 patients came back, while 182 did not. Among those who came back, 324 (82.45%) filled the diary completely, while the remaining 69 (17.55%) filled it in only partially or did not fill it in at all.
Discussion and conclusions On the basis of these data it is possible to affirm that the majority of patients showed a very satisfactory compliance to the diary compilation.

PATIENT COMPLIANCE TO THE DIAGNOSTIC APPROACH IN HEADACHE

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Introduction The usual diagnostic approach to the patients at the Headache Centre of the University of Turin starts with an initial visit, in the course of which as much information as possible is collected from the patient's interview, and a symptomatic therapy is suggested. This is followed after three months by a second visit, when a more definitive diagnosis is formulated and, if it is deemed necessary, prophylactic therapy is suggested to the patient.
According to some critics, this diagnostic approach is too long, and the patients do not like it.
Objective The purpose of this study was to evaluate how many patients do not come back for the second visit that forms the usual pattern of our approach, and why they do not return, to clarify if this criticism is correct.
Materials and methods A total of 575 patients (133 males and 442 females, age range 18–85 years), attending for the first time the Headache Centre of the University of Turin in the period January 1 - December 31, 2004, were enrolled in the study. All patients suffered from various kinds of primary headache diagnosed according to the International Headache Society criteria ICHD-II. It was determined if they had returned for the second visit or not. All patients who did not return were contacted by phone to explain their reasons.
Results After the first visit 393 (68.35%) patients returned, while 182 (31.65%) did not. The principal reasons for their not returning, as reported by those same patients were: the therapy was effective at the first attempt or viceversa; headache attacks reduced their number after the

first visit; the diary compilation was too complicated (it was a very difficult task for the patients with chronic headache); the diary was a nuisance because the headache attacks were so few; the fee paid for the visit was too high and the visit itself did not offer a solution to their problem; and the patient did not like the doctor's approach at the first visit.
Discussion and conclusions On the basis of these data it is possible to note that the majority of the patients accept and understand this diagnostic approach, so the criticism towards it does not seem to be realistic. Considering the most frequent motivations reported by the patients who did not come back, it appears likely that providing more information could improve the situation.

PREVALENCE OF ARTERIAL HYPERTENSION IN THE RELATIVES OF MIGRAINE PATIENTS

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Introduction Migraine and some cardiovascular disorders should have common pathogenic mechanisms, and genetic factors should play an important role in the possible development of migraine in a subject with a positive gender for cardiovascular disorders [1]. Moreover, in the clinical history of patients affected by migraine the presence of arterial hypertension in their relatives is frequently observed.
Objective The aim of our study was to assess how common this phenomenon is in a population of children and adults.
Materials and methods The study sample included 190 patients affected by episodic migraine without aura (according to ICHD-II criteria, 2004 [2]), without other forms of headache and without other comorbidity. Seventy-four subjects (38.94%, 50 F, 24 M, age range 10–72 years, mean age 39.05 years – Group A) did not refer gender positivity for arterial hypertension, while 116 (61.06%, 86 F, 30 M, range 6–77 years, mean age 33.97 years – Group B) referred the presence of arterial hypertension in almost one relative of first (parents), second (sister, brother, grandparents) or third degree (uncles or aunts). Before the visit, a dedicated, specific and simple questionnaire was given to the patient for compilation.
Results In Group B, 83 subjects referred the presence of arterial hypertension in one or both first degree relatives, 76 in second (with or without first) degree relatives, 20 in third (with or without second and first) degree relatives. The mean number of attacks per month was 4.51 in Group A and 5.49 in Group B.
Conclusions This study has two limitations, the small patient cohort and the absence of a control group (without migraine). Nonetheless, we can suppose that migraineurs have a remarkable prevalence of relatives with arterial hypertension, according to previous studies, and that the number of attacks seems to be higher in the group with gender positivity for arterial hypertension.
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FOOD INTOLERANCE IN MIGRAINE

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Objective Several factors can trigger migraine; among them, dietary factors play a very important role in the onset of migraine attacks. The aim of our study was to evaluate the incidence of food intolerances in a group of migraineurs, by using the Cytotoxic test.
Materials and methods Thirty consecutive patients suffering from migraine presenting to the Headache Centre of S. Luca Hospital, Vallo della Lucania (SA) were examined. Twenty-three were women, mean age was 28.2 years, range 13–47 years; 7 were men, mean age was 39.33 years, range 28–62 years. The Cytotoxic test is capable of identifying the presence of specific food intolerances by observing the appearance, the size, the shape or the integrity of leukocytes exposed to extracted food antigens or other materials derived from specific foods.
Results An intolerance was found to: tyramine in 12 women (52.17%) and 3 men (42.85%); milk, 3 women (13.05%); yeast, 4 women (17.39%) and 1 man (14.28%); solanaceae, 4 women (17.39%) and 1 man (14.28%); coffee, 5 women (21.74%); cocoa, 5 women (21.74%); tea, 2 women (8.69%); eggs, 1 woman (4.35%) and 1 man (14.28%); pork, 1 woman (4.35%); and sugar, 1 woman (4.35%).
Conclusions Our study showed a high incidence of food intolerance in migraineurs (in women more than in men). The dietary factors which gave more significant results were tyramine, yeast, solanaceae, coffee and cocoa. These results are in agreement with those of other studies found in the literature, proposing tyramine, coffee and cocoa as very important migraine-precipitating factors. Conversely, there is little evidence of a comorbidity between migraine and intolerance to solanaceae. For this reason, further studies are warranted to confirm this hypothesis.

ALTERATIONS IN GLUCOSE-INSULIN METABOLISM IN MIGRAINEURS: PROSPECTIVE STUDY ON THE CLINICAL IMPACT OF DIET ON MIGRAINE SEVERITY AND METABOLIC DATA IN A MIGRAINEUR POPULATION – PRELIMINARY RESULTS

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Introducion Migraine is characterized by a complex biochemical dysfunction attributed to a disorder of the trigeminal and hypothalamic pathways. Impairment of glucose and insulin metabolism has been reported in migraine [1], and insulin alterations seem to be specific to migraineurs.
Objective The main aim was to verify if a proper diet, eventually associated with a insulin-sensitizing drug where indicated, could modify the headache severity together with the glucose-insulin metabolic alteration in migraineurs who presented alterations in glucose-insulin metabolism.
Patients and methods The study population included all migraineurs consecutively seen at the headache centre of our hospital during a one-year period; all the recruited people underwent a general blood test and a standard oral glucose tolerance test (OGTT) after a 12-hour fasting period, measuring levels of glucose and insulin. A daily fragmented low-percentage carbohydrate diet was suggested to those patients who showed an alteration in glucose and or insulin metabolism. Each patient was followed-up during a 3–6 month period, and another standard OGTT was performed, following a 3–6 month period of diet after a 12-hour fasting period, measuring levels of glucose and insulin. Evaluation of headache severity was expressed in severity index, calculated on the basis of number of days with headache and each day headache severity in 1–3 severity scale (1 mild, 2 moderate, 3 severe).
Results In a 12-month period, we recruited 173 migraineurs (138 women, 35 men), 132 patients had a metabolic glucose-insulin alteration (102 women, 30 men), and 41 patients had normal metabolic profile. Until now, 64 patients have been followed-up for at least 3–6 months. Headache severity index of the studied population was 31

(SD±27) before diet and 12 after diet (SD±21) (p<0.000). Fasting blood glucose levels (FBG) and after OGTT (in mg/dL) were slighty lower after dieting (before diet, FBG: 96, at 30 minutes: 143, at 60 minutes: 113, at 120 minutes: 93; after dieting, FBG: 99, at 30 minutes: 131, at 60 minutes: 104, at 120 minutes: 83; p<0.3). Migraineurs after dieting presented significantly lower insulin levels at any time of the test, both fasting and after glucose loading (before dieting, FBG: 10, at 30 minutes: 100, at 60 minutes: 99, at 120 minutes: 55; after dieting, FBG: 7, at 30 minutes: 74, at 60 minutes: 75, at 120 minutes: 38; p<0.1).

Discussion and conclusions A daily fragmented low percentage carbohydrate diet can be useful as migraine non-pharmacological therapy. A clinically positive impact of diet correlates with glucose and even more with insulin levels, both fasting and after glucose loading. High insulin levels are recorded in migraineurs, and these data seem to be specific to this headache type. These findings are in keeping with recent reports on the effects of insulin on brain functions and lend support to the possible involvement of insulin in the pathogenesis of migraine [2].

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POST-PRANDIAL MOTILITY INDEX IS SIGNIFICANTLY REDUCED IN MIGRAINE PATIENTS WITH DYSPEPTIC SYMPTOMS

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Background and aims We have recently shown that in patients with migraine and dyspepsia the intake of a low-caloric low-fat meal induces a significant reduction of post-prandial discomfort thresholds. This abnormality is not evident in patients with functional dyspepsia, thus suggesting that post-prandial reduction of discomfort thresholds may characterize migraine patients. As variations of gastric motility index (MI) were described in a subset of dyspeptic patients, the aim of this study was to evaluate whether abnormalities of this parameter may have a role in the pathophysiology of dyspeptic symptoms in migraine patients.

Materials and methods Eighteen patients with migraine without aura, diagnosed according to ICHD-II criteria and dyspeptic symptoms (11 F, mean age 32±5 years), 16 patients with functional dyspepsia, diagnosed according to Rome II criteria (10 F, mean age 39±5 years) and 16 healthy volunteers (HV) (9 F, mean age 28±6 years) underwent gastric barostat test, which monitors gastric motor activity (contraction or relaxation) as changes in intraballoon volume (reduction or increase, respectively) at a constant intrabag pressure. After an overnight fast, a double lumen polyvinyl tube with an adherent, infinitely compliant plastic bag (1200 mL capacity), finely folded, was inserted into the stomach through the mouth. The polyvinyl tube was connected to a computer-driven programmable volume-displacement barostat device. During the test we evaluated gastric accommodation reflex and phasic contractility, quantified using MI during fasting and during the first and second 30-min period after administration of a low-caloric liquid meal. A baseline reconstruction was performed using a computerised algorithm and MI was calculated as the area between the signal and the baseline normalised over time.

Results Both in dyspeptic patients with migraine and without migraine, the mean increase of post-prandial gastric volume was indicative of a physiological accommodation. Fasting MI was similar in patients (migraine 27.5±7.1 mL x min; dyspepsia 26.9±4.6 mL x min) and HV (24.8±4.3 mL x min). On the contrary, during the first post-prandial 30-min period, post-prandial MI was significantly reduced (p<0.003, ANOVA) in patients with migraine (13.4±4.8 mL x min) than in HV (19.6±6.6 mL x min) and in dyspeptic patients (22.6±7.4 mL x min).

Conclusions Our results show that patients with migraine and dyspeptic symptoms suffer from an alteration of post-prandial gastric sensorimotor function. In addition to the previously shown post-prandial hypersensitivity, a reduction of post-prandial MI is also present.

EPIGONE MIGRAINE VERTIGO (EMV): A LATE MIGRAINE EQUIVALENT

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Introduction The term Migrainous Vertigo (MV) [1] describes all the vertiginous and postural disturbances that are variably expressed by migrainous subjects. In 1988, Pagnini [2] proposed a classification of the vestibular symptoms in migraine using a specific criterion: the temporal relationship between headache and vertigo. According to this classification we can find two large groups of MV: the associated and the equivalent. The first represents the vestibular disorder that adds to headache. The second represents the vestibular crisis that substitutes the single spell of headache. The equivalent form can occur before the onset of headaches (precocious equivalent). It could appear during the headache period (intercritical equivalent), or it can develop after the headache ceases (epigone equivalent). This study concerns the latter form.

Subjects and methods In a clinical observation of 13 years at the Audiological Clinic of the University of Florence, we studied 28 migrainous patients with some features of recurrent vestibular disorders: they suffered from late vertigo with onset only after headache had ceased; their vertigo was not specific for other recurrent otoneuropathies; there were no specific radiological signs or blood risk factors. With a follow-up at least of two years, we studied this patient group with audiovestibular and neurological examinations and imaging, focusing on the characteristics of headache and vertigo and how they interchanged between each other.

Results and discussion Females represented 82% of the study group, mean age of headache onset was 18 years and for vertigo was 38 years. Migraine without aura was present in 78% of patients, kinetosis in 78%. The vertigo described by the patients was variable: 64% of patients referred exclusively rotatory crises (mean duration 15 hours); 14% described dizziness or postural instability (mean duration 73 hours); 22% suffered from a combination of these features. The headache passed to vertigo with a free interval in 26% of patients. A period of alternation of headache and vertigo was present in 29% of patients. In 45% of patients headache passed directly into vertigo. There were no specific signs from audiovestibular examination during intercritical periods, but in 36% we found a vestibular hyperreflectivity during stimulation. We saw a specific highly repetitive behaviour for this new entity: the response to migraine prophylaxis. Vertigo improved in all patients, furthermore, full recovery from vestibular symptoms was obtained in 68% of patients.

Conclusions With this clinical observational study, we attempted to characterize a new clinical picture of migraine, the epigone migrainous vertigo, which should be considered when considering vertigo in migraine.

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MUSCLE TENDERNESS IN CRANIOMANDIBULAR AND CERVICAL REGIONS AND PSYCHOMETRIC CORRELATES IN A POPULATION OF MIGRAINE PATIENTS WITH AND WITHOUT CHRONIC TENSION-TYPE HEADACHE AND HEALTHY CONTROLS

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Background A relationship has been shown between pericranial muscle tenderness and psychiatric disorders in migraine patients. In particular, this association has been observed in patients with both migraine and chronic tension-type headache (CTTH).
Objective The aim of the study was: 1) to evaluate the function of the temporomandibular system and of the cervical spine in a population of migraineurs with and without CTTH; 2) to evaluate the relationship between muscle tenderness, personality profile and psychiatric symptoms in migraine patients with and without CTTH.
Materials and methods Migraineurs with and without CTTH were consecutively recruited according to IHS criteria (ICHD-II). A healthy control group was also recruited. All subjects of the study were submitted to: 1) clinical investigation of the temporomandibular system according to the "Craniomandibular Index" (CMI); 2) pericranial muscle evaluation according to "Total Tenderness Score" (TTS); 3) physical examination of the cervical spine (PECS); and 4) electrognathography (EGG) of the temporomandibular joint. As regards personality profile and psychiatric symptoms, the following tests were administered: Tridimensional Personality Questionnaire (TPQ), Toronto Alexithymia Scale – 20 items (TAS-20), State and Trait Anxiety Inventory (STAI-1-2), and Beck Depression Inventory (BDI). All migraineurs underwent Migraine Disability Assessment (MIDAS) and Headache Impact Test – 6 items (HIT-6) for evaluation of migraine disability.
Results Forty-two migraineurs (mean age 35±10 years), 35 migraineurs with CTTH (mean age 34±12 years) and 32 healthy controls (mean age 32±11 years) were admitted to the study. All migraineurs showed significantly higher scores in CMI, TTS and PECS than healthy controls ($p<0.05$). Comparing EGG data between migraineurs and healthy controls, we observed in the migraine population a reduction of mandibular movement associated with muscle rigidity ($p<0.05$). In regard to the psychometric data, migraineurs showed higher scores in BDI and STAI, Harm Avoidance dimension of the TPQ and TAS-20 than healthy controls ($p<0.05$). All clinical and psychometric findings cited above were more evident in migraineurs with CTTH than those without ($p<0.05$). Duration of illness, frequency of attacks as well as MIDAS and HIT-6 scores were positively correlated with the total number of craniomandibular and cervical tender points ($p<0.05$).
Conclusions Migraine patients present subclinical temporomandibular and cervical spine disorders. These clinical findings are more evident in migraineurs with CTTH and are associated with psychiatric symptoms and with a peculiar personality profile. It might be important to identify these clinical features not only for the therapeutic implications but also to prevent and understand the pathophysiological mechanisms that may lead to chronic migraine.

MIGRAINE AS PRESENTING SYMPTOM OF CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY (CADASIL)

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Background CADASIL is an inherited (autosomal dominant) vascular disease clinically characterized by recurrent transient ischemic attacks and/or strokes, migraine, mood disorders, cognitive impairment, and seizures. Radiological hallmarks are diffuse white matter abnormalities and/or lacunar infarcts visible on MRI or CT. Genetic mutations are located on chromosome 19p13.1 on the Notch3 gene.
Migraine is the symptom of onset of the disease in 40% of cases [1] and has been described in up to 77% of patients in the advanced phase of the disease. Migraine with aura has been reported in up to 40% of cases. About 30% of patients have atypical aura, and atypical plus typical aura has been described in 27% of cases [2].
Methods We describe the clinical characteristics of 14 consecutive CADASIL patients (5 males) belonging to 9 unrelated families.
Results The time of the first neurological evaluation was at an advanced age (mean 51±15 years). Onset of the disease was retrospectively judged to be earlier (mean age 29 years±16) with migraine as the presentation symptom in 64% of patients. On presentation no patient had migraine with aura. Migraine was present in 86% of patients in the advanced phase of the disease. Three patients (21%) had migraine with aura, 2 of them (14%) had typical and prolonged aura. The other clinical features were TIA/strokes (57%), cognitive deficits (71%), and mood disturbances (79%).
All patients presented confluent or partly-confluent MRI white matter changes with the exception of 2 young patients (26 and 28 years) clinically characterized by isolated migraine. Involvement of the temporal lobes was variable in terms of severity. Family history was positive for at least one CADASIL clinical hallmark in all cases. Notch3 mutations involved exon 11 (3 families), 19 (2 families), and exons 3, 4, 6, and 10 in one family each.
Conclusions CADASIL appears to be an underestimated disease. The phenotypic spectrum is variable ranging from pauci-symptomatic cases to severe disease. Migraine is frequently the earliest symptom of the disease occurring at a relatively young age. CADASIL should be suspected in patients with migraine who have MRI white matter alterations of moderate to severe degree and a positive family history for at least one clinical hallmark of the disease.
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PRIMARY CHRONIC HEADACHES IN ITALY: ANALYSIS OF DIAGNOSES WITH THE AID OF A DEDICATED SOFTWARE BASED ON ICHD-II CRITERIA

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Background We recently developed a software, the Primary Headaches Analyser 1.0 INT (PHA), to analyse the clinical data from patients affected by primary headaches [1]. This programme is based exclusively on the International Classification of Headache Disorders 2nd edition (ICHD-II) criteria [2]. This software examines all the diagnoses of primary headaches on the basis of the variables needed to fulfil these mandatory criteria.
Methods We tested the diagnoses of chronic primary headaches with the aid of the software PHA, by entering and analyzing data reported in the clinical chart and headache diaries from 200 consecutive patients affected by primary chronic headaches and evaluating the corresponding output diagnoses.

Results The diagnosis of 1.5.1 Chronic migraine was obtained in 68 cases (34%), and that of probable 1.6.5 Chronic migraine + 8.2.8 Probable medication-overuse headache in 46 (23%). 2.3 Chronic tension-type headache and 2.4.3 Probable chronic tension-type headache + 8.2.8 Probable medication-overuse headache were diagnosed in 24 (12%), and 2 (1%) patients, respectively. Probable medication-overuse headache (n=46) included combination analgesics (n=12), analgesics (n=11), triptans (n=9), a combination of acute medications (n=7), opioids (n=4), and ergot derivatives (n=3). In the two patients with a diagnosis of 2.4.3 Probable chronic tension-type headache + 8.2.8 Probable medication-overuse headache, combination analgesics were responsible for medication overuse. Moreover, 4 and 12 patients, respectively, received both the diagnosis of 1.5.1 Chronic migraine +2.3 Chronic tension-type headache and of 1.6.1 Probable migraine without aura + 2.3 Chronic tension-type headache. In the remaining 44 cases (22%), none of the chronic primary headaches defined by ICHD-II were given as an output diagnosis by our software. This was mainly due to the fact that insufficient criteria were fulfilled for the diagnoses of 1.1 Migraine without aura + 1.5.1 Chronic migraine or, more infrequently, 2.3 Chronic tension-type headache.

Output diagnoses included 1.1 Migraine without aura, 1.6.1 Probable migraine without aura, 2.4.1 Probable infrequent episodic tension-type headache + 2.4.2 Probable frequent episodic tension-type headache, and 14.1 Headache not elsewhere classified. None of the patients whose clinical sheets were examined received a diagnosis of 4.7 Hemicrania continua or 4.8 New daily-persistent headache.

Conclusions Our software (PHA) allowed the diagnoses of chronic migraine or chronic tension-type headache or their probable forms in the case of medication overuse in 78% of the patients with more than 15 days per month examined. In the remaining cases, the inability to provide the above diagnoses can be explained in about one quarter of cases by the fact that the mandatory criteria for both diagnoses are too stringent and do not reflect modifications of the headache patterns in these chronic forms.

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DISABILITY AND CHRONIC DAILY HEADACHES: WHO-DAS II VERSUS OTHER SPECIFIC AND NON SPECIFIC DISABILITY TOOLS

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Introduction The present study was conducted in order to compare the sensitivity of the newly developed World Health Organization Disability Assessment Schedule II for detecting disability due to chronic pain with two established instruments, one generic (SF-36) [1] and one specific for headache (HIT-6) in patients affected by chronic daily headache (CDH) with and without analgesics overuse. WHO-DAS II consists of 36 items, grouped into 6 domains, 5 being related to personal activities and 1 to social life events: D1 communication abilities; D2 mobility impairment; D3 self care; D4 interpersonal relationship; D5 familial/working daily activities; D6 social life participation rate.

Methods Forty consecutive patients (30 females and 10 males), affected by CDH with or without analgesic overuse and observed during a 6-month period were interviewed through SF-36, HIT-6 and the 36-item version of WHO-DAS II scales, each one in its validated Italian version. Headache diagnosis was made according to ICHD-II criteria [2]. No patient had taken prophylactic medications for headache during the 6 months preceding the observation. Statistical analysis included partial correlation tests between items of the three instruments and alfa Cronbach parameter for evaluation of WHO-DAS II internal consistency.

Results A positive correlation was found between all items of SF-36 and some items of WHO-DAS II, in D4, D5 and D6 domains, with statistically significant differences (p<0.01). D5 and D6 WHO-DAS II domains correlated positively with all HIT-6 items (p<0.01), D4 domain correlated with items 3, 4, 5, 6 of HIT-6 (p<0.01), D1 domain with items 4, 5, 6 (p<0.05) and D2 domain with item 3 only (p<0.05).

Discussion and conclusions The above findings show that WHO-DAS II is comparable to SF-36 and HIT-6 as a tool for disability measurement. No correlations were found between WHO-DAS II items and headache clinical features, such as disease duration or duration of analgesic overuse. Some SF-36 items, instead, showed a statistically significant correlation with duration of illness, but not with the duration of analgesic overuse. To identify internal consistency between all items of WHO-DAS II, we used alfa Cronbach parameter. Its value was between 0.8 and 0.9 for all domains analysed indicating a high internal consistency, which supports the use of WHO-DAS II as a sensitive instrument for detecting disability in headache patients, In particular, it may prove to be a valuable measurement tool for disability in chronic headache patients, and it could be useful for indicating effectiveness of therapy and guiding clinical management in these patients.

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CLINICAL CHARACTERISTICS OF MEDICATION-OVERUSE HEADACHE

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Introduction The International Classification of Headache Disorders (ICDH-II, 2004) remarkably modified the diagnostic criteria of medication-overuse headache (MOH), and also proposed clinical criteria to differentiate headache between different overused medications. Subsequently, these clinical criteria were excluded in the revision of the International Headache Seminar held in Copenhagen in March 2004, due to lack of reliable data from the literature.

Objective The aim of the present study was to analyse, for the first time in a systematic way, the clinical characteristics of headache in a sample of patients suffering from MOH.

Patients and methods We studied 51 patients with chronic daily headache who took analgesics ≥ once per day for more than three months, and were treated for detoxification as in-patients. The study included 46 women (90.2%) and 5 men (9.8%), with a mean age of 53 [SD 12] years. The patients were divided according to the medication overused. The quality, the site, the severity, and the accompanying phenomena were evaluated, taking into account also the characteristics of the pre-existing headache and the response to the medication used. The data were analysed using the Statistical Package for the Social Sciences (SPSS 12.0).

Results The overused medications were: combination analgesics in 20 patients (39.2%), simple analgesics in 17 patients (33.3%), triptans in 10 patients (19.6%), and ergotamine in 4 patients (7.8%). The more common pre-existing headache was migraine without aura (39 patients, 76.5%). The pain was more frequently pulsating (28 patients, 54.9%), bilateral (29 patients, 56.9%), and of severe intensity (34 patients, 66.7%). Accompanying phenomena were present in 43 patients

(84.3%), the more frequent being nausea associated with phonophobia and photophobia. The quality, site and intensity of pain, and the type of accompanying phenomena did not differ significantly among overusers of different medications (p=NS). The overused medications were effective in reducing headache and the mean time to the resolution of pain was 72 [SD=87] minutes.
Conclusions The headache in this sample of patients with MOH was more frequently pulsating, bilateral, severe and associated with nausea and phonophobia and photophobia. The clinical characteristics were not different according to the various types of overused medications, supporting the revision of the International Headache Seminar of Copenhagen (2004). The pre-existing headache and the response to overused medications did not influence the characteristics of MOH.

SUICIDE RISK IN CHRONIC DAILY HEADACHE

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In the Western world, 2%–4% of deaths are due to suicide, incidents and murders. Suicide is experienced as a predictable, and therefore preventable death; its occurrence causes a sense of anguish in relatives and frustration and impotence in physicians. Chronic somatic pathologies, such as diabetes, cardiopathy, cancer, stroke and correlated problems like pain, weight loss, insomnia etc. increase vulnerability and predispose to the risk of suicide. Our aim in this study was to evaluate the presence of both humoral disorders and suicide risk in 300 patients affected by chronic daily headache and medication-overuse headache, who were observed for 24 months in our Centre.
We based our work relying upon interviews, collection of anamnestic data related to the premorbid period, information given by patients concerning the sufferers' behaviour during the day, attitudes towards others, maintaining of previous interests, and modifications of the biological rhythm.
Moreover, psychometric tests were administered, revealing a remarkable correlation between humoral disorders and headache, impairment of working activity, relationships and family life.
Through structured interviews with patients and family, the presence of both depressive symptomatology and suicide ideation before the appearance of chronic daily headache has been evaluated.
Finally, our purpose was also to establish if, unlike other pathologies, suicide risk was high or remained just intentional.
Preliminary data indicate 42 patients (21%) with positive results; more specific tests (SSI, BRFL) were performed in order to quantify the importance, intensity and pervasiveness of suicide ideation.

CASE REPORTS

DIFFICULTIES IN MIGRALEPSY DIAGNOSIS: A CASE REPORT

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Migraine and epilepsy are paroxysmal disorders showing clinical and epidemiological comorbidity whose possible relationship remains to be clarified. When a seizure begins during or close to post-aura symptoms, we refer to migralepsy. This phenomenon is described in subjects suffering from migraine with aura; the ICHD-II (2004) diagnostic criteria codify this new entity at 1.5.5 (in the chapter on migraine). A 36-year-old man was referred to our headache centre with aura symptoms. The patient's history (birth, physiological history and psycho-physical development) was normal. His history of migraine (without aura and showing a weekend pattern) started at age 20. At 34, he began experiencing frequent visual bilateral symptoms lasting 10 minutes and never followed by headache (12 episodes/month). These occurred, in particular, in the evening, after work. He described flashing lights, diffuse in the visual hemifield on the headache side, lasting 5–10 minutes. He also recalled two episodes of dejà-vu symptoms associated with nausea. At age 36, he reported an episode of his typical visual symptoms associated with a dejà-vu perception, perception of a "clean" smell (of fresh laundry), and nausea, lasting about 10 minutes. He then lost consciousness, fell to the ground, and displayed tonic seizure of the limbs with laceration of the tongue. After about five minutes, he resumed normal respiration, but remained rather unresponsive and confused until the arrival of rescue workers. Apparently, this episode was not followed by headache. MRI and basal EEG were normal, whereas sleep deprivation EEG showed a diffuse and large theta frequency in the left cerebral hemisphere. The diagnosis was tonic seizure in migraine with/without aura. The patient began treatment with topiramate (200 mg daily).
This patient was referred to us with recurrent migraine attacks and the appearance of visual symptoms sometimes followed by headache. We investigated possible comorbidities of the aura: patent foramen ovale was excluded by transcranial Doppler; we found heterozygous C677T mutation in the methylene tetrahydrofolate reductase gene. We prescribed acetylsalicylic acid (100 mg daily).
At follow-up (the most recent was three years after the first visit), he reported a reduction of aura symptoms (about five episodes/month) not always followed by headache and no migraine attack without aura. No other seizure occurred and the most recent EEG was normal.
Migralepsy is a rare form with very few reported cases. Even in the cases that have been described, the diagnosis is not clear-cut. The difficulty of arriving at a precise differential diagnosis of visual disturbance (aura *versus* occipital partial seizures and elementary hallucinations) does not support the hypothesis that migralepsy is a primary entity in its own right.

ACUTE MANIA INDUCED DURING A CLUSTER HEADACHE EPISODE: A CASE REPORT

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Background Cluster headache often leads to mood changes in patients, in particular, to depressive reactions and sometimes to suicide. However, there are no controlled studies on the comorbidity of cluster headache and affective disorders such as manic-depressive illness. We report on a patient who developed his first manic episode while suffering from a cluster episode.
Case report A 34-year-old male patient has been suffering from episodic cluster headache according to IHS criteria for 8 years. He experienced one cluster episode per year with a duration of about 2 months. The left-sided cluster attacks occurred about 4 times a day with a single duration of about half an hour. Oxygen inhalation, and subcutaneous sumatriptan promptly aborted an attack. In recent episodes, verapamil at a dosage of 360 and 480 mg per day was effective as prophylactic agent. At the beginning of his last cluster episode, he received steroids from his general practitioner at a daily dosage of 125 mg per week, which was progressively decreased. At first the attacks stopped, but then recurred after 10 days; thus the patient was

admitted to our Headache Centre. However, a few days later, while still under steroids, the patient rapidly developed manic symptoms and had to be admitted to a psychiatric isolation ward. Treatment with quetiapine 300–600 mg per day was started, and after 10 days the manic symptoms disappeared; cluster attacks occurred occasionally under this monotherapy.

Conclusions To our knowledge, this is the first report on the onset of manic symptoms during a cluster episode. Since the patient had some endogenous depressive episodes in the past, the diagnosis of manic-depressive illness was made according to the International Classification of Disease, 10th edition (ICD-10). The manic episodes were probably induced by steroids or by steroid withdrawal. We conclude that cluster headache patients with a history of affective diseases should not be treated with steroids but with quetiapine or lithium, which are effective in both conditions.

HYPNIC HEADACHE WITH A SPORADIC PATTERN

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Hypnic headache (HH) is a primary headache disorder, classified in the fourth chapter of ICHD-II, which occurs exclusively during sleep and usually begins after the age of 60 years [1]. The natural evolution of HH is not well known, but it is assumed that it tends to be chronic unremitting. A follow-up of at least 2 years is described for only 25 patients among the 85 cases reported in the literature; according to the outcome data obtained from these patients, we recently proposed to distinguish between chronic and episodic HH [2].

A 63-year-old woman complained of a dull, severe headache in the vertex, which developed only during sleep and awakened the patient, without any accompanying signs or symptoms; the headache completely resolved 30 minutes after awakening. She referred the first episode two years before our visit and its recurrence with a very low rate (one attack every six months, for a total of four episodes, the last one just before the observation). Due to the short duration of the attack, the patient did not take any drug. A detailed interview revealed the presence of two more forms of primary headache (migraine without aura and infrequent episodic tension-type headache). General and neurological examinations, laboratory tests, and brain MRI with gadolinium were normal.

To our knowledge, this is the first case of a headache fulfilling ICHD-II criteria for HH with an infrequent pattern, and it supports our previous observations regarding the possibility of an episodic evolution of this rare primary headache.

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PRIMARY STABBING HEADACHE IN THE ELDERLY: A CASE REPORT

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We present the case of a 74-year-old man referred because of the onset in the previous month of a severe head pain occurring as a series of stabs (generally 3–5) in the left parietal area, lasting up to two seconds and recurring with irregular frequency without any accompanying signs or symptoms. He never experienced a recurrent headache before. The pain occurred every hour during the morning, and two or three times in the afternoon. The stabs presented with an average frequency of four days per week. His medical history revealed the presence of ischemic heart disease with atrial fibrillation and hypertension. Because of his heart condition, a cardiac pacemaker was implanted and he regularly took anticoagulants and hypotensive drugs. The general and neurological investigations were normal. A brain CT scan with contrast medium revealed no alteration; it was not possible to perform a brain MRI because of the presence of the heart pacemaker. We suggested indomethacin at the dose of 50 mg daily. From the second day of therapy the stabs disappeared. He is still headache-free after 3 months of follow-up.

Primary stabbing headache is classified in ICHD-II within chapter 4 "Other Primary Headaches". The short-lasting duration and the irregularity of its frequency justify the low rate of consultation, despite the relative diffusion of the condition, which occurs in 35% of the general population, according to recent data. In the same population-based study, the peak was reached in the third decade; the onset in the elderly is rarely reported [1].

The peculiarities of our case are: i) the sudden onset in the elderly; ii) the prompt response to low indomethacin dose. Further studies are warranted to better specify the diagnostic criteria for this form of primary headache and its treatment.

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A MIGRAINE-LIKE HEADACHE

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The cornerstone of migraine diagnosis, in the absence of pathognomonic biological or imaging markers, are the anamnestic data, with particular regard to the clinical features of the headache, and the general and neurological examinations. Neuroimaging or laboratory tests are useful to exclude a secondary origin, when: *i.* the characteristics of the headache do not fulfil ICHD-II criteria for the diagnosis of migraine; *ii.* the general or neurological examinations are abnormal; *iii.* the anamnestic data show the presence of alarm features, the so-called red flags.

A 37-year-old woman presented with a one-month history of daily, severe, diffuse headache with phonophobia, photophobia, nausea, and vomiting. She attributed these symptoms to migraine, a condition she suffered from since her twenties with an average frequency of 2 attacks per month. She decided to undergo a medical consultation because of the lack of response to the usual therapy (triptans and NSAIDs) and the progressive worsening of the symptoms. General and neurological examinations did not reveal any abnormalities. A brain CT scan showed the presence of several metastases in both hemispheres with a dislocation of the mid-line structures. Further investigations demonstrated a primary ovarian neoplasm. The patient died two months later. The possibility of a secondary origin was suggested by the accelerating pattern of a previous well-known headache and the lack of response to treatment, both of them to be considered as red flags. The peculiarity of this case is essentially represented by the normal general and neurological examinations despite the dramatic neuroimaging picture.

Secondary headaches fulfilling ICHD-II criteria for the diagnosis of a primary headache are described also for other forms (e.g. cluster headache, TACs) [1–2]. The adherence to major TACs ICHD-II criteria and a normal general and neurological visit are necessary, but not sufficient to exclude a secondary process. Thus, the appearance of a "red flag" in a headache patient should always prompt a re-evaluation to exclude the presence of a secondary cause.

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TRIPTAN OVERUSE AND EPISODIC SEROTONIN SYNDROME

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Serotonin syndrome (SS) is a rare pathological condition related to the concomitant use of drugs that increase 5-HT availability; the pathophysiology of SS seems to be ascribed to the stimulation in the brainstem of 5-HT_{1A} receptors and the inhibition of 5-HT_{1A} dopaminergic transmission, secondary to serotonergic hyperactivity. SS includes several neurological and autonomic manifestations that follow administration or an increased dosage of serotonergic drugs, and is clinically defined in the presence of at least three of the following signs/symptoms: mental status changes, myoclonus, hyperreflexia, tremor, fever, diaphoresis, shivering, and diarrhoea [1]. Because of their actions, triptans have been implicated in the pathogenesis of SS, in particular, if taken with drugs which increase 5-HT levels. We describe the case of a 61-year-old woman, who presented at a first visit a headache fulfilling ICHD-II criteria for probable chronic migraine without aura and probable triptan overuse headache. She treated her attacks with triptans, taking an average 29–30 doses per month for at least 6 months; sometimes (once a week) she had to take triptans twice daily. Furthermore, she took mirtazapine 30 mg/day for a depressive syndrome. She referred episodes of intense sweating, mental confusion, shiver, tremor, and inconstant diarrhoea, lasting 3–4 hours and leaving her prostrate. She complained of such episodes a few hours after taking a second dose of triptan. She first reported these symptoms five months before our observation, but she attributed them to her depressive status. Symptoms disappeared after the withdrawal of mirtazapine and a detoxifying treatment (follow-up 3 months), whereas the headache frequency remained unchanged; therefore, the final diagnosis was chronic migraine without aura.

The peculiarities of this case are: *i.* the temporal pattern and the spontaneous remission of each episode, indicating a recurrent and mild form of SS; *ii*. the correlation between taking a double dose of triptans and the onset of SS symptoms, documented by a diary; *iii*. the concomitant use of mirtazapine, a drug rarely implicated in generating this syndrome.

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CONTRIBUTION OF NEUROBIOLOGICAL AND PSYCHOLOGICAL TRAITS IN MEDICATION-OVERUSE HEADACHE (MOH) DEVELOPMENT: A CASE REPORT

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Even though it is not yet clear whether the misuse and/or abuse of analgesics or triptans in migraine may be involved in headache chronicity, chronic pain and pain relief are considered the most important features in inducing a habitual behaviour as therapeutic need. It is well known that complex brain areas, as well as different neurotransmitter systems and complex responses participate in the biology of the reward brain system. Comorbidity for psychiatric disorders, such as anxiety and depression, as well as negative life events, exacerbate headache and quality of life in patients suffering from headache [1]. Stressful periods, can induce disruption in these interneural interactions and result in a craving for drugs to relieve the pain and bad feelings. Serotonin plays an important role in migraine pathogenesis, and drugs such as triptans, 5-$HT_{1B/1D}$ agonists, are the first choice for acute migraine therapy. Recent findings support the hypothesis that serotonin could contribute to the development of mechanisms underlying the reward system in the brain, inducing a compulsive habit for consumption of antimigraine analgesics [2]. The present paper would like to contribute to clarifying the above described mechanisms. For this purpose, a case report is introduced and discussed.

A 45-year-old woman complained of primary migraine for many years. The headache occurred two, sometimes three times a week. Prodromic symptoms, such as tension in the orbital region and nausea, preceded the headache. For about two years, the patient abused of analgesics (NSAIDs), and during the last year she took triptans (9 to 10 times a month during the last three months) and analgesics. Despite the drug treatment, headache recurred more frequently, and the characteristics of the pain changed, from being sharp and starting abruptly to often presenting in one hemiscalp and spreading subsequently to the entire head. The clinical story of the patient revealed psychiatric co-morbid disorders for anxiety and depression following a stressful period for job-related problems (mobbing?). A genetic study was carried out to investigate inherited predisposition to thrombophilia and verify the possibility of sinus venous thrombosis. A Factor V gene mutation was found. Moreover, neuroimaging investigations (MRI and intracranial venous MR angiography) did not show any pathological brain conditions but revealed a dominant dilated and tortuous right transverse sinus, whereas the left transverse sinus was hypoplastic. During hospitalization, drug treatment was stopped and prophylaptic therapy was started.

In conclusion, this case report suggests that headache chronicity might be caused by biological as well as psychological traits. Correct management of migraine and headaches may contribute to modifying habitual behaviour and reducing consumption of drugs in chronic sufferers.

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A CASE OF UNSATISFACTORY HEADACHE MANAGEMENT SUPPORTING THE NEED FOR INFORMATION AND EDUCATION ABOUT HEADACHE DISORDERS

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Introduction With this case report we want to emphasize how important it is, and how much work still needs to be carried out in terms of patient education and divulgation of information about headaches.

Case A 41-year-old man suffered from headache (the first episode occurred about 15 years ago). This affection became worse in frequency, intensity and refractory to the rescue dose in the last 12 months, compromising his job. The characteristics of this headache were: daily frequency; right-sided localization, beginning in the posterior region of the head; absence of aura except for tension located in the cervico-occipital area over the paravertebral muscles, associated with pain in the point of emergency of Arnold's nerve; bilaterally lasting ≥24 hours. Pain intensity was measured with Visual Analogue Scale (VAS). Phonophobia and photophobia were so strong during the crises that they forced the patient to abandon his activity. Under prescription, the patient had taken 500 mg effervescent tablet as rescue dose. Consecutively, because the headaches did not resolve, he took 10 mg of rizatriptan RPD, which he defined has being unsatisfactory for pain relief. The patient did not receive any information about the rescue dose nor prophylactic drugs from the previous doctors, even though he had been suffering from headache for the past 15 years and was experiencing increased headache frequency.
The patient underwent algological examination: finger pressure caused pain at the paravertebral cervical muscles conserving flex extension and laterality of the first trigeminal branch. The trigger point was on the right trapezoidal muscle.
Chronic sinusitis was found in the patient, who worked in an area subject to climatic variations. He was allergic to acetylsalicylic acid. Instrumental diagnosis, x-rays of the head and cervical spine in two separate moments (23/02/06), showed a reduction of physiological cervical lordosis, which resulted in osteoarthritis. The patient was prescribed the following therapy:
Fluxarten 5 mg at 9 p.m.
Laroxyl 5 mg gtt at 9 p.m.
Sirdalud $^1/_2$ tablet bid
Rizatriptan RPD 10 mg s.l., when needed.
Therapeutic efficacy was and is still being evaluated monthly by VAS.
Results The described therapy was followed continuously considering the high tolerability of the prophylactic drugs. After 4 weeks, the monthly frequency of crisis decreased to three, with VAS=7 and the patient responded to rizatriptan taken at the beginning of the crisis. After 8 weeks, the frequency decreased to 2 crises, VAS=5, and the patient responded to rescue dose. Currently, the patient is drug free and refers two headache crises per month. He has returned to work and now considers his social life normal.
Conclusions This case represents the paradigm of an incorrect treatment for headache symptoms, regarding both the most suitable strategy to use and when to take the symptomatic drug. It is evident how a symptomatic strategy for daily headache exposed the patient to drug overuse and to an unsuccessful therapy causing social and working problems. It should be mentioned that the lack/absence of correct information regarding early prophylaxis also contributed to the unsuccessful resolution of headache pain.

HEMIPLEGIC MIGRAINE WITH PROLONGED SYMPTOMS IN ATYPICAL STURGE-WEBER SYNDROME

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Introduction The Sturge-Weber Syndrome (SWS) is a rare disease characterized by an encephalotrigeminal or leptomeningeal angiomatosis and facial vascular nevus (port-wine stain). It is part of a phenotypic spectrum, which includes other syndromes with capillary angiomatosis malformations in various sites, such as Klippel Trenaunay Weber Syndrome with malformations not only of the capillaries, veins, arteries, and lymphatic vessels, but also of soft tissues and bone hypertrophy [1].
Case report We report a patient with a mixed phenotype, of a facial nevus on the right forehead, right arm and left leg soft tissues and bone hypertrophy, obesity, high blood pressure, and epileptic seizures, who presented at 14-years of age with pulsating unilateral headache with visual disorders and acute - prolonged left hemiparesis. None of the episodes were preceded or accompanied by loss of consciousness or ictal clonic jerks. The EEG was normal during the headache episode, MRI showed the typical Sturge-Weber angiomatosis without ischemic lesions.
Results and discussion Our case report suggests a Sturge-Weber atypical syndrome that could be responsible for symptomatic migraine-like headache. According to criteria of the ICHD-II classification 2004, this syndrome could be clinically diagnosed with probable migraine with aura (subtype 1.6.2) with atypical features.
Vasomotor modifications in venous flow in relation with pial angiomatosis are probably at the origin of these migraine-like episodes. Chronic oligoemia and the pre-existent metabolic cortex damage caused by hypoperfusion would worsen the clinical symptomatology [2].
Epileptic seizures between the prodromic and pain phase of migraine attack are rarely reported in paediatric age and in patients affected by SWS. Probably, the migraine attacks, like the seizures, are to be considered another expression of brain damage as a result of microvascular disturbances.
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A CASE OF POSTERIOR SCLERITIS: HEADACHE ATTRIBUTED TO OCULAR INFLAMMATORY DISORDER

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Introduction A case of posterior scleritis is described. Posterior scleritis is an uncommon form of scleral inflammation, which can be confused with several inflammatory and non-inflammatory ocular diseases or ocular tumors. Anterior scleritis can be associated with this condition. It may be idiopathic or associated with systemic disease, particularly connective tissue disorders [1]. In the International Headache Society Classification [2] it is included in the chapter "Headache attributed to ocular inflammatory disorder" (11.3.4). Periocular pain, pain on movement and decreased vision are the most frequent symptoms [1]. Pain can also be referred to the forehead, maxilla, or sinuses and is described as penetrating in character. Redness of the affected eye can be observed. Ultrasonography is the key investigation necessary to make the diagnosis of posterior scleritis [1]. CT scan and fundus fluorescein angiography can also be used.
Case history We report a case of a 26-year-old woman who began to complain of right-sided ocular and periocular pain, exacerbated by ocular movements, irradiating to the ipsilateral temple and zygoma, not associated with visual disturbances. Admitted to our Emergency Department, she underwent an ophthalmological consultation, which showed a normal fundus oculi and visual acuity. Trigeminal neuralgia was suspected and she was then treated unsuccessfully with analgesics. Seven days later, she underwent a second ophthalmological and a neurological consultation, which were both normal. After one week, she experienced a worsening of facial pain associated with conjunctival injection, eyelid edema, and developed a central scotoma. She was then admitted to our clinic. Fundus oculi showed in the right eye a hyperemic optic disc with blurred margins. Blurred vision in the right eye with a central scotoma was referred. The remaining neurological examination was normal. A third ophthalmological consultation showed a visual acuity of 1/10 in the right eye (10/10 in the left) with conjuncti-

val injection. Fundus oculi confirmed the above reported findings and some retinal folds; ultrasonography revealed scleral thickening and exudative retinal detachment, suggesting a posterior scleritis. Chest X-ray, routine blood tests, brain MRI with gadolinium and cerebrospinal fluid examination were normal.
The patient was treated with methylprednisolone i.v. 1 gr/day for 10 days with complete regression of pain and clear improvement of visual disturbances. Ultrasonography performed 10 days after the end of treatment showed a reduction of scleral thickening, fluid in the Tenon capsule, and regression of retinal detachment. Visual acuity was 6/10 in the right eye. A month after discharge the patient began to complain of left periocular pain, without visual loss. Ultrasonography showed posterior scleritis in the left eye; she fully recovered after a further course of steroid treatment.
Discussion Posterior scleritis is a common form of scleritis and should be suspected in patients who present with ocular pain and visual loss. It is one of the most commonly misdiagnosed conditions in ophthalmology, especially when, as in our case, pain is not associated with visual disturbances or ocular signs at the onset of symptoms.
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HEADACHE AND ISOLATED PARALYSIS OF THE 12TH CRANIAL NERVE AS A PRESENTING SYMPTOM OF DISSECTION OF THE INTRAPETROSAL TRACT OF THE INTERNAL CAROTID ARTERY

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Case description A 60-year-old man came to our attention for the onset of symptomatology characterized by continuous, left-sided, fronto-orbital headache of moderate intensity, associated with photophobia, which did not regress after taking common analgesics. After about three days, the patient presented with a worsening of the headache, which was of stronger intensity and with the appearance of dysphagia and dysarthria.
The neurological examination revealed a deficit of the left XIIth cranial nerve. Brain CT, brain MRI, Echo-colordoppler of the supra-aortic vessels, and ultrasound of the neck were normal. Angio-CT and subsequent angio-MRI of the vessels of the neck showed findings compatible with dissection of the intrapetrosal segment of the left internal carotid artery.
Discussion Carotid artery dissection is an important cause of stroke in the young. Headache and facial pain, often associated with Horner's syndrome, constitute a common onset symptom and may precede stroke by a few days [1]. Headache associated with deficit of the hypoglossal nerve is not a common onset symptom, and only a few cases are described in the literature [2]. More frequently, this symptomatology may be secondary to diseases of the jugular foramen, and in this case, is associated with paralysis of other cranial nerves (IX^{th} and X^{th}).
In the case described, brain MRI excluded intracranial diseases. Echo-colorDoppler of the supra-aortic vessels could not visualise the dissection, in that this involved the intraosseous segment of the internal carotid artery, thus warranting a specific study of the complete intracranial course of this artery.
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PAINFUL RECURRENT BILATERAL OPHTHALMOPLEGIA SECONDARY TO BILATERAL CAROTID CAVERNOUS FISTULA

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Case description A 68-year-old woman presented to us one week after onset of symptoms characterized by a stabbing headache of strong intensity, in the retro-orbital and left fronto-temporal regions, with nausea, photophobia and phonophobia associated with diplopia. The neurological examination revealed paresis of the left VIth cranial nerve, tactile hypoesthesia, and left-sided pain of the first division of the trigeminal nerve.
Brain CT revealed slight enhancement with gadolinium in the left cavernous sinus. Blood tests, Echo-colorDoppler ultrasound of the supra-aortic vessels and the superficial temporal arteries were normal. The patient was treated with prednisone 50 mg/day for one week and subsequently 25 mg/day. After 48 hours the headache regressed, but the diplopia persisted.
After two months, the patient also presented diplopia on right gaze, eyelid edema, conjunctival injection in the right eye, associated with unilateral retro-orbital pain. The neurological examination revealed: proptosis, eyelid edema, conjunctival chemosis, partial deficit of the right IIIrd cranial nerve, and deficit of the left VIth cranial nerve.
Brain MRI was repeated and in the norm. Subsequently, brain angio-MRI was performed, which revealed a bilateral dural fistula of the cavernous sinuses and the occiptal foramen.
The lesion was treated with embolization via the left transjugular approach.
Discussion Dural arteriovenous fistulas (AVFs) are a rare condition, with a rate of incidence of 0.16 per 100 000 inhabitants/year; with respect to other intracranial vascular malformations they can be acquired, often as a consequence of cerebral venous thrombosis, previous head traumas, aneurysmal rupture, and local and systemic infections [1].
Cavernous carotid fistulas constitute 20%–40% of all dural AVFs [2], and are formed by an abnormal communication between the carotid artery and cavernous sinus.
Venous hypertension subsequent to shunt formation results in retrograde venous drainage into the ophthalmic venous system, which is responsible for the ocular symptoms, cortical venous reflux, and tendency to haemorrhage.
Headache is rarely a presenting symptom, but when present, it is associated with ophthalmoplegia. The differential diagnosis is with other forms of painful ophthalmoplegia.
Neuroimaging studies are normal or furnish indirect signs (often non-specific) of fistula presence; the only certain diagnostic investigation is brain angio-MRI [1].
In the case of carotid-cavernous fistulas, among the various therapeutic options endovascular embolization is the least invasive method, and when possibile, the transvenous access can lead to complete obliteration of the fistula [1].
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PAINFUL OPHTHALMOPLEGIA WITH CSF ALTERATIONS: A CASE REPORT

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Introduction Painful ophthalmoplegia (PO) is a syndrome characterized by the occurrence of periorbital pain and ophthalmoparesis, with or without the involvement of other cranial nerves, caused by several different etiologies.
Case histority A 46-year-old man was admitted to our ward, with a severe dull and steady pain in the right orbit and in the surrounding area of the forehead, associated a few days later with the appearance of diplopia and right eyelid ptosis. The neurological examinations showed a paresis of both the right third and fourth cranial nerves. Physical and laboratory examinations, trigeminal reflexes, cerebral MRI, arterial and venous MR angiography were all normal.
A CSF sample showed an elevated protein content (93 mg/dL), with a positive Pandy reaction and alteration of blood-brain barrier indices, and was negative for the presence of common infectious agents. Two days after the clinical admission, the headache disappeared, and the third and fourth nerve palsy improved significantly, with full recovery from diplopia a few days later. The increase in CSF proteins persisted at 2 weeks (73 mg/dL) and 1 month (64 mg/dL).
There are several causes of PO: vascular, inflammatory, infections, dismetabolisms, neoplasia, trauma, recurrent demyelinating neuropathy and ophthalmoplegic migraine (OM). OM may be suspected when a severe headache is associated with ophthalmoparesis, normal MRI investigations and a benign course [1]. In our case this diagnosis could be hypothesized. In this regard, it is noteworthy that the IHS criteria (1988) required a single episode (probably because of its rarity), while ICHD-II criteria require its recurrence [1]. In our patient, the CSF abnormalities, the single episode and the "non-migrainous" features of the headache, except for the severity, are consistent with an uncommon viral infection. Because OM is more a syndrome than a specific disease, this case suggests that if a diagnosis of OM is suspected, the possibility of a benign inflammatory disease should be considered, in particular, when ICHD-II criteria are not fully satisfied [1].
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HEADACHE IN A PATIENT WITH CEREBRAL SINUS THROMBOSIS AND SPONTANEOUS INTRACRANIAL HYPOTENSION

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Cerebral venous sinus thrombosis (CVST) is an uncommon, life-threatening condition that mostly affects middle-aged women. The principal, and also earliest symptom is headache (80%–90%), followed by other neurological symptoms. The headache has no specific characteristics, is most often diffuse, progressive, severe and associated with other signs of intracranial hypertension. It can also be unilateral and sudden, and sometimes mimick migraine, primary thunderclap headache, cerebrospinal fluid (CSF) hypotension or subarachnoid haemorrhage (ICHD-II, 2004). CVST recognizes a wide variety of risk factors and causes. In 20%–35% of cases, where aetiology remains unknown, CVST is classified as idiopathic.
Intracranial hypotension (ICH) syndrome is a very infrequent clinical condition. Its most common symptoms are orthostatic headache associated with nausea and/or vomiting, diplopia, hearing disturbances (hypoacusia, tinnitus), neck pain, visual deficit and vertigo.
We report the case of a 43-year-old female who presented with headache, which began three days before, characterised initially by pressing/tightening, and later on, pulsating quality localised at the vertex, of mild intensity, without accompanying symptoms, associated with mild nausea and tinnitus and occurring only on standing. Brain CT scan showed less evident cortical sulci, small basal cisterns, small ventricular cavities, without parenchymal alterations. Neurological examination showed brisk reflexes and bilateral Babinski sign; fundus oculi was normal. Brain MRI with contrast and angio-MRI showed thrombosis of the transverse and sigmoid sinuses and of the internal jugular vein on the left side, along with alterations suggestive of ICH (pachymeningeal contrast enhancement and Arnold-Chiari-like descent of cerebellar tonsils). The clinical history was unremarkable, in particular for thromboembolic risk factors. Complete blood count, thrombophilia tests, and neoplastic markers were normal, as were ECG, chest X-rays, somatosensory evoked potentials, and epiaortic vessels and transcranial EchoDoppler.
Spinal MRI with contrast showed signs of CSF leak (deliquoration) in the dorsal spine. Then, the clinical history was specifically reassessed and no possible causes of CSF leak were identified. The patient was treated with anticoagulant therapy: an angio-MRI performed 18 days later showed a partial recanalization. At discharge and at two months follow-up the patient was asymptomatic.
Cases of CVST in patients with ICH secondary to CSF leak are found in the literature, but only 4 cases of CVST have been associated with spontaneous ICH. Based on these observations, and on our case, it could be possible that compensatory venous sinus dilation and consequent hematic stasis conditions associated with ICH may predispose to CVST.

MIGRAINE WITH VISUAL AURA ASSOCIATED WITH ARTERIOVENOUS MALFORMATION

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Objective To describe two cases of migraine with aura associated with cerebral arteriovenous malformation (AVM).
Case 1: A 57-year-old woman complained of headache of unusual severity. She had a history of migraine since age 17, characterized by an aura of scintillating scotoma for 20–30 minutes on the right side. Thereafter, a strictly unilateral (left-sided in all cases) throbbing headache with nausea, vomiting and photophobia occurred. Pain was mild and responsive to simple analgesics. MRI showed an arteriovenous malformation in the left occipital lobe.
Case 2: A 22-year-old woman had a history of migraine since age 15 with visual aura of scotoma and fortification (zig-zag patterns) on the left side, occasionally accompanied by numbness in the left hand and face. Her mother had a history of migraine. Three times she had tongue biting; EEG showed epileptiform discharges. She started valproate therapy and the visual aura terminated. The aura always occurred on the left suggesting a possible right-sided structural lesion. MRI showed a right parietal AVM.
Discussion Arteriovenous malformation is a congenital anomaly that consists of abnormal arteries and veins without the presence of a capillary bed. The majority of patients initially show intracranial haemorrhage, while others may present symptoms of seizures, headaches and progressive neurological deficits. In the general population, AVMs are an extremely infrequent cause of headache. Headache occurs in 10%–50% of patients with AVM. The headache may be typical of migraine. Migraine headaches have a complex pathophysiology, and (both vascular and neuronal mechanisms) have been proposed. One possible scenario begins with brain initiated events evolving to cortical spreading depression (CSD). Susceptibility to CSD appears to be genetically determined. Structural lesions may cause the initial event.

When a patient with migraine manifests symptoms always on the same side, neuroimaging workup is warranted. This should aid in the early diagnosis of cerebral AVM in order to start treatment before the occurrence of cerebral haemorrhage.

TRIGEMINAL NEURALGIA AS PRESENTING SYMPTOM OF ARNOLD CHIARI TYPE 1 MALFORMATION: A CASE REPORT

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Introduction Clinical presentation of Arnold Chiari type 1 malformation is highly variable. About 13% of patients are asymptomatic; headache may be the sole clinical manifestation of the malformation; however, it is one of the most frequent. No headache type seems to be particular to the malformation; both short- and long-lasting headaches are described [1].
Case history A 36-year-old woman presented with throbbing-stabbing pain in the left supraorbital region, which started 3 years earlier. Pain occurred three or four times a day; the paroxystic pain was severe, and lasted 7–10 seconds. There were no warning symptoms; trigger factors were coughing, sneezing, defecation, and nodding movement. There were no accompanying symptoms but mild nausea. Between attacks, she was completely pain-free. She was treated with NSAIDs and carbamazepine without any improvement. Neurological examination and laboratory blood tests were normal. MRI showed an Arnold Chiari type 1 malformation with downward herniation of the cerebellar tonsils through the foramen magnum into the upper cervical spinal canal. A CT scan of the maxillary and frontal sinuses was normal. Neurosurgical intervention was suggested.
Discussion Our patient satisfied all the criteria for a symptomatic neuralgia probably caused by the Arnold Chiari type 1 malformation. In this view, we excluded other types of headaches, such as rhinosinusitis, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), supraorbital neuralgia and idiopathic trigeminal neuralgia. The otolaryngologic examination and CT scan excluded the possibility of rhinosinusitis.
Due to the location, duration and frequency of the pain described, it could be compatible with a SUNCT, however, the neurovegetative disturbances, such as conjunctival injection and lacrimation, were absent. Regarding the supraorbital neuralgia, it lacked tenderness over the nerve in the supraorbital notch, and there was no pain in the medial aspect of the forehead in the area supplied by the supraorbital nerve. Unlike trigeminal neuralgia, there were no trigger points, a very rare location only in the first branch, and the lack of any response to high carbamazepine dosage [1].
Conclusions To our knowledge, this is the first case with Arnold Chiari Type 1 malformation and symptomatic trigeminal neuralgia exclusively in the first branch. It is probable that the pain is caused by an anatomical compression on the trigeminal nucleus, and that the difference in pressure found in the intracranial and intraspinal compartments, evoked by the Valsalva maneuvre, emphasises this compression, setting off the short-lasting sharp pains [2].
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HEADACHE ATTRIBUTED TO BRAIN ABSCESS: A CASE REPORT

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Brain abscess is a focal suppurative process in the brain parenchyma that still contributes to high mortality rates. Outcome is closely related to correct and early management. In order to evaluate early management, we have reviewed the brain abscesses treated in our Department of Neurosurgery during the last five years, choosing to describe one case among these. We present a 38-year-old male who was admitted to the Emergency Department (ED) complaining of a frontal headache and fever (37.5C°), unresponsive to treatment with NSAIDs. The patient described weakness and numbness of the right limb, which resolved in 20–30 minutes. After CT scan resulted normal, the patient was discharged. The day after, the patient returned to the ED complaining of two new episodes, characterized by weakness and numbness involving the right limb with spontaneous resolution in ten minutes, while an intense, diffuse bilateral headache persisted. The patient was admitted to our department. The neurological examination was unremarkable. However, within five days the patient showed right hemiparesis; the inflammatory index was elevated and MRI revealed a productive, expanding lesion with marked edema in the left parietal region. The modality of treatment was surgical excision with catheter drainage-aspiration of the left parietal abscess. Outcome was excellent: the patient recovered promptly from the hemiparesis, and there was progressive attenuation of headache until it disappeared. Brain abscesses are severe infections with lethal outcome in the case of delay in diagnosis and treatment. Predisposing factors are sepsis of adjacent organs and bacteraemia. The most frequent clinical manifestations are fever and headache. Headache is usually the most frequently encountered symptom. When under observation our patient continuously complained of bilateral, constant headache with increasing intensity to severe grade, aggravated by straining and accompanied by nausea. A new type of headache associated with general feeling of illness and/or fever should direct attention toward an intracranial infection.

IS THE TREATMENT OF HEADACHE BY SPONTANEOUS CERVICAL CSF LEAK WITH LUMBAR EPIDURAL BLOOD PATCH A RATIONAL CHOICE?

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Background Spontaneous intracranial hypotension (SIH) generally results from spinal spontaneous CSF leakage [1]. Treatment is usually conservative. Sometimes an autologous EBP at the site of CSF leakage may be necessary [2].
Objective To evaluate the spread of blood injected into the epidural space during lumbar epidural blood patch (LEBP) for treatment of spontaneous cervical CSF leakage (SCCSFL) by MRI.
Materials and methods We report one case of SCCSFL [among the 32 with this condition evaluated between 1992 and the present].
Results A 45-year-old man presented sudden, intense, gravative fronto-occipital orthostatic headache. Neurological examination, routine blood tests, and brain CT scan were normal. Brain MRI showed diffuse pachymeningeal enhancement. Gadolinium spinal MRI showed CSF epidural collection from C2 to D3. After one month of bed rest, orthostatic headache was still present. The patient was treated with autologous lumbar EBP (25 mL) at the L2-L3 level. The blood was mixed with 0.05 mL of gadolinium. During and after injection, he remained in the Trendelenburg position (TP) approximately 30° for 1 hour. Spinal post-patch MRI showed gadolinium mixed with blood in the epidural space from the lumbar to cervical level (C2-C3). He subsequently remained in the TP for 22 hours. He was asymptomatic within 24 hours after LEBP. At 6-month follow-up he was asymptomatic.
Discussion and conclusions We demonstrate that EBP, even though injected at the level of the lumbar spine (i.e., far from the site of CSF

leak), may move upward reaching the cervical segments. This is possibly favoured by the TP. A rapid coagulation response at the level of the dural hole stops CSF leakage. Thus, EBP at the level of the cervical spine, where the procedure is difficult to attempt, may not be necessary. To our knowledge, this is the first report that shows the spread of blood from lumbar to cervical epidural space with LEBP and demonstrates that the treatment of spontaneous cervical CSF leak with autologous lumbar epidural blood patch is a rational choice.

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REFERRED FACIAL PAIN AS A SYMPTOM OF NON-METASTATIC LUNG CANCER: A CASE REPORT AND REVIEW OF THE LITERATURE

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Introduction Facial pain is a common clinical symptom caused by a wide variety of underlying conditions, including neurological, odontological, and otolaryngological pathologies. A patient who developed an intractable facial pain as an unusual first manifestation of a remote lung carcinoma is described.

Case Report A 39-year-old woman presented with a 2-month history of pain localized in the left jaw, with extension into the ipsilateral orbit and temple. The pain was continuous, moderate to severe in intensity, and possibly associated with tearing, eye redness, and mild nausea. She had been smoking 1 pack of cigarettes a day, for at least 20 years. An odontological visit, a brain MRI and a carotid Doppler ultrasound were normal. The pain was unresponsive to a number of analgesics as well as carbamazepine, gabapentin, and prednisone. About 2 weeks before presentation the patient developed cough and poor appetite. The neurological examination was unremarkable. The physical examination revealed diminished breath sounds in the left-upper lobe and right supraclavicular lymphadenopathy. A CT scan of the chest showed a large solid mass in the superior aspect of the left mediastinum surrounding the supra-aortic vessels and hilus. A fine-needle biopsy of the supraclavicular node confirmed the presence of a large cell carcinoma. The ESR was markedly elevated at 83 mm/h. A few days later, the patient became dysphonic, with laryngoscopic evidence of paresis in adduction of the left vocal cord. The facial pain gradually improved and then spontaneously ceased before starting chemotherapy. The patient was still pain-free after a 6 months follow-up.

Discussion Referred facial pain is a rare symptom of nonmetastatic malignant lung lesions, and was first described by Des Prez and Freemon in 1983. Since then, 36 patients (17 M, 19 F) have been described, including the present patient. The presumed mechanism by which a thoracic mass can provoke a pain referred to the face is compression of the vagus nerve, which drives pain signals originating from thoracic and abdominal viscera. Convergence of the visceral and somatic afferents at the level of the descending nucleus of the trigeminal system may explain the ipsilateral referred facial pain. The most frequent locations are the ear (about 90% of cases), jaw and temple. The diagnosis can be delayed from 1 month to 4 years after the onset of the pain. All patients described were smokers. ESR is increased in most patients. Unlike the previous cases, in the present case the pain spontaneously disappeared after the patient became dysphonic, indicating the putative importance of the integrity, at least in part, of the laryngeal nerve.

Conclusions Lung cancer should be included in the differential diagnosis of facial pain with atypical signs and/or refractory to treatment.

A CASE OF ATYPICAL INTRACTABLE FACIAL PAIN SECONDARY TO METASTATIC LUNG CANCER

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Introduction Persistent idiopathic facial pain is defined by the International Headache Society Classification (ICHD-II) (chapter 13.18.4) as a pain in the face, present daily and persisting for all or most of the day, confined at onset to a limited area on one side of the face, deep and poorly localised. According to the classification, pain around the ear or temple may precede the detection of an ipsilateral lung carcinoma [1]. Nearly 30 cases of intractable facial pain secondary to lung neoplasm are described in the literature [2]. We report a case of intractable facial pain associated with metastatic lung cancer.

Case history A 70-year-old woman presented to the clinic with a 15-month history of constant, right-sided facial pain, with paroxysms of the upper teeth, irradiating to the auricular and temporal areas. Six months after the onset of pain she underwent CT scan and EEG, which were both normal. She was unsuccessfully treated with amitriptyline (40 mg per day) and gabapentin (up to 2000 mg per day). She had additional complaints of poor appetite with weight loss of 4 kg in the last 6 months and a 9-month history of persistent cough with recent onset of chest pain on the right side. Auscultation of the lungs revealed abnormal breath sounds on the right hemithorax; neurological examination revealed a sensory loss on the right side of the face. Routine blood tests were normal. Chest X-ray revealed a mass in the right hylar region, confirmed by chest CT. She underwent bronchoscopy with lung biopsy; the histological examination revealed pulmonary adenocarcinoma. Brain MRI with gadolinium revealed small multiple supratentorial and infratentorial brain lesions, none of them localized near the right trigeminal nucleus and pathways. The patient was treated with chemotherapy with slight improvement of facial pain. She died shortly thereafter.

Discussion Facial pain secondary to lung cancer is usually described as a unilateral constant ache, ipsilateral to the lung mass, frequently involving the auricular area, and often associated with signs suggesting a lung cancer (weight loss, digital clubbing, cough, etc.). The pain seems to be due to invasion of the vagus nerve [2]. Our case referred to a metastatic lung cancer, but none of the lesions seen on brain MRI could possibly explain the pain referred by the patient and probably occurred at a distance from the onset of pain. It is important to consider lung neoplasm as a possible cause of facial pain, especially if it presents with the characteristics seen above and in smokers.

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CONFINIA CEPHALALGICA: 15 YEARS OF ITALIAN PUBLISHING ON HEADACHES

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Introduction In recent years the quality of medical research in the field of headaches has reached levels of excellence that have amazingly broadened our panorama of knowledge and justified the development in the international publishing field of specialized journals.
Discussion *Confinia Cephalalgica* was born at the Neurological Institute C. Mondino in Pavia, at the end of the 1980s. At the beginning, it was the official journal of the Italian Society for the Study of Headaches, and then it became the official journal of the University Centres for Adaptive Disorders and Headache. The journal is published 3 times a year and contains original articles, clinical cases of interest, impossible cases, reviews, editorials, therapeutic and historical notes, book reviews and congress reports. The goal of the journal is to constitute a forum for integrating different ideas and expertise through an open dialogue among experts from different disciplines in order to contribute to the advancement and development of knowledge in the field of headaches. The editorial board has always supported the role of the journal as a tool for communication and cultural exchange on headache themes, among Italian-English communities in the world and between Italy and others countries with neolatin language and culture. Not less important is its role as the expression of the patient associations (AL.CE. Group – CIRNA Foundation) that financially supported the journal. During the last ten years (1997–2006), the journal published upon invitation or by direct submission more than 120 papers, furnished by 354 authors. The journal publishes integrated scientific information, promoting a multidisciplinary environment that involves first of all neurologists, but also philosophers and psychiatrists, physiologists and men of literature. After the restyling of the journal cover in 2004, beginning this year, *Confinia Cephalalgica* is editing, except for special events, only in an online version (free download at the website *www.cefalea.it*).
Conclusions Although the paper version will be missed, the new electronic online version is looked at as a challenge, with the desire to be of valuable assistance for physicians and researchers. Thus, the future challenge will be the confrontation and exchange of headache information on the Web.

HEADACHES: THERAPEUTIC ASPECTS

TOPIRAMATE IN MIGRAINE PROPHYLAXIS: AN OPEN STUDY

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Introduction Patients who suffer frequent severe migraine or chronic daily headaches are often prescribed prophylactic drugs. A number of beta-blockers, calcium-channel blockers, serotonin agonists, and antidepressants have been tested as prophylactic agents. Topiramate is a new antiepileptic agent that has GABA agonist properties and has few side effects when used in low doses.
Objective and methods The aim of this study was to examine the effects of topiramate on the frequency and intensity of migraine attacks during prolonged use. Patients who demonstrated 3 to 10 migraine attacks per month; in addition to migraine, also had chronic daily headaches from a variety of causes, and all patients had failed treatment with a number of prophylactic agents.
Results We present 35 patients, who kept a daily diary that recorded the frequency, severity of headaches, and the amount and type of rescue medication used. Over a 3–9 months follow-up, 11 patients (30%) had a very significant improvement in headache frequency (headaches decreased by over 60%), and 11 patients had a moderate improvement in headaches (decrease of 40%–60%). Three patients discontinued therapy due to side effects (lightheadedness, tinnitus, and numbness in hand) and eight patients did not report any improvement despite having been on therapy for over 12 weeks. The remainder of patients had only 8 weeks of therapy.
Conclusions Our open uncontrolled study in patients with resistant headaches suggests that topiramate may be a useful prophylactic medication with limited side effects. A large placebo-controlled study is needed, however, before the results are generalized.

PROPHYLAXIS OF HEMICRANIA CONTINUA WITH TOPIRAMATE: REPORT OF 2 CASES

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Introduction Hemicrania Continua (HC) is an uncommon and underrecognized primary headache disorder. It is characterized by a strictly unilateral continuous headache of moderate intensity with possible exacerbations, and it is associated with ipsilateral autonomic features, such as ptosis, miosis, conjunctival injection, lacrimation or rhinorrhoea, that tend to be less pronounced than those seen with cluster headache [1]. The pathophysiology of HC is poorly understood.
HC has generally a prompt and enduring response to indomethacin 25–300 mg daily, although 25%–50% of treated patients develop gastrointestinal side effects and unresponsive forms have been described. Patients who cannot tolerate indomethacin pose a difficult management challenge as no other drug is consistently effective in HC. Recently, Matharu et al. [2] reported 2 patients affected by atypical forms of HC that showed good response to topiramate.
Case reports Here we describe two patients who fulfil both the IHS diagnostic criteria for HC. The physical and neurological examinations and brain magnetic resonance imaging with gadolinium were normal in both patients.
The patients demonstrated a very good response to indomethacin but both developed the most common side effect, gastritis, that led us to stop this treatment. Thus, these patients were started on topiramate with slow titration to 100 mg b.d, and they had a complete benefit with the prophylatic treatment with topiramate after 30 days. The dose of topiramate required to give complete relief of pain was somewhat less than that usually needed for the antiepileptic effect of the drug. There were no side effects during the treatment with topiramate.
Discussion and conclusions Topiramate has multiple mechanisms of action, which include: blockade of the voltage-mediated sodium channels, enhancement of GABA-mediated chloride influx to GABA antagonism of the glutamate kainate/AMPA receptor and carbonic anhydrase inhibition. The mechanism(s) of action responsible for the beneficial effect in various headache syndromes is currently unknown. Whatever the mechanism, if the favourable response observed in our patients can be confirmed in other cases, it would broaden the therapeutic armamentarium available for the treatment of this severe and sometimes incapacitating condition.
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EFFICACY AND TOLERABILITY OF LEVETIRACETAM IN EPISODIC AND CHRONIC MIGRAINE

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Background Because of its effect in stabilizing neuronal hyperexcitability, the antiepileptic drug levetiracetam is a promising molecule for the prophylaxis of migraine.

Methods Twenty-five patients with episodic migraine without aura (at least 4 attacks per month of moderate-severe intensity; Group 1) and 18 patients with chronic migraine (no drug abuse; Group 2) were treated with levetiracetam 500 mg/day for 5 days, increased to 1000 mg/day in two administrations, after 5 days. Number of days with headache/month, accompanying symptoms (mild-moderate vs severe), use of symptomatic drugs for migraine attacks (number of drugs), and side effects of levetiracetam were recorded at baseline and at the end of the 3-month treatment period in both groups.
Results One patient in Group 1 did not complete the study because of intolerable side effects (somnolence and asthenia). Patients in Group 1 reported a mean reduction in the number of days/month with headache from 8.4 at baseline to 4.1. In Group 2, 12 patients were nolonger classified as chronic (from 23.8 to 10.3 days/month, mean values), four patients had an improvement of their chronic headache (from 23.8 to 16.2 days/month, mean values) and two had no improvement at the end of the treatment period. Severe accompanying symptoms became mild-moderate in 83% of patients in Group 1 and in 62% of patients in Group 2. Drug intake for acute attacks per month changed from 12.3 at baseline to 5.2 drugs in Group 1 and from 32 to 13 drugs in Group 2. Side effects were somnolence (6 patients - 5 patients), asthenia (4 and 3), postural instability (2 and 0) in Groups 1 and 2, respectively.
Conclusions This study confirms the role of levetiracetam as a potential preventive treatment for migraine.

COMBINED NEUROMUSCULAR RELAXING AND SHIATSU TREATMENT INTEGRATED WITH MELATONIN IN TENSION-TYPE HEADACHE

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Objective The aim of this study was to evaluate a combined neuromuscular relaxing and Shiatsu programme integrated with melatonin in the treatment of tension-type headache. We tried to consider a possible positive role of physical activity in reducing the frequency and intensity of headache attacks and, in particular, in decreasing activity limitations at a working, social and family level, and therefore, to evaluate the overall improvement in the patients' quality of life.
Patients and methods Before enrolment in the study, 20 middle-aged female subjects underwent psychodiagnostic evaluation with the following scales: MIDAS, MSQOL, MQoLQ, HIT, and MSQ. We utilised the MIDAS scale in this study because it is an objective measure of the severity of a headache attack; it specifies the level of inability and is suitable for identifying the appropriate therapy on the basis of the severity level of each patient. MIDAS scores for our patients were between 6 and 10, which indicated no need for pharmacological therapy, excluding headaches with mild (level 1) and severe inability (levels 3–4).
The study group, consisting of 10 females aged 35 – 60 years, underwent combined neuromuscular, relaxing and shiatsu treatment every week, integrated with melatonin retard formulation, 1 tablet per day, for the entire length of the study. For the combined treatment there was a successive prolongation phase: at first, every 15 days for an additional three months, then every month for a further three months. A control group of the same number of subjects did not carry out any treatment programme. At the end of nine months, both the study and control groups underwent another psychodiagnostic evaluation.
Results Comparison of the MIDAS scores between the first and last evaluations showed a decrease of six points in 10% of cases, five points in 20%, four points in 15%, two points in 25%, with no change in 30% of cases in the study group. No statistical difference was observed in the comparison of the same group of MIDAS scores in the control group, indicating a positive result only for the combined neuromuscular relaxing and Shiatsu programme integrated with melatonin.
Conclusions On the basis of our results, we can assert that in the study group, which underwent combined neuromuscular relaxing and Shiatsu treatment integrated with Melatonin retard formulation, the quality of life as evaluated by the MIDAS scale was improved significantly. This combination programme seems to have a positive role in reducing the frequency of headache attacks and in alleviating their severity.

EFFECTS OF DENTAL MALOCCLUSION CORRECTION ON PAIN FROM CHRONIC TENSION-TYPE HEADACHE

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Introduction Dental malocclusion is a very frequent finding in patients with chronic tension-type headache. The aim of this study was to investigate how malocclusion contributes to both the subjective (number and intensity of attacks) and objective (pain thresholds in muscles of the cervical and upper shoulder regions) painful symptomatology of this type of headache.
Methods Twenty-five patients (18 women and 7 men, aged 18–36 years) were studied. They had been suffering from chronic tension-type headache for at least 1 year prior to examination (diagnosis performed according to IHS criteria) and also presented dental malocclusion. Their headache pain was located in the occipital, parietotemporal and, in 11 cases, also fronto-orbital regions, bilaterally. In all of them pain thresholds to electrical stimulation were measured bilaterally in the trapezius, sternocleidomastoid and splenius muscles before and 30 days after application of the bite to correct dental malocclusion. Measurements were performed in the pain-free interval. Number and maximal intensity (VAS scale) of headache attacks were also recorded in the month of treatment and compared with those relative to the 30 days preceding treatment.
Results Before treatment, pain thresholds in all muscles were significantly lower when compared to thresholds recorded in corresponding sites of 20 non-headache sufferers ($p<0.001$) (hyperalgesia). In the month of application of the bite there was a significant reduction in the number of headache attacks ($p<0.003$) but not of their peak intensity; pain thresholds on day 30 were still lower than normal ($p<0.05$) but significantly increased with respect to pre-treatment values ($p<0.008$ for trapezius, $p<0.004$ for sternocleidomastoid, $p<0.007$ for splenius). A significant linear correlation was found between the decrease in headache pain and the increase in threshold ($p<0.01$).
Conclusions In patients with chronic tension-type headache, dental malocclusion contributes directly to the triggering of the painful attacks, probably through sensitization of muscles of the cervical/upper shoulder regions.

EFFICACY OF A WORKPLACE COGNITIVE AND PHYSICAL PROGRAMME ON PSYCHOSOMATIC SYMPTOMS IN A WORKING COMMUNITY WITH HEADACHE, NECK AND SHOULDER PAIN: A LONGITUDINAL CONTROLLED STUDY

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Objective Our purpose was to examine the effect of a workplace cognitive programme on psychosomatic symptoms in a working community.
Materials and methods Three hundred and eighty-four employees of the city of Turin, whose working activities involved public contact (registry and tax office), were divided into two groups: study group (n=192) and controls (n=192). In all subjects data regarding headache, neck and shoulder pain, if present, were collected in a standardized fashion. Each subject underwent a physical examination and muscle palpation of pericranial and cervical muscles. The presence of 28 symptoms, mainly psychosomatic in nature, (such as colitis, gastritis, swallowing difficul-

ties, digestive difficulties, phobias, sleep disorders, palpitations, dizziness, cramps, etc.) were also assessed. These items that belong to those generally investigated when taking a medical history showed in previous studies a significantly higher prevalence in pain patients in respect to a normal population. An instruction programme was then administered to the study group: it consisted of brief shoulder and neck exercises, a relaxation exercise and instructions on how to reduce hyperfunction of the craniofacial and cervical muscles during the day. After six months, all subjects were re-examined in the same way as at baseline and the presence of psychosomatic symptoms was assessed again. In the two groups, the difference between the data at baseline and those at the end was calculated and the data compared (Student's test).
Results In the study group, the mean amount of psychosomatic symptoms decreased significantly (p=0.002) from baseline (7.27±5.19 SD) to the end (5.73±4.77 SD). In the control group no significant difference was observed (baseline: 6.65±5.07 SD; end: 6.55±4.93 SD; p=0.78).
Discussion The data demonstrate that the administration of a simple cognitive instruction programme can significantly decrease psychosomatic symptoms in a working community. This finding, in contrast, may be the direct consequence of the cognitive programme, or may be partially due to the beneficial effects of such programme on the headache, neck and shoulder pain in the study population.
Conclusions A cognitive instruction programme can significantly reduce the presence of psychosomatic symptoms in extensive population samples.

EFFECTIVENESS OF AN INTEGRATED APPROACH IN THE PROPHYLACTIC TREATMENT OF CHRONIC TENSION-TYPE HEADACHE

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Introduction Retrospective study of patients from our clinics, suffering from chronic tension-type headache (CTTH), diagnosed in accordance with the criteria of the ICHD-II classification, code 2.3 (OMS G44.2).
Objective The purpose of this study was to demonstrate the effectiveness of an integrated pharmacological and non pharmacological approach compared with an approach that was exclusively pharmacological.
Materials and methods We selected 14 patients suffering from CTTH, 14 F, mean age 33 years (range 15–59)±14.1 years, who used an integrated prophylactic therapy, compared with 14 patients suffering from CTTC, 1 M and 13 F, mean age 33 years (range 13–50)±11.7 years, treated solely with medication. The study was carried out over a period lasting from 60 to 180 days. The patients using the integrated approach received daily medication in addition to a weekly session of relational systemic psychotherapy consisting of individual and familial meetings (7 patients) or osteopathic treatment consisting of craniosacral therapy and visceral manipulation (7 patients). The patients in the control group (14) underwent only daily pharmacological prophylactic treatment.
The clinical diary regarding the headache of each patient was reviewed to determine the number of crises per month and to monitor the percentage decrease of the crises.
Results The patient group following the pharmacological prophylaxis had only an average decrease of 64% in the number of headaches per month.
The patient group using the integrated approach with weekly psychotherapy had an average decrease of 88%, while the patients who underwent craniosacral/visceral manipulation treatment had an average decrease of 92%. Comparison of the two treatments indicated a statistically significant decrease (p<0.005).
Discussion and conclusions The integrated approach in patients with CTTH is more effective than the pharmacological approach alone, as it affects treatment motivation, therapeutic reliability, compliance and the consequent improvement of quality of life.

RATIONAL EMOTIVE BEHAVIOUR THERAPHY (REBT) IN TENSION HEADACHE

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Introduction During the last few years, many studies have demonstrated how an emotional condition can influence pain. This aspect is especially evident for headache, in which the connection between emotionality, pain, intensity and frequency is very important. In the Centre for Pathophysiology and Pain Therapy of the Catholic University Medical School of Rome, we studied a Rational Emotive Behaviour Therapy (REBT) that underscores the importance of patients' cognitive processes in the genesis and feeding of emotive and behavioural disturbances.
Materials and methods From September 2004 to April 2006, after informed consent, we studied 60 patients (35 females and 25 males, mean age 35 years). Their tension headaches (ICHD-II criteria, 2004) were bilateral with occipital localization, without aura, vomiting, photophobia and phonophobia; they had eight crises per month and visual analogue scale (VAS) score=7.
Their clinical history, objective and neurological examinations excluded a secondary headache. We had an indepth conversation with each patient, and we noticed that everyone was depressed or anxious or hostile; we gave them some forms to fill out and a headache diary to complete before and after the start of therapy. They were divided into two randomised groups of 30 patients. The first group was treated with cognitive, emotional and behavioural techniques; the second group was treated with pharmacological therapy with amitriptyline 30 mg/day, alprazolam 0.25 mg/day and celecoxib 200 mg, if needed. They were treated for 6 months.
Results In the first group, treated with cognitive psychotherapy, VAS decreased from 7 to 3, the crises decreased from 8 to 2, and the emotional condition improved with a reduction of depression, anxiety and hostility. In the second group, treated with pharmacological therapy, VAS decreased from 7 to 2, and the crises decreased from 8 to 3.
Conclusions From our results we observed that patients treated with cognitive psychotherapy showed improvement in VAS scores and their emotional condition, and reduction in the number of montly crises, while patients treated with pharmacological therapy also had improved VAS scores and reduction in the number of crises, but with no modifications of their emotional condition.

GYMNASTIC-PHYSICAL ACTIVITY: PERFECT SHAPE FUNCTION IN MIGRAINE AND CLUSTER HEADACHE

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Objective The aim of this study was to evaluate the effects of a programme of gymnastic-physical activity (Perfect Shape System) on the quality of life in a group of subjects suffering from migraine and cluster headache. We tried to consider a possible positive role of physical activity in reducing the frequency and intensity of headache attacks and, in particular, in decreasing inability at a working, social and family level, and therefore, improving overall the patients' quality of life.
Patients and methods Before enrolment in the study, forty subjects suffering from primary headaches (30 with migraine and 10 with cluster headache) underwent clinical evaluation with the following scales: MIDAS, MSQOL, MQoLQ, HIT, and MSQ. We utilised the MIDAS scale in this study since it is an instrument which objectively measures the severity of a headache attack; it specifies the inability level and is suitable for identifying the appropriate therapy on the basis of the

severity level of each patient. MIDAS scores for our patient group were between 6 and 10, which indicated no need for pharmacological antimigraine therapy, excluding headaches causing mild (level 1) and severe inability (levels 3–4).
The study group consisted of 20 females aged 35–60 years, who underwent gymnastic-physical activity through the methodical Perfect Shape System, which lasted two months, followed by further activities for an additional six months. A control group of equal number of subjects did not carry out any gymnastic-physical programme at all. At the end of eight months, all 40 patients of both the study and control groups, underwent another clinical evaluation.
Results Comparison of the MIDAS scores between the first and last evaluations showed a decrease of seven points in 5% of cases, six points in 5%, five points in 15%, three points in 10%, one point in 20%, with no change in 45% of cases for the subjects who practised Perfect Shape. No statistical difference was observed in the comparison of the same group of MIDAS scores in the control group, indicating a positive result only for the patients who followed the Perfect Shape programme.
Conclusions On the basis of our results, we can assert that in the study group, which followed the Perfect Shape System, the quality of life as evaluated by the MIDAS scale improved, although in a different way, with reduction in negative social, working and family effects. This is in marked contrast to the control group, who showed no improvement in quality of life parameters. Gymnastic-physical activity and, in particular, the Perfect Shape programme, seem to contribute in a positive way to reducing the frequency of headache attacks and to alleviating their severity. However, there were no relevant changes in terms of quality of life parameters between the different forms of primary headaches.

USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE BY PATIENTS WITH CLUSTER HEADACHE: RESULTS OF A MULTI-CENTRE HEADACHE CLINIC SURVEY

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The use of complementary and alternative medicine (CAM) in cluster headache (CH) is a phenomenon about which little is known. This study was undertaken to evaluate the rates, pattern, satisfaction and presence of predictors of CAM use in a clinical population of patients with CH. One hundred CH patients attending three headache clinics were asked to undergo a physician-administered structured interview designed to gather information on CAM use.
Past use of CAM therapies was reported by 29% of the patients surveyed, with 10% having used CAM in the previous year. Only 8% of the therapies used were perceived as effective, while a partial effectiveness was reported in 28% of CAM treatments. The most common source of recommendation of CAM was a friend or relative (54%). Approximately 62% of CAM users had not informed their medical doctors of their CAM use. The most common reason for deciding to try a CAM therapy was that it offered a "potential improvement of headache" (44.8%). Univariate analysis showed that CAM users had a higher income, had a higher lifetime number of conventional medical doctor visits, had consulted more headache specialists, had a higher number of CH attacks per year with disease and had a significantly higher proportion of chronic CH *vs* episodic CH. A binary logistic regression analysis was performed and two variables remained as significant predictors of CAM use, the income level (OR=5.7, 95% CI=1.6–9.1, p=0.01), and the number of attacks per year with disease (OR=3.08, 95% CI=1.64–6.7, p<0.0001).
Our findings suggest that CH patients, in their need of and quest for care, seek and explore both conventional and CAM approaches, even if only a very small minority finds them satisfactory. Conventional MDs and CAM practitioners should be made aware of this redefinition of the role of modern biomedicine, given that they are in a unique position to provide patients with help and guidance.

STANDARDIZED APPROACH TO PATIENTS WITH MIGRAINE IN A HEART-BRAIN CENTRE: 6-MONTH EXPERIENCE

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Background Because a pathogenic relationship between patent foramen ovale (PFO) and migraine with aura is assumed, percutaneous closure of PFO has been recently proposed as an effective treatment. However, definitive criteria to identify *a priori* migraine patients who will benefit from PFO closure and those whose migraine will not be influenced by this treatment are lacking. We propose the standardized approach to these patients in use at the Heart-Brain Centre of the Clinica St Rocco of Ome, Brescia.
Methods During a 6-month period, 120 patients with migraine with aura, 48 patients with migraine without aura, and 18 patients with cluster headache were evaluated. All subjects underwent a contrast-enhanced transcranial Doppler (TCD) investigation to detect the presence/absence of PFO. This was diagnosed in 62.5% of cases with aura, 37.5% of those without aura, and 38.8% of cluster headache. In the case of a positive finding, a standardized work-up including brain MRI, thrombophilic tests (proteins C and S, antithrombin III, APCR, antiphospholipid antibodies, total plasma homocysteine, vitamin B12 and folate levels, G1691A polymorphism of factor V, G20210A polymorphism of factor II, C677T polymorphism of MTHFR), ultrasound evaluation of the deep veins of the legs and the carotid-vertebral arteries was carried out. Transesophageal echocardiography was performed in cases of PFO-positivity with curtain effect, MRI evidence of ischemic lesions (MRI+), or evidence of a prothrombotic state (T+). This allowed the identification of co-existent atrial septal aneurysm (ASA).
Discussion and conlusions Based on these findings, PFO closure can be considered in cases with co-existent ASA when at least one of the following conditions is present: curtain pattern on TCD, MRI+, or T+. It can also be considered in those cases without co-existent ASA in which MRI+ or T+ are present.
Although the management of PFO in patients with migraine is still a matter of debate, the proposed standardized approach can be of help in selecting patients who will benefit from percutaneous closure in clinical practice.

EPIDURAL BLOOD PATCH IN THE TRENDELENBURG POSITION TO TREAT HEADACHE BY SPONTANEOUS CSF LEAK

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Background Spontaneous intracranial hypotension (SIH) generally results from spontaneous spinal CSF leakage [1]. Treatment is usually conservative but epidural blood patch (EBP) has emerged as the most important nonsurgical treatment for SCSFL [2].
Objective To evaluate the efficacy of epidural blood patch (EBP) in the Trendelenburg position in the treatment of headache by spontaneous CSF leakage (SCSFL).
Materials and methods We observed 30 patients with SCSFL between 1992 and 2005. Eleven patients (6 women and 5 men; age range 31–66 years, mean age 40) received EBP. All patches were performed in the lumbar region, using 15 to 30 mL (mean 23 mL) of autol-

ogous blood. All patients mantained a 30° Trendelenburg position during the procedure and for 24 hours after the procedure. Follow-up ranged from 6 months to 2 years.
Results All patients had orthostatic headaches. Other manifestations were nausea, vomiting, mild neck stiffness, tinnitus, blurred vision, diplopia and bilateral upper limb numbness. CT myelography, spinal MRI or brain MRI or radionuclide cisternography showed CSF leakage sites in 6 out of 11 patients; 2 sites were at the cervical level, the others at the lumbar level. In 10 out of 11 patients, brain MRI showed diffuse pachymeningeal gadolinium enhancement (neuroimaging of intracranial hypotension). All patients failed an initial conservative treatment, which consisted of bed rest and hydration, over a period of 1 to 13 months. All treated patients became asymptomatic, 1 responded only after 3 EBP, and 1 had a residual mild headache during the Valsalva manoeuvre for 2 months. Until now, none has had a relapse.
Discussion and conclusions Our data confirm the efficacy of EBP in the SCSFL headache and suggest also the importance of a prolonged Trendelenburg position especially when the leak site is at the cervical level and the autologous blood patch in the lumbar region is performed.
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HEADACHE IN CHILDHOOD AND ADOLESCENCE I

CLIMATIC VARIATIONS AND MIGRAINE IN CHILDHOOD

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The incidence of migraine in childhood has increased in recent years. Up to now that increase has been attributed to the worsening of childern's conditions: the job of both parents, the long distance to school, the high number of separations, divorces etc. [1, 2].
Regardless, the environmental situation, unexpected climatic variations, and elevated levels of pollutants, may also have had a specific influence on migraine.
We tried to estimate the influence of these factors in a group of 120 children (72 F, 48 M, age range 5–17 years) affected by migraine without aura (n=112) and migraine with aura (n=8), assessed from 1995 to 2005. For these patients the headache triggers were evaluated (Table 1).
No significant variations were found in the percentage of stress as a trigger factor, whereas the number and percentages of patients referring atmospheric variations and solar exposure as a triggering factor increased over time.

Table 1 Trigger Factors

	1995	1997	1999	2001	2003	2005	Total
Emotional stress, %	90	90	80	90	100	70	83
Physical stress, %	50	30	30	40	60	30	40
Environment stress, %	70	80	90	50	90	60	73
Lights, %	50	40	60	30	70	40	48
Smell, %	40	20	40	60	30	40	33
Smoke, %	20	40	20	40	10	20	25
Food, %	20	20	20	10	00	10	15
Climatic Variations, %	40	50	60	60	70	80	60
Solar exposure, %	10	20	40	60	90	70	48

These preliminary data need to be confirmed by further studies. Among triggers examined, solar exposure as a controllable trigger should be avoided or limited to reduce its influence in inducing migraine attacks.
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TENSION-TYPE HEADACHE IN CHILDREN

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Introduction Tension-type headache is a common problem among children in primary school. Dental malocclusion can often be the cause of this form of primary headache [1].
Materials and methods Twenty schoolchildren who had already received a diagnosis of primary headache treated with analgesic substances came to our clinic. An orthodontic evaluation and orthopanoramic X-ray film were performed. All patients were found suffering from malocclusion. Limitation of the functional mandible's movements, teeth abrasions, and hypertrophy of the mandibular elevator muscles were present. To treat muscular problems originating from the stomatognathic system, an occlusal splint was performed. Intensity [using a graphic rating scale (GRS)] and frequency (daily, weekly, monthly) of headache before treatment (T0), after one month (T1), after three months (T2) and after six months (T3) were recorded. Wilcoxon test was applied for statistical evaluation.
Results All patients showed a considerable reduction of their symptoms. A significant improvement of the intensity and the frequency of headache attacks was registered after treatment (p<0.0001).
Discussion and conclusions The high occurrence of malocclusion in the subjects with tension-type headache seems to play an important role in the genesis of headache. At present, the treatment for patients who suffer from these disorders has increasingly required the need for a collaborative team approach. An orthodontic treatment should be suggested, both for an improvement of the headache and the functional aspects, but the results may not be significant before 2 years [2]. An application of a plate bite, without any drug therapy, can be the treatment of choice to reduce the symptomatology in children suffering from tension-type headaches.
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HEADACHE AND QUALITY OF LIFE IN A CHILD AND ADOLESCENT COHORT

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Introduction Up to 10% of children between the ages of 5 and 15 have migraines [1], while an even higher number of adolescents have migraines [2].
The primary aim of this study was to evaluate the quality of life in young patients, using the PED-MIDAS, the QLH-Y Questionnaire and

Children's Depression Inventory (CDI) scales. A secondary end-point was to examine the changes in clinical picture and diagnoses related to headache treatment.
Methods and patients The study included 70 patients (32 F, 38M; age range: 8–15 years, mean age 12.34±1.91 years) visited in the Modena Headache Centre between January 2002 and June 2004. At the initial visit, each patient underwent complete history-taking and general and neurological examinations in the presence of a parent. A second follow-up visit was performed in the period January-June 2005; headaches were diagnosed according to the International Headache Society criteria (ICHD-II).
Questionnaire At the follow-up visit, the patients were asked to check MIDAS, QLH-Y and CDI Questionnaires in the presence of a trained doctor. They were urged to express their own judgements, but they could ask a parent for advice.
Results All 70 patients completed the study. Mean illness duration was 44.31 months. Forty-two patients had migraine without aura, 10 had migraine with aura, 18 had tension-type headache (16 with episodic tension-type headache (ETTH) and 2 with chronic tension-type headache (CTTH)). Sixty-eight out of 70 patients confirmed the first diagnosis. The frequency of headache was related to the degree of disability, while the intensity was moderate-severe in almost all patients in spite of disability scores.
Pathological values found in Children's Depression Inventory (CDI) at the follow-up visit showed that almost 50% of patients had a bad perception of themselves with devaluation and often with feelings of desperation, and thus referred disobedience, asthenia and a negative body image. According to the QLH-Y data, our patients seemed to experience stress, fatigue and somatic symptoms. The most used drug for headache attack was acetaminophen.
Discussion The results of this study suggest that the prevalence of migraine without aura and ETTH decreases with increasing age. Optimal care for children and adolescents with headache can be realized with collaboration among primary care practitioners and headache specialists; behavioural treatment is a foundation for provision of such care.
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HEADACHE AND EPILEPSY IN CHILDREN

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Introduction The association between headaches and epileptic seizures is a well-known phenomenon. The headache could be peri-ictal and interictal, in 50% of epileptic patients [1]. The incidence of interictal headache is not clear, but many authors have shown that the incidence of interictal migraine headache was significantly higher in patients with migraine-like postictal headache [2].
Materials and methods Forty-three children aged 4–18 years, 22 males and 21 females, affected by epilepsy and suffering from headache, were studied in order to verify the correlation between peri-ictal and interictal headache. Headache was diagnosed according to ICHD-II criteria, and epilepsy according to ILAE 1989 criteria.
Epilepsy was diagnosed as: Benign focal epilepsy with vertex spikes and waves (BVSWE) in 9 children; reflex photosensitive epilepsy in 11 children, occipital epilepsy in 5 children, juvenile myoclonic epilepsy in 4 children, and generalized epilepsy in 12 children.
The headache diagnosis was: migraine without aura (MO) in 18 children, migraine with aura (MA) in 4 children, tension-type headache (TTH) in 4 children, migraine-like and tension-type like headache in 6 children, and stabbing headache in 5 children.
Results In 20 children, the headache started before epilepsy began and in 5 children after epilepsy began. In 26 children, the diseases were contemporary. There was no correlation between the region of EEG anomalies and the side of pain. Only 3 children, suffering from BVSWE, and 5, suffering from generalized epilepsy, showed headache in the vertex region.
In 11 children (25%), there was a temporal relationship between headache and epilepsy. In 4 patients with seizures while sleeping, the headache occurred upon awakening, in 3 children with occipital epilepsy the headache was postictal, and in 4 children with photosensitive epilepsy the headache was preictal and was triggered by photic stimuli (TV, play station).
The preictal headache was defined by children as stabbing, the postictal headache as migraine-like.
Conclusions Migrainous-like headache is prevalent among epileptic children during the peri-ictal and interictal periods. In fact, migraine-like headache was found in 50% of patients with photosensitive epilepsy and migraine in 100% of children with rolandic epilepsy.
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PREVALENCE OF MIGRAINE IN FAMILIES OF CHILDREN WITH PANAYIOTOPOULOS SYNDROME

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Introduction Early-onset benign occipital seizure susceptibility syndrome or the "Panayiotopoulos type" of childhood epilepsy with occipital paroxysms (PS) is a partial form of epilepsy that occurs in 13% of children aged 3–6 years with one or more non-febrile seizures [1]. Although many authors have studied the relationship between headache and PS, there do not seem to be any clear results [1].
Aim The aim of our study was to determine the relationship between migraine and PS in childhood and the prevalence of family history of migraine and epilepsy in patients with PS.
Patients and methods This was a retrospective study conducted at the Child and Adolescent Neuropsychiatry Unit of our University Hospital, in patients recruited between 1999 and 2006, diagnosed as PS on the basis of the ILAE Task Force on Classification and Terminology criteria. Anamnestic, clinical, and instrumental data were collected to clear the semiology and the frequency of the seizures. All patients underwent a video-EEG during wake and sleep cycles with HP and ILS, and a brain MRI. All patients were given the specific record for headache in children and adolescent patients of the Italian Child and Adolescent Neuropsychiatry Society Group. The diagnosis of migraine was based on the criteria of The International Classification of Headache Disorders, 2nd edition (ICHD-II).
Migraine prevalence in children with PS and in their families was compared with a member of the general population of the same age group.
Results We evaluated 20 patients with PS, 11 males and 9 females, mean age at the end of follow-up=8.5 years, range 4 to 14 years. Among these, 7/20 (35%) had migraine (six migraine without aura and one with visual aura). Regarding family history: 13/20 cases (65%) were positive for migraine, 5/20 (25%) for epilepsy, 4/20 (20%) for both, and 4/20 for febrile seizures.
All children with migraine also had a family history of migraine. The headache usually started in the same year in 2/7 cases (29%) or after the diagnosis of epilepsy in 5/7 (71%).
Conclusions So far, no study has showed a clear relationship between a family history of migraine and PS. In particular, Panayiotopoulos says "there is no family history of similar disorders of benign childhood seizure susceptibility, epilepsies or migraine" in children with PS [2].

To our knowledge, this is the first retrospective study to report a prevalence of 65% for migraine, 25% for epilepsy, and 20% for both in family members of affected children. PS and migraine are probably genetically determined. Our study supports the hypothesis of a clinical continuum between migraine and epilepsy, particularly PS that share similar characteristics and a familial spectrum.

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HEADACHE AND CARDIO-EMBOLIC STROKE: THE IMPORTANCE OF CLINICAL SUSPICION. REPORT OF A PAEDIATRIC CASE

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A 14-year-old boy, with an underlying history of asymptomatic *ostium secundum* atrial septal defect and a family history negative for vascular diseases or coagulation disorders, was admitted to the emergency department of a general hospital because of a severe headache and visual disturbance that began during a school examination. As brain CT scan and fundoscopic examination were normal, he was dismissed with the diagnosis of migraine with aura and symptomatic therapy. Twelve hours later for the persistence of the same complaints, he was newly admitted: physical examination showed right homonymous hemianopsia and a systolic ejection murmur, but no other abnormalities. EEG showed bioelectric abnormalities on the left temporal and occipital regions and magnetic resonance imaging revealed acute left occipital infarction and normal head and neck vessels. He was then transferred to our tertiary care paediatric hospital; in the following days his clinical conditions were stable. An expanded investigation for an underlying prothrombotic tendency showed increased plasma homocysteine (29 micromol/L) and homozygosity for the methylenetetrahydrofolate reductase gene C677C>T polymorphism. Anticoagulant therapy, folic acid and vitamin B12 supplementation was given and the 6-month follow-up was uneventful: right temporal hemianopsia persisted. Atrial septal defect was subsequently closed via percutaneous approach.

Arterial ischemic stroke is being increasingly diagnosed and recognized in childhood. Recognition of clinical stroke may be difficult, particularly in infants and young children. Ischemic events are usually suspected when a child presents with abrupt onset of a hemiparesis but the initial symptom can be a common complaint, such as isolated headache and/or subtle and difficult to recognize focal sensory deficits or visual disturbances.

A detailed history focused on the most frequent risk factors, such as congenital thrombophilic states, cardiac diseases, infections, trauma and sickle cell anemia, represents the initial screening for the diagnosis of paediatric stroke since multiple risk factors commonly coexist in individual patients [1]. As demonstrated by our case report, magnetic resonance is the imaging modality of choice to confirm that an acute ischemic event has occurred and to determine the extent and location of acute cerebral injury, the patency of major neck and intracranial arteries and relative cerebral perfusion.

It is crucial to increase clinician awareness of stroke also in children as clinical suspicion can reduce the time lag to diagnosis and to appropriate treatment of this disease [2].

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HEADACHE IN ADOLESCENTS: SYMBOLIC MEANING BETWEEN CLINICAL DATA AND INNER PSYCHIC LIFE

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Introduction Primary headaches can present occasional and nonspecific anatomical and/or functional anomalies, but although they do not have an aetiological and pathophysiological role in producing painful attacks, they can influence the symptomatic course through the symbolic meaning that they have for the patients and their family. We present and analyse three cases of adolescents with these characteristics.

Case 1: A twelve-year-old boy with a story of migraine-type attacks occurring every weekend for the last three months; brain MRI showed a pineal cyst and for this reason he underwent neurosurgical consultation and another MRI with gadolinium; during the clinical evaluation, migraine appeared the day before every examination and afterward, he was migraine-free for long periods.

Case 2: An eleven-year-old boy suffering from tension-type headache and depressive symptoms: his father was operated on for cerebral aneurysm, the boy's EEG showed positive occipital sharp waves, evoked by all IPS frequencies; undergoing MRI, which was normal, and clinical interviews regarding the family's fears, in the last two years, the boy nolonger suffered from headache.

Case 3: A fourteen-year-old girl presented with very frequent and severe migraine-type attacks for about two months; she had been wearing an orthodontic appliance for over two years. The decision to remove the orthodontic appliance resulted in the disappearance of the headache.

Discussion The nonspecific anomalies, considered as symbols, found in these three clinical cases are "dumb elements" [1], but they represent an important meaning in the patients' inner psychic life and may induce the manifestation of some developmental emotional problems. In the first case, pineal cyst may represent a need of dependence in the relationship between the patient and his busy family and help him to receive attention and be listened to. In the second case, the abnormal EEG and the father's history of cerebral aneurysm produced in the boy an identity problem with a father who was always absent. The clinical and psychological therapy and normal brain MRI examination disintegrated the "symbol" with the disappearance of the headache. In the third case, the relationship with a very perfectionist mother resulted in the onset of migraine-type attacks. The removal of the orthodontic appliance allowed the patient to become independent without being forced to accept a self-image that the mother imposed.

Conclusions The three cases, with their different data and life events, confirm that nonspecific signs need attention, because their symbolic meaning may be significant and influence the course of pain.

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PRESENT AND PAST PSYCHOPATHOLOGY IN CHILDHOOD MIGRAINE: A STUDY WITH THE CHILD BEHAVIOUR CHECKLIST

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Introduction A strong association has been observed between migraine and psychiatric problems such as depression and anxiety.
Objective The aim of this study was to describe the premorbid state of migraine in children by using a structured questionnaire, designed to obtain standardized reports of children's behavioural problems and capabilities, as observed by parents.
Subjects and methods Thirty subjects with migraine and 30 healthy subjects were enrolled in a case-control study. Using the Child Behaviour CheckList (CBCL), ratings were obtained for maternal memories of the past for two age periods (0–3 years and 4–6 years) and for the present state (7–16 years). The CBCL scores of the migraine group (MG) were compared to those of the control group (CG) for the three periods. A longitudinal analysis was performed to evaluate the evolution of psychopathology, by comparing the CBCL scores of the MG in the three age periods.
Results In the 7–16 year group, children of the MG had significantly higher mean CBCL scores – i.e., nearer to the clinical threshold – than those of the CG in several scales: total problems ($p<0.01$), internalizing ($p<0.001$), somatic ($p<0.001$), anxious/depressive ($p<0.01$), thoughts ($p<0.05$) and attention problems ($p<0.01$). At 4–6 years, significantly higher scores between the MG and the CG were found in the total problems scale ($p<0.001$), internalizing ($p<0.001$), somatic ($p<0.001$), anxious/depressive ($p<0.001$), attention ($p<0.01$), social problems ($p<0.01$) and withdrawn ($p<0.05$). At 0–3 years, significantly higher scores between the MG and the CG were found in the total problems scale ($p<0.01$), internalizing ($p<0.05$), somatic ($p<0.001$), and anxious/depressive ($p<0.01$). In a longitudinal perspective we did not demonstrate statistically significant differences between 7–16 and 4–6 year age periods. Comparing the age periods of 4–6 years and 0–3 years, significant differences were found in total problems ($p<0.01$), internalizing ($p<0.001$), somatic ($p<0.01$) and also in externalizing ($p<0.01$) and aggressive syndrome scale ($p<0.01$), but not in the anxious/depressive scale.
Discussion Our study suggests the association between migraine, depression and anxiety during childhood and adolescence. The internalizing component (depression and anxiety) may represent a persistent factor that feeds the migraine. The demonstration of an internalizing score in a headache patient, by means of the CBCL, could be of the utmost importance to prevent migraine from becoming chronic.
Conclusions Migraine may begin during childhood/adolescence with a symptomatology, which may have its roots in previous behavioural problems. Even if they rarely reach the clinical threshold with the CBCL questionnaire, children who develop migraine are different from healthy children for the higher rate of behavioural problems. Migraine could be considered the expression of a previous vulnerability.

HEADACHE: WHAT DO CHILD AND MOTHER WANT FROM THEIR PHYSICIAN?

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Introduction To establish a good "strategic compliance" between the doctor, and the young headache patient and the patient's family, it is important to know what the mothers or the children want from paediatricians and neurologists.
Objective The aim of this study was focused on child's and mother's expectations regarding the diagnostic and therapeutic approaches from the paediatrician and neuropsychiatrist. Moreover, we wanted to know the doctors' opinions.
Methods We selected 100 consecutive children older than 10 years with primary headaches, admitted for the first time to our department. A questionnaire was administered individually to the children and to all 100 mothers before the visit. It had several multiple choice questions about the child's and mother's fears, their expectations and opinions regarding medical visits, and symptomatic and prophylactic therapy. A short questionnaire was also administered to 50 paediatricians, having common characteristics previously selected with a questionnaire.
Results The principal reasons for seeking consultation were because the pain was more frequent and severe (72% and 24%, respectively). The mothers' main questions concerned the reasons for headache and reassurance about their fears (respectively 61% and 46%). Fifty-six percent of the mothers thought that the use of symptomatic drugs was necessary, while only 33% thought that preventive drugs were useful and 34% of mothers feared that they cause dependency or serious side effects. The children wanted to be mainly reassured (60%), know the reasons for the headache (45%), and if they would suffer from headaches in adulthood (36%) (mothers and doctors only 4%). The children thought that the use of symptomatic drugs was necessary (68%) and that preventive therapy was useful (61%). Fifty-eight percent of doctors believed that the principal reasons for the consultation were the frequency (58%) and intensity (26%) of headache, and the fear of tumour (24%). In the opinion of the doctors, the more important mothers' questions concerned reassurance about their fears and the prescription of medical diagnostic tests (60% and 50%, respectively). They believed that the children wanted to be mainly reassured, cured and to have explanations about the headache (62%, 38% and 44%, respectively). The paediatricians (90%) believed that symptomatic drugs were necessary and that preventive therapies were useful (74%).
Discussion These data suggest that the child's and mother's main concerns pertain to explanation of headache and reassurance about it, while the prescriptions of drugs or medical tests are not believed necessary. The doctors' opinions seem in part similar. The main differences regarded the use of diagnostic tests and pharmacological therapies and the question about headache progression into adulthood made by children.

HEADACHE IN CHILDHOOD AND ADOLESCENCE II

DEPRESSION AND CHRONIC HEADACHE IN CHILDHOOD AND ADOLESCENCE

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Introduction The role and importance of the psychiatric and psychological aspects in determining and influencing the insurgence and evolution of chronic headache in childhood and adolescence have been the object of numerous studies. Many authors have tried to analyse the possible correlations between depression, anxiety disorders and headache.
Objective The aim of our study was to analyse the possible correlations between chronic headache and depressive disorder with or without anxiety disorder.
Materials and methods Sixty-two children (38 males, 24 female; mean age 9 years, 5 months; range: 6–13 years) were enrolled from 493 subjects seen from 2003 to 2005 among the outpatients from the Departments of Headache and Psychology of the "Ospedali Riuniti "G. Salesi" Children's Hospital. Fifty-two patients affected with chronic headache were subdivided into 3 subgroups: chronic tension-type headache (CTTH), chronic daily headache (CDH) and mixed headache (CTTH and headache); 10 patients affected from episodic tension-type headache (ETTH) were identified according to IHCD-II 2004 criteria. The patients under investigation were evaluated by the juvenile headache flow-chart (haematological, clinicians, neurophysiologic and neuroimaging exams) and by a psychodiagnostic protocol that we use in our centre.
Results Following the DSM IV criteria the subjects of the two groups

were subdivided in:
- Depressive Disorder Mood (DDM);
- Depressive Disorder Mood + generalized anxiety disorder (DDM+GAD);
- Depressive Disorder Mood + Learning Disorder Not Otherwise Specified (DDM+LDNOS);
- Depressive Disorder Mood + Oppositional Defiant Disorder (DDM+ODD);
- Generalized Anxiety Disorder (GAD);
- Others.

The clinical history of the 62 subjects was negative for psychiatric pathologies or history of acute traumatic events. Depressive disorders were comorbid in 37/52 of the subjects with chronic headache, primarily represented by DDM + GAD (30/52). The GAD subgroup was present in 13/52 chronic headache patients and in 3/10 ETTH patients. Male gender was more represented, but female gender prevailed in the group of chronic headache with DDM + GAD. Chronic headache was not associated with DDM + ODD but was present in 2 patients affected by ETTH. The prevalence of depressive disorders was greater in chronic headache (71.1%) than in ETTH (40%). DDM was more frequently associated with GAD (57.6%).

Conclusions Chronic headache is frequently associated with depressive and anxiety disorders both in adult and paediatric patients. Headache can be the first symptom silently expressed by the depressed child.

Therefore, headache that evolves to acquire chronic characteristics must be carefully evaluated because it could mask important psychiatric disorders that should be considered for the diagnosis and therapy.

PSYCHOLOGICAL ASSESSMENT OF MIGRAINOUS CHILDREN AND ADOLESCENTS

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Introduction General population studies suggest a non-casual association between headache, major depression and anxiety disorders [1]. The consensus is that migraine sufferers are at higher risk of depression, bipolar disorders and certain forms of anxiety – this is particularly true for migraine with aura. Co-morbidity with psychiatric disorders has also been described for chronic tension-type headache and for chronic daily headache [2]. The data available in the literature are still relatively scarce and contradictory, especially for young people.

Objective The aim of our study was to evaluate the association between headache and different psychological characteristics, including tendencies toward depression, perfectionism and repressed aggression, in children and adolescents.

Methods Clinically referred children and adolescents (n=45) 8–18 years of age, subdivided into two age groups: 8–10 years (n=19) and 11–18 years (n=26), suffering from primary headache according to the diagnostic criteria of the International Headache Society, 16 with migraine with aura (MA), 29 with migraine without aura (MO), and 1 021 normal controls without headache (NC), were assessed using the Parent Child Behaviour Checklist (CBCL), the Youth Self Report (YSR), Children's Depression Inventory (CDI), and the Centre for Epidemiological Studies Depression Scales (CESD).

Results According to the literature, our data confirm that children with migraine have significantly higher levels of total internalizing, particularly for somatic complaints with respect to those without headache. Attention has been focused on the YSR interview, a self-report assessment, never used until now in this field, that was administered to adolescents aged 11–18 years. Both thought problems and internalizing symptoms in migraineurs have been demonstrated by YSR. We wish to emphasize that thought problems are not significantly different between the general paediatric population and migraineurs in some studies in parental reports (CBCL). Moreover, CDI (self rating of depression) results show statistically significant differences between migraine and non-headache paediatric subjects, in comparison with other studies published in the literature.

Conclusions We stress the importance of the use of YSR for the assessment of psychological traits in migrainous children and adolescents, because generally parents have been found to be poorer at internalizing symptoms than the child, and parents' reports of CBCL may underestimate anxiety symptoms. This holds not only for the diagnostic and therapeutic implications but also for the prognostic aspects.

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EFFICACY OF TOPIRAMATE IN PAEDIATRIC MIGRAINE PROPHYLAXIS

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Introduction Migraine is the most common type of primary headache in childhood and often hampers common daily routines.

Objective The aim of our study was to investigate the efficacy and safety of topiramate in the prevention of paediatric migraine.

Materials and methods Twenty-five children (mean age 11 years, range 5–16 years; 10 females, 15 males) were recruited. In 23 children, migraine without aura was diagnosed according to the International Headache Society classification (ICHD-II, 2004), while the remaining 2 children had migraine with aura.

Results Before treatment, our patients showed 8±5.7 (mean±standard deviation) pain attacks per month. The children received a mean topiramate dose of 1.3 mg/kg/day, ranging from 0.5 to 1.8 mg/kg/day, for a period of 3.2±1.2 months. Treatment was effective (reduction in attack number ≥ 50%) in 19 out of 25 children (76%). In particular, 3 patients (12%) became free from migraine episodes. One patient (4%) interrupted the treatment for adverse side effects (excessive drowsiness). Seven patients in which the initial treatment was effective underwent a worsening in migraine frequency after topiramate interruption and needed a further treatment after 4.3±2.8 months. Six patients had a reduction in the frequency of pain episodes greater than 75%, while in one child the therapy was ineffective. Two patients had a third treatment at 3 and 4 months, respectively, after interrupting the second topiramate cycle. The therapy was ineffective in both patients. Adverse events were observed in 6 out of 25 children (24%). They consisted of drowsiness (3 patients), anxiety (1 patient), weight loss (2 patients), and behavioural disturbances (3 patients).

Discussion and conclusions Our results suggest that topiramate is a useful and safe tool in paediatric migraine prophylaxis. Even low doses allowed us to control migraine in most of our paediatric patients, thus improving their quality of life.

MELATONIN, 3 MG, IS EFFECTIVE FOR MIGRAINE PREVENTION ALSO IN SCHOOL-AGED PATIENTS

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Background Hypothalamic dysfunction may be present in migraine

and in circadian periodicity of headache attacks, more specifically, the suprachiasmatic nucleus and melatonin have been suggested to play a role in the pathogenesis [1]. Altered melatonin levels have been found in cluster headache, migraine with and without aura, menstrual migraine, and chronic migraine. Melatonin may have many metabolic effects, such as anti-inflammatory effects (melatonin and indomethacin share similar chemical structure), reducing the up-regulation of proinflammatory cytokines, and inhibiting nitric oxide synthase activity and dopamine release. Melatonin administration is thus a possible candidate for migraine prevention [2].

Objective The aim of this open trial was to test the hypothesis of the potential effectiveness of melatonin for migraine prophylaxis also in school-aged children.

Patients and methods We performed an open-label trial of melatonin, 3 mg, for migraine prevention. Twenty-three patients (11 M, 12 F) aged 6–15 years (mean 12.8 years, SD±1.38) with episodic migraine with or without aura according to ICHD-II 2004 criteria, were screened for the baseline period. All patients started prophylactic treatment with melatonin, 3 mg, 10 minutes before bedtime for 3 months. A complete clinical interview and examination as well neurophysiological recordings (wake and sleep EEG) were performed for each patient. Study participants experienced between two and six attacks per month. Exclusion criteria included the presence of sleep disorders, as confirmed by the mothers of all subjects who filled out the Sleep Disturbances Scale for Children [SDSC]. The SDSC is a sleep questionnaire that consists of 26 items subdivided into 6 sleep disorder subscales according to American Sleep Disorders Association criteria: DIMS (disorders in initiating and maintaining sleep), SDB (sleep disordered breathing), DA (disorders of arousal), SWTD (sleep-wake transition disorders), DES (disorders of excessive somnolence), SHY (sleep hyperhydrosis).

Results Twenty out of 23 patients completed the study (86.95%). That patients (85%, 17/20) who completed the study had at least a 50% reduction in intensity and frequency of headache attacks. Nobody reported an increase in headache frequency. Complete (100%) response was achieved in 12 patients (60%) and no adverse effects were recorded.

Conclusions There is increasing evidence to indicate that the hypothalamus plays a major role in the pathophysiology of several of the primary headache disorders, such as migraine, and hypnic headache [1, 2]. Melatonin, an indole compound derived from serotonin, was reported safe and effective in adult patients [2], but no data were available for school-aged children. This is an original study to assess melatonin, 3 mg, for prophylactic treatment of headache also in childhood.

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EMERGENCY IN CHILDREN. BRAIN TUMOUR: CLINICAL CASES

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Brain tumours in children, due to their characteristic of slow invasiveness and easy infiltration in the nervous tissue, tend to give specific symptoms only when they are of a large size.

We present a few cases which came to our attention last year.

Martina is an eight-year-old girl, who came to us due to widespread headache that started three years before. She was a child presenting a conflicting separation since the age of 3, which she responded to initially with hyporexia; she was anxious, agitated, very attached to her mother. The symptoms seemed linked more to the psychological aspects. Neurological testing was negative. During Day Hospital she presented an intense headache crisis, which receded without treatment with NSAIDs. A MRI identified a new formation in the posterior cranial fossa. Surgical intervention revealed an adenoma, 2 months later, the headache had fully disappeared.

Giorgia is 13-years old, suffering from migraine for two years. Her parents are separated, and she is very attached to her mother, who still sleeps with her. In the past 3 months, she has suffered from sleep disturbances, sleep talking and frequent accentuated awakenings, with intense headache almost daily during the same period. Vomiting with coughing was present, but the girl had been following a diet for one month. The neurological examination was negative. Emotional tension was evident in the family. During hospitalisation she experienced slight difficulty in climbing the stairs. TAC shows a 6 cm hypodense formation in the temporal occipital area. Surgical resection of a grade 1 medulloblastoma was followed by one cycle of chemotherapy.

Gianluca is 5-years old, and had been complaining of intense cluster headache for a few months after occipital cranial trauma without loss of consciousness. The headache worsened overtime with an increase in severity. During Day Hospital, 10 days after the trauma, he complained of diffuse violent headache, with crying. Neurological examination was negative except for slight fluctuations on Romberg. CT showed a voluminous new formation in the posterior cranial fossa. He was transferred to the Neurosurgery Unit, where neurological signs began with vomiting, drowsiness, dysmetria, and dysarthria. Surgical resection of a Grade 4 medulloblastoma was followed by chemotherapy and radiotherapy. The following year he relapsed, and was operated on again, followed by another cycle of chemotherapy, but his condition worsened. Sixteen months after being diagnosed, he died.

Conclusions In the cases presented above the specific symptoms of intracranial pressure, vomiting and papilledema stasis without headache, as well as those linked to focality, are absent. Also, the neurological examination yielded no precise indications. The same psychological characteristics could have led to the wrong diagnosis. Observation overtime of the reactions of children to headache during Day Hospital had led us to select neuroimaging testing, which led to the diagnosis. Therefore, we believe that a child with an important headache must always be visited during a crisis.

HEADACHE IN A PAEDIATRIC EMERGENCY DEPARTMENT

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Objective The aim of this study was to determine the prevalence of headache as the chief complaint in patients presenting to a paediatric Emergency Department (ED), to assess its characteristics, to study the spectrum of primary and secondary headache diagnoses and to analyze the diagnostic tests and the treatment applied.

Methods We retrospectively analysed the clinical records of patients presenting to the ED of the Paediatric Hospital A. Meyer of Florence, Italy with the chief complaint of headache from January 1, 2005, to June 30, 2005. All the patients underwent a clinical evaluation/case history, and if necessary also had laboratory or imaging tests performed. The ED records were searched for triage color code, age, gender, location of pain, associated symptoms, case history, physical examination (particularly neurological examination), assessments and specialists' visits, therapy at the ED, time spent at the ED, and outcome (discharge – hospitalization – further assessments at the Centre for Headache in Childhood and Adolescence).

Nosology was established using the International Classification for

Headache Disorders ICDH-II.
Results Two hundred and twenty-three clinical records (2.2% of the total number of visits) concerning 203 patients (121 male and 82 female) were analyzed; the average age was 8.9 years (range 2.1–17.1 years). Primary headaches (migraine and tension-type headache) were recorded in 33 subjects (16.2%): 10 patients with migraine without aura, 10 subjects with probable migraine, 2 cases of migraine with aura, 2 subjects with benign paroxysmal vertigo of childhood; from all the tension-type headaches, 7 were frequent, 4 infrequent, and 1 chronic. Three subjects were found to have both migraine and tension headache (mixed headache). Secondary headaches were mainly attributed to infections in 80 subjects (39.4%) and to sinusitis in 16 patients (7.9%). Five cases (2.5%) were found to be attributed to serious neurological conditions: 1 cerebral empyema, 1 cerebral ischemia, 1 intracranial haemorrhage attributed to arteriovenous malformation, and 2 patients with intracranial hypertension already treated at the Oncohematology Centre for cerebral expansive lesion. After the clinical assessment/case history, 144 patients (64.6%) were discharged from the ED without further tests. Radiological and laboratory assessments and/or specialists' examinations were performed in 35.4% of the patients. Neuroimaging tests were performed in 27 patients of whom 44.4% presented pathological results. Eighteen subjects (8.8%) were hospitalized.
Conclusions This study confirms that headaches in the paediatric ED have different etiology. In 57 subjects (28.1%) headache could not be classified. Future prospective studies may be useful to assess the follow-up in this group of patients.

HEMORRHAGIC PROLACTINOMA IN THE PAEDIATRIC AGE GROUP: TWO CASES WITH DIFFERENT CLINICAL PRESENTATION

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Introduction Pituitary juvenile adenomas are rare (2% to 6% of all supratentorial neoplasms) and prolactinoma is the prevalent tumour [1].
Subjects and methods We present two paediatric cases of hemorrhagic prolactinoma. The first case was a 7-year-old boy, with an acute left-sided visual loss (acuity 1/10 and fundus oculi was normal). Visual evoked potentials (VEPs) showed increased latencies after left eye stimulation. MRI showed a suprasellar lesion hyperintense on T1- and T2-weighted images without enhancement and bordering on the optic chiasm. The serum prolactin was 439 μg/L (normal <15), with decreased cortisol (88 nmol/L, normal >198) and ACTH (3 ng/L, normal >10). After steroidal therapy, visual acuity improved (8–9/10). He then underwent a transphenoidal complete resection of the prolactinoma and subsequently presented panhypopituitarism. The second case was a 17-year-old girl with a three-month last recurrent, moderate, biparietal headache associated with photophobia, especially in the afternoon. In the previous year an oligomenorrhea was treated with hormonal therapy. This treatment was stopped because of headache, which was unresponsive to pill withdrawal. Neurological examination was normal. MRI showed a T1- and T2-weighted hyperintense suprasellar lesion without enhancement. As in the first case, these findings indicated a hemorrhagic pituitary macroadenoma. The serum prolactin was 203 μg/L (normal <25). Visual acuity and visual field were normal. After the surgical resection, she needed substitutive hormonal therapy and, since then, she has never suffered from headache.
Discussion and conclusions Hemorrhagic prolactinomas are rare in children [2]. Patients usually present headache and visual field deficits. Other findings are gynecomastia and puberal delay in males and amenorrhea in females. The cases reported are characterized by peculiar clinical features. The first one presented a pituitary apoplexy, rare in paediatric age group, and a monolateral visual loss with VEPs abnormalities consistent with an optic neuritis. In the second one, instead, the oligomenorrhea although of a mild pattern was the key-sign for the correct diagnosis of a secondary headache.
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SPHENOID MUCOCELE IN CHILDREN: DESCRIPTION OF TWO CASES

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Introduction Sphenoid mucoceles are very rare, benign cystic lesions (1% of all localizations) [1, 2]. Due to connection with several structures (cavernous sinuses, pituitary, orbits and choanas), clinical manifestations can be extremely variable.
Subjects and methods Case 1: An 8-year-old male presented with a subcontinuous mild-moderate, bifrontal, pressing headache on awakening for seven days, without any associated symptoms. On the eighth day, an acute left III cranial nerve palsy with exotropia, ptosis and mydriasis appeared. CT scan showed an erosion of the parasellar structures and MRI revealed a lesion of the sphenoid body, hyperintense on both T1-T2 sequences without enhancement. The maxillofacial CT scan confirmed the sphenoid body lesion. Hormone levels, visual fields and acuity were normal. After ten days the headache spontaneously disappeared, but nerve deficit persisted. Endoscopic trans-sphenoidal permitted total removal of the lesion, followed by histological confirmation and complete resolution of the third cranial nerve palsy. He was asymptomatic at the 5-year follow-up.
Case 2: A 12-year-old male since last year suffered from recurrent, pulsating, weekly headache, localized to the right frontal-ocular region, with photophobia and phonophobia, sometimes nausea, rarely vomiting and responsive to NSAIDs. His father suffered from migraine without aura. During the recent admission to our hospital the neurological examination was negative. Brain MRI showed hypointense signal on T1 and hyperintense signal on T2 in the left part of the sphenoid sinus, with partial involvement of the ipsilateral ethmoid and maxillary sinuses. Sinus CT confirmed a left-sphenoidal mucocele, with indication for an endoscopic sphenoidotomy.
Discussion and conclusions The first case presented a painful ophthalmoplegia which, considering only the clinical picture, could be diagnosed as ophthalmoplegic migraine (ICHD-II, 2004 classification, point 13.17), a very rare condition in young patients, or as Tolosa–Hunt syndrome (ICHD-II, 2004, point 13.16), which also presents with similar features, although with unilateral pain. Neuroimaging, however, documented a rare benign pathology.
In the second case, the patient may be affected by migraine without aura, considering the family history, the type and stability of attacks over time, the resolution with vomiting after the attacks, and the lateralization of the sphenoid lesion, contralateral to the pain. Thus the discovery of a sphenoid mucocele at an early stage can be considered accidental, even if this diagnosis is confirmed after surgery.
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TWO CLINICAL CASES OF RED EAR SYNDROME (RES) CONNECTED WITH HEADHACHE

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Introduction The Red Ear Syndrome (RES) is characterized by sudden events when the patient feels a kind of uneasiness (sometimes a real painful sensation) mainly localized in one ear, which becomes red and warm. Sometimes it happens in a spontaneus way, sometimes it is caused by triggers, like touching the ears, feeling warm or cold, moving the neck, chewing, drinking, coughing or sneezing, The first description of RES dates back to 1996 thanks to Lance [1] who studied its characteristics in 12 patients, some of them having a past of headache. More recently, Raieli et al. 2002) [2] discovered a closer connection between RES and migraine in eight patients. Here, we present two clinical cases that might confirm what is reported in the recent literature. The first one concerns a little boy of 11 years affected by an almost daily headache bilaterally localized to the forehead, causing heaviness of variable intensity lasting about 30 minutes together with nausea, vertigo, phosphenes, pallor, perspiration and hyporexia. The second case concerns a little boy of 7 years who was observed because of a symptomatology of weekly headaches, localized on the parietotemporal side, characterized by pulsating, variable intensity, and lasting no more than 30 minutes. In both cases, the headaches were accompanied by the reddening of a single ear.

Materials and methods Before admittance a careful clinical history was taken according to our protocol for headache diagnosis, and through an accurate clinical and instrumental neurological examination, following the guidelines of the Italian Headache Society for the Study of Headache (SISC).

Results This diagnostic approach allowed us to place the patients' symptomatology in a context of headache connected with RES, bypassing the difficulty in classifying the kind of headache they were affected by, as often happens in patients of that age.

Conclusions Our experience is further proof of the observation made by other authors regarding the connection between RES and headache symptomatology. This suggests the possibility that RES, when present in patients suffering from headache, is epidemiologically understated at present, and the debate is still open on the possibility of including RES in an unclassified category of headache disorders according to the IHS classification.

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