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The Italian Society for the Study of Headaches is one of the oldest societies of the scientific world dedicated to research, education, clinical aspects and lay activities.

This is not by chance.

The Italian School of headache has long and deep venues, starting with Daniele Langhermans' descriptive studies at the end of the XVIII century, to the main contributions of Enrico Greppi, Federigo Sicuteri and Alessandro Agnoli, in the second half of the past century, and is still full of energy and actively involved at an international level, also with scientific contributions.

Different specialists have always been involved to reach this goal: from Neurologists to Psychiatrists, from Child Neuropsychiatrists to Pediatricians, from Internists to Pharmacologists, from Psychologists to Gynaecologists and lastly, General Physicians.

The "Open Minded" idea, a key aspect of society, is based on the cooperation of different backgrounds and on the union of different strengths to reach the result (John Nash).

This is the main reason for having chosen Bari as the Congress location.

Bari, since the beginning of the past millennium, has been a melting pot of different cultures, functioning as an incubator of ideas and a bridge between east and west, north and south of the Mediterranean area.

This is "Democracy"! and we can, while in Bari, feel the wind coming from Athens, the nest of Democracy, also visible with the interactive function of the different sessions of the Congress.

The exciting content of the Congress itself is focused on the multidisciplinary approaches to headache, with the main comorbidities involved, in the attempt to update knowledge and to continue, as in the past, to stress the cooperation with other societies such as SIAARTI - Società Italiana di Anestesia, Analgesia, Rianimazione e Terapia Intensiva and SINC - Società Italiana di Neurofisiologia Clinica.

We are certain that this collection of abstracts will help all of us to be even more involved and stimulated to enrich new research in the headache field.

*Vincenzo Guidetti and Paolo Livrea
Presidents of the XXIII Congress of the Italian Society for the Study of Headaches*

Biological and genetic markers**ENDOCANNABINOIDS AND CGRP**

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A dysfunctioning of the endocannabinoid system has been demonstrated in episodic and chronic migraine (CM) without medication overuse, as well as, in medication-overuse headache (MOH). In episodic migraineur women an increased in N-arachidonoyl-ethanolamide (anandamide, AEA) degradation by platelets has been demonstrated suggesting a reduced concentration of AEA in blood which may reduce the pain threshold and possibly explain the prevalence of migraine in women [1].

Conversely, a decrease in the enzyme AEA hydrolase [fatty acid amide hydrolase (FAAH)] and AEA membrane transporter (AMT) activity has been found in CM and MOH with particular regard to males. This finding suggests that in both the above conditions chronic head pain is associated with a downregulation of the biochemical mechanisms degrading endogenous cannabinoids as an adaptive response to chronic head pain [1].

An impairment of the endocannabinoid system is also supported by the finding of a reduction of the cerebrospinal (CSF) concentrations of AEA in patients with both CM and MOH compared to nonmigraineur controls which were negatively correlated with CGRP CSF levels. A similar trend emerged between this endocannabinoid and nitrite levels. The reduction in CSF levels of AEA appears to be related to chronic head pain per se because it does not seem specific for CM but was also evident in the CSF of MOH patients and not dependent from overused symptomatic drugs suggesting the potential role of the cannabinoid (CB)1 receptor as a possible therapeutic target in both chronic head pain conditions [2].

Based on these findings, it can be hypothesized that the failure of the inhibitory role of AEA can contribute to maintaining central sensitization in chronic head pain, and represents a further mechanism which intervenes in increasing the release of the sensory neuropeptide CGRP and NO production during trigeminovascular activation.

Recent experimental findings suggest that AEA, the endogenous ligand of CB(1) and CB(2) receptors, is tonically released to play a modulatory role in the trigeminovascular system. Furthermore, activation of type-1 cannabinoid (CB1) receptors has been shown to inhibit trigeminal neurons whose activity has been suggested to play a critical role in migraine pathogenesis [3].

AEA appears to act both presynaptically, to prevent CGRP release from trigeminal sensory fibres, and postsynaptically to inhibit the CGRP-induced nitric oxide (NO) release in the smooth muscle of dural arteries.

Other aspects related to CB dysfunctioning need to be clarified. Some experimental evidence allows, in fact, to hypothesize other targets for AEA or analogs other than CB(1). In several *in vitro* settings, AEA has been demonstrated to activate TRPV1, the nonselective cation channel that belongs to the large family of TRP ion channels, activated by the pungent ingredient of hot chilli peppers, capsaicin. They are expressed in some nociceptor efferent neurons, where they act as a molecular sensor of noxious heat and low pH. The activation of TRPV1 receptors in the trigeminovascular system activation via AEA promotes CGRP release and causes vasodilation independent of any action at the CB(1) receptor, and therefore

exerts an opposite effect of that attributed to endocannabinoids through metabotropic receptors.

Whether and how the above mechanisms play a pivotal role in episodic migraine and CM with or without medication overuse remains to be established in the search for new therapeutic strategies in migraine. In this regard, other endogenous substances have been discovered, which need to be investigated in future research: the endovanilloids, which are defined as endogenous ligands of the TRPV1 protein.

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PROSPECTS OF NEUROSTIMULATION FOR PRIMARY HEADACHES

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Objectives To review recent advances in neurostimulation for the treatment of primary headaches.

Background Conventional treatment in chronic headaches, such as chronic migraine (CM), chronic cluster headache (CCH), and hemicrania continua (HC), are often limited. Neurostimulation has recently emerged as a potential treatment option for patients with chronic, disabling, intractable primary headache disorders. At present, deep-brain stimulation (DBS), occipital-nerve stimulation (ONS), and repetitive transcranial magnetic (rTMS) have been tested.

Results *Deep brain stimulation* has been used to treat intractable CCH and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). To date, over 50 CCH patients underwent hypothalamic DBI. Stimulation has proved successful in controlling the pain attacks in approximately 50% of CCH patients implanted at various centres. However, electrode implantation procedures carry a risk of mortality due to intracerebral haemorrhage and prospective multi-centre studies are necessary to evaluate its effectiveness. Some studies have assessed the safety and efficacy of *occipital-nerve stimulation* (ONS) in drug-resistant chronic headache syndromes. In a group of 14 CCH patients, at a median follow-up of 17.5 months, ONS was effective in approximately 70% of patients. ONS appeared to be safe and effective also in a group of 6 patients with HC. ONS has the advantage of being harmless and reversible, however more work is required to evaluate and understand the biological mechanisms underlying this therapeutic strategy. Several studies suggested that *repetitive transcranial magnetic stimulation* shows beneficial effects in the treatment of neurological and psychiatric disorders. A recent study evaluated safety and efficacy of rTMS in the prophylaxis of migraine. The rTMS treatment was well tolerated. Treated patients showed a significant reduction in both the number of migraine attacks and migraine days. However, the comparison with the placebo group did not reach the level of statistical significance. The results of this study suggest the need for further research.

Discussion and conclusions There is accumulating experience with the use of neurostimulation for the treatment of chronic headache disorders. However, neurobiological mechanisms underlying the effects of these therapeutic strategies have been scarcely investigated and safety and efficacy data are limited in quantity. DBS of the posterior inferior hypothalamus is an effective therapeutic option in a subset of patients with chronic cluster headache. Future controlled multicentre trials will need to better define predictive factors for non-responders. ONS appears to be a safe and effective treatment for both CCH and HC and could be safer than deep hypothalamic stimulation. Finally, further research is warranted to evaluate rTMS efficacy in migraine prophylaxis.

ASSOCIATION ANALYSES OF GENETIC VARIANTS OF THE *HCTR1* GENE IN MIGRAINE

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Background Migraine has a clear genetic background and several studies have suggested that genetic factors play an important role in migraine. Although several genes have been supposed to be involved in the pathophysiology of the disease, no major gene related to migraine has yet been found. Recent studies in animals suggested a role for the hypocretin neurotransmitter system in pain transmission. Several of the functions regulated by the hypocretinergic system are significantly impaired in patients with migraine and this could be relevant to the pathophysiology of the disease. Consequently, we hypothesized that genetic variants within the hypocretin system would modify the occurrence and the clinical features of migraine patients. To test this hypothesis, we performed a case-control association study in a cohort of Italian migraine patients and in healthy controls.

Methods Three hundred and eighty-six consecutive unrelated migraine patients (mean age \pm SD = 40.3 \pm 9.4 years) and 259 healthy sex, age and geographically matched control subjects (mean age \pm SD = 50.9 \pm 12.8 years) were selected for the study. The diagnosis of migraine was made according to the International Classification of Headache Disorders-II criteria. All the subjects were genotyped for three polymorphisms: rs10914456, rs4949449, and rs2271933 (Ile408Val) in the hypocretin receptor-1 (*HCRTR1*) gene.

Results The genotypic and allelic frequencies of the rs10914456 and rs4949449 polymorphisms were similarly distributed between cases and controls. Conversely, both allelic and genotypic frequencies of the rs2271933 (Ile408Val) polymorphism in the *HCRTR1* gene resulted significantly different between cases and controls ($p=0.0046$ and $p=0.0032$, respectively). The carriage of the A allele was associated with a significantly increased disease risk (OR:1.42, 95% CI, 1.11 – 1.81). Comparison of the clinical features of the disease with the I408V genotypes showed no significant difference.

Discussion and conclusions Our study suggests for the first time that the *HCRTR1* gene or a linked locus significantly modulate the risk for migraine and hypothesizes an involvement of the hypocretin neurotransmitter system in the pathogenesis of the disease. Further studies are warranted in order to elucidate the precise neurobiological mechanisms and to evaluate potential therapeutic perspectives of our findings.

THE POLYMORPHISM OF ENZYME MTHFR IN CHILDREN SUFFERING FROM MIGRAINE AND EPILEPSY

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Introduction The C677T variant in the methylenetetrahydrofolate reductase (MTHFR) gene is associated with increased levels of circulating homocysteine and is a mild risk factor for vascular disease. Mild Hcy elevation (>15 mmol L⁻¹) in the adult population is associated with increased risk of myocardial infarction, stroke, peripheral arterial disease and venous thrombosis [1–3]. The MTHFR 677CT mutation is frequent in Caucasians; MTHFR mutant allele occurs commonly in 5% to 15% of the population, and the heterozygosis is over 40%. The C677T polymorphism of the MTHFR gene has been associated with different diseases such as stroke, coronary artery disease, bipolar disorder, schizophrenia and depression. Homozygosis for MTHFR 677CT mutations is more frequent in epileptic patients compared with healthy controls (23% vs. 12%) and heterozygosis is about 52%. The authors [1, 2] showed that Hcy may have excitotoxicity to neurons as an agonist of the glutamate binding site of the N-methyl-D-aspartate (NMDA) receptors. Migraine, with and without aura (MA and MO), is a prevalent and complex neurovascular disorder that may also be affected by genetically influenced hyperhomocysteinaemia.

Objective To evaluate the incidence of mutation of enzyme MTHFR in children suffering from two diseases, epilepsy and migraine with comorbidity, and without comorbidity.

Materials and methods The sample of this study consisted in 32 patients suffering from headache observed for 3 months and 34 children affected by epilepsy observed during the same time. At the first observation in Day Hospital the homocysteinaemia levels and mutation C677 of enzyme MTHFR were determined. The sample underwent MR brain and EEG. In the familial history, headache, epilepsy, stroke and cardiovascular disease were considered. The homocysteinaemia was evaluated by immunological fluorescent method (FPIA). The mutation of enzyme C677 was studied by the qualitative *Real-Time PCR* technique.

Results Twenty-seven patients suffered from generalized epilepsy, and 7 from partial epilepsy. In the 18% of these patients there was C677 enzyme mutation and 7% showed homozygous condition. Among 32 children suffering from headache, 17 had TTH, 9 MO, and 6 MA. MTHFR mutation was found in 50% of patients. The allele was present in 83% of MO and in 87% of MA and homozygosis condition was present in 22% of children. The values of homocysteinaemia were higher in the homozygous than heterozygous patients (9.48 μ mol/L vs. 8.3 μ mol/L) and this condition was more evident in migraine than epileptic patients. In 50% of the sample with C677 mutation, there were MR lesions as related to cerebrovascular disease. One child showed the results of an ischemic event in the foetal life.

Discussion Scher et al. [2] originally reported a positive association between the MTHFR C677T variant and migraine in a Japanese case-control cohort. These researchers indicated an increased risk of migraine in Japanese individuals possessing the homozygous T/T genotype. Stratified analyses specifically showed that the T/T genotype was significantly over-represented in these Japanese patients with MA compared to non-migraine controls (40% vs. 9.6%), producing an OR of ~6. These positive findings were reinforced by another recent migraine case-control study conducted in a Turkish population. These researchers reported that the MTHFR C677T was associated with migraine and also indicated that the T/T genotype specifically increased risk of MA (OR ~10). It is important to note that the frequency of the MTHFR 677T allele, and indeed migraine prevalence, is known to vary substantially among different ethnic populations. Thus, this study supports the findings of other authors and shows the hypothetical role of this genetic aspect in migraine - epilepsy comorbidity.

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Neuroradiological and neurophysiological markers

PAIN PATHWAYS AND FUNCTIONAL MRI

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Pain is an unpleasant experience that involves the conscious awareness of noxious sensations, hurting and aversive feelings associated with actual or potential tissue damage (International Association for the Study of Pain, 1994).

The human pain sensation is a multidimensional experience involving sensory-discriminative, cognitive and affective-motivational components.

The recent developments of functional magnetic resonance imaging (fMRI) have led to a better knowledge of pain processing, have clarified some of the features of the CNS in the complex pain modulation networks and have provided means for the elucidation of the functional anatomy of the pain matrix.

According to the available studies, the anterior cingulate cortex may play a role in the emotional-affective component of pain, as well as, in pain-related attention and anxiety; in the somatosensory cortices in encoding spatial and temporal aspects of noxious input; in the insula which may be involved in both affective and sensory-discriminative aspects of the pain experience; in the prefrontal cortex in the pain-related attention processing; and in the thalamus it appears to be a multifunctional transmission centre. Such regions, as recently showed, may play an important role in the pathophysiology of chronic pain and might be one of the main focuses of future neuroimaging studies in chronic pain patients.

NON INVASIVE BRAIN STIMULATION TECHNIQUES IN HEADACHE: FROM PATHOPHYSIOLOGICAL INVESTIGATION TO TREATMENT PERSPECTIVE

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Abnormalities of neuronal cortical excitability are believed to play an important role in the pathophysiology of migraine [1]. Neurophysiological techniques have given important contributions in the understanding of such issues, highlighting possible mechanisms of cortical dysfunctions in migraine.

The most relevant studies with Evoked Potentials (EPs) have evidenced that migraine patients present impairment of habituation to repeated sensorial stimulation. This abnormal behaviour was observed in many studies and across all sensorial modalities, making it a neurophysiological hallmark of the disease. The development of techniques for non invasive brain stimulation like transcranial magnetic stimulation (TMS) and, more recently, transcranial direct current stimulation (tDCS) have allowed a more direct evaluation of cortical activation and responsiveness in migraine

patients, by testing pathophysiological hypotheses and opening also interesting therapeutic perspectives [2]. TMS acts through magnetic fields that are able to perform transcranially, effective non invasive, painless stimulation of the cerebral cortex. Differently, direct current techniques, like tDCS, do not induce cortical stimulation but act by modulating cortical excitability, likely acting on neuronal membrane polarity. The application in migraine did not give univocal results, pointing towards hyperexcitability or, on the contrary, to reduced preactivation of sensory cortex. Together with these reports other evidence showed impairment of inhibitory circuits and analogies have been proposed between migraine and conditions of sensory deafferentation in which down-regulation of GABA circuits is considered the more relevant pathophysiological mechanism. Interestingly, new data by our group shows that response to rTMS pulses that normally activate facilitatory circuits of the motor cortex are also impaired in migraine.

Whatever the mechanism involved, it has been found that repeated sessions of high-frequency rTMS trains that have been shown to up-regulate inhibitory circuits could persistently normalize habituation in migraine. This could give interesting insight into pathophysiology establishing a link between cortical inhibition and habituation opening also to new treatment strategies in migraine.

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RELIABILITY OF NEUROPHYSIOLOGICAL TECHNIQUES IN MIGRAINE: PROS AND CONS

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Functional studies of SNS provided much interesting information about migraine pathophysiology, which have had great relevance also from a therapeutic point of view. Although many have accepted these findings, some doubts have been cast on their reliability.

The recent progressive implementation of functional MRI techniques and their use in studies of migraine pathophysiology showed that some cortical and subcortical areas are involved in initiating and maintaining migraine attacks and possibly in migraine chronicization. These techniques are characterized by a very high spatial resolution; by contrast, they provide a very low temporal resolution, absolutely inadequate to illustrate the correct sequence of activation of the neural structures under study.

Neurophysiological techniques are particularly useful, however, to investigate cortical activation by many methods of study, because of their very high temporal resolution. Many generators of cortical events have been indirectly identified, until now, so that they can also provide information about the temporal involvement of the brain structures implicated in the events under investigation. The implementation of more sophisticated methods to analyse the bioelectric signal, through the resolution of the “inverse problem” by using realistic MRI scalp models, could be useful to improve the spatial resolution of neurophysiological techniques, moreover when supported by the contemporary use of functional MRI, providing then more specific and reliable information about migraine pathophysiology.

NORMAL RECOVERY CYCLE OF THE SOMATOSENSORY EVOKED POTENTIALS OF MIGRAINE WITHOUT AURA PATIENTS

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Background Migraineur patients' lack of habituation during the stereotyped repetition of any kind of sensory stimuli, comprises somatosensory. Even if the exact cause of this abnormal sensory processing is still unknown, two main hypotheses have been made so far. In fact it has been attributed to an increased cortical excitability, probably due to reduced GABAergic inhibition, or to a reduced cortical preactivation from the subcortical modulatory structures. The latter should affect the entire network of excitatory and inhibitory cortical neurons. Whether the former or the latter contributes more to the habituation deficit cannot be determined simply by analysing the somatosensory responses in a conventional paradigm of stimulation.

A measure of cortical somatosensory area excitability, directly depending on the inhibitory interneuron function, is the suppression of the cortical response by preceding identical stimulation and its recovery curve after paired stimuli at different interstimulus intervals (ISIs).

Objectives To shed light on the mechanisms of the interictal cortical dysfunction in migraine, we studied habituation and recovery curve of the somatosensory evoked potentials (SSEPs) after conditioning by median nerve electric stimuli in untreated migraine without aura patients (MO) between attacks and in healthy volunteers (HV).

Methods We recorded the recovery curve of the N9, N13 and N20 amplitude components of SSEPs in 29 MO patients (16 recorded interictally, 13 ictally) and in a group of 22 age- and gender-matched HV, by paired median nerve at the right wrist identical stimuli. We plotted the recovery curve at different ISIs (5, 20, and 40 ms; 500 sweeps each) as percentage changes of the baseline single unconditioned stimulus. Moreover, in order to assess the degree of habituation in the same patients, during the same recording session, we partitioned the baseline unconditioned 500 sweeps in 5 averaged blocks.

Results Amplitude changes in cortical N20 SEP component along the 5 blocks (i.e., habituation) during the baseline condition differed between groups ($F[8, 192]=2.78, p=0.006$). Post hoc analysis showed that in both HV and in MO recorded ictally N20 SEP amplitudes decreased progressively. It was not the case in MO recorded interictally since N20 amplitudes increases already at the second block, i.e., lacked habituation.

In migraineurs recorded either ictally and interictally the recovery curves of each somatosensory component were similar to HV (for N20, $F[4, 92]=0.73, p=0.56$).

Conclusions These results are not in favour of an interictal faster recovery cycle, i.e., reduced GABAergic inhibition, in the peripheral and cortical somatosensory system as a possible explanation for the lack of habituation in migraine. Other mechanisms must therefore underlie the interictal abnormal information processing in migraineurs.

EFFECTS OF AFFECTIVE PICTURES ON PAIN SENSITIVITY AND CORTICAL RESPONSES INDUCED BY LASER STIMULI IN HEALTHY SUBJECTS AND MIGRAINE PATIENTS

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Introduction Visually induced analgesia has been correlated with the affective content of pleasant, neutral or unpleasant pictures.

Objectives The aim of the present study was to assess the effect of viewing affective images on laser evoked potentials and pain perception, in a cohort of healthy subjects and migraine patients.

Methods Twenty-two healthy subjects and 24 migraine without aura patients (recorded during the inter-critical phase) participated in the study. Eighty-four colour slides, arranged in two blocks, each consisting of 14 pleasant, 14 unpleasant and 14 neutral images, in random presentation, were chosen from the International Affective Picture System. The CO₂ laser stimuli were delivered on the dorsum of the right hand and supra-orbital zone at 7.5-watt intensity and 25 ms duration, in basal condition and during the viewing of affective pictures.

Results Migraine patients expressed higher scores of valence and arousal for pleasant and unpleasant pictures, compared to controls. In both groups, a late positive potential in the 400–700 ms time range was clear for pleasant and unpleasant pictures, but its amplitude was significantly reduced in migraine patients. The pain rating was reduced in both groups during the visual task compared to basal condition.

Discussion In migraineurs and controls the P2 wave was reduced during the vision of pleasant pictures, compared to basal condition. This indicates that stimulation by images with different affective content reduces subjective pain for a cognitive mechanism of attentive attraction, while a special inhibition of later LEPs is produced by a positive emotional impact.

Conclusions In migraine, affective images are able to modulate pain perception and LEPs, differently from other modalities of distraction, for a possible interference with the emotive elaboration of painful stimuli.

Probable headaches: differential diagnosis

MIGRAINE AND PROBABLE MIGRAINE

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The International Classification of Headache Disorders 2 edition (ICHD-II) introduced the new category of probable migraine, defined by the existence of all but one of the typical criteria, which remain unmodified with respect to the first edition; moreover, no criterion has been identified as sufficiently sensitive and specific to be considered pathognomonic. A probable migraine diagnosis is made when the clinical picture fulfils all but one criteria for this category of headache disorders. Qualitative features of the pain (side-locked, pulsatility, disability, accompanying symptoms, increase after common exertions), frequency and duration of the attacks represent the milestones for the diagnosis of a migraine headache. Although the ICHD-II criteria provide specific features for each form of primary headaches, in the daily clinical practice the reported characteristics of one headache could fulfil two different sets of explicit diagnosis criteria. In this case, other information should be obtained to be utilized in the diagnostic process. Most probable migraine diagnoses miss number of previous episodes, duration of the attack and accompanying symptoms criteria. Since migraine crises often start slowly, in the beginning they could mimic a tension-type headache attack, until they get worse and clearly become migrainous; therefore, an early treatment of the attack could hide the migraine features, which may not have time to develop. Another important consideration concerns the lack of accompanying symptoms, a most important element for the diagnosis. Patients could ini-

tially miss to report their presence, with particular regard to phonophobia and photophobia. This aspect should be carefully investigated using detailed close-ended questions, with the aim to detect whether they prefer to remain in a dark and quite room instead of staying in bright sunlight with loud noises. In addition, about 50% of migraineurs report the occurrence of osmophobia, defined as an unbearable perception during a migraine attack of smells that are non-aversive or even pleasant outside the attacks: this symptom actually appears among the major criteria in the ICHD-II appendix, where new forms of headaches or modified proposal criteria for well known headache disorders are listed. An in-depth analysis of this particular feature shows that it appears to be structurally integrated into the patients' migraine history and seems to be a peculiar symptom favouring the diagnosis of migraine, especially in the differential diagnosis with tension-type headache. An over-diagnosis of probable migraine should be avoided by asking additional and detailed questions during the medical interview; the introduction of osmophobia among the major diagnostic features for migraine should add sensibility and specificity to the ICHD-II criteria.

TENSION-TYPE HEADACHE

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"Probable tension-type headache" is the last subtype of Tension-Type Headache (TTH) according to the 2nd edition of the International Classification of Headache Disorders (ICHD-II), like the last one of Migraine and Cluster Headache. It is further divided into 3 subforms: "probable infrequent episodic TTH", "probable frequent episodic TTH" and "probable chronic TTH". The first two subforms include episodes fulfilling all but one of the diagnostic criteria for infrequent and frequent episodic TTH. The third one instead includes headache occurring on ≥ 15 days per month on average for > 3 months, fulfilling diagnostic criteria for chronic TTH, in which there is or has been within the last 2 months medication overuse according to the diagnostic criteria for this form of secondary headache.

Very few epidemiological data exist about this form of headache. Pfaffenrath et al. [2] recently published an article on three population-based studies in different German regions and assessed headache prevalence and headache characteristics in face-to-face interviews, applying standardized methods. They analysed the 6-month prevalence of migraine, TTH and their probable subtypes based on the ICHD-II criteria. Among the 7417 participants in all three regions, the pooled 6-month prevalence of TTH and probable TTH was 19.86% and 11.61%, respectively. Despite the application of standardized classification methods, regional variations between 15.44% and 23.64% were observed, indicating differences in the local headache burden.

Queiroz et al. [3] conducted an observational, cross-sectional, population-based study to estimate the 1-year prevalence of TTH of a representative sample of the adult population of Brazil. They conducted telephone interviews on 3848 people, randomly selected from the 27 states of Brazil. The prevalence of TTH and probable TTH was 13.0% and 22.6%, respectively.

The difference in the results of these two studies indicates a need for further discussion about the value of probable headache types in epidemiological studies.

Patients meeting the diagnostic criteria for probable TTH may also meet the criteria for one of the subforms of "probable migraine". In such cases, according to the indications of the ICHD-II, all other available information should be used to decide which of the alternatives is more likely.

According to some authors' ideas TTH does not exist, but it is only a different clinical aspect of migraine. The overlapping of the diagnostic criteria of these two forms could be in favour of this hypothesis.

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CLUSTER HEADACHE AND OTHER TACs

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Introduction The trigeminal autonomic cephalalgias (TACs) are classified in section 3 of the revised International Classification of Headache Disorders (ICHD-II, 2004). This group of primary headaches includes Cluster Headache (CH), Paroxysmal Hemicrania (PH), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). They are characterized by unilateral head pain with different duration in each form of TACs, associated to ipsilateral cranial autonomic features.

Cluster Headache is one of the most painful primary headaches. Its prevalence in the general population is 0.1–0.3% and it begins after the age of 20–30. The onset in adolescence is rare and its observation under 10 years of age is quite singular. CH has a male preponderance, with a male to female ratio of 2.5–3.5:1. The attacks are characterized by severe, strictly unilateral pain, usually localized to orbital, supraorbital or temporal sites, accompanied by ipsilateral autonomic symptoms (lacrimation, conjunctival hyperemia, nasal obstruction or rhinorrhea, myosis, eyelid oedema) and sometimes nausea and vomiting may occur during an attack. The crises last for 15–180 minutes and their frequency can vary from one to eight times daily and usually they occur at the same hour. Despite the typical clinical features, it is not always correctly diagnosed, especially in young patients: children suffering from CH have bizarre behaviour, frequently they are agitated and often considered affected by psychiatric headache and/or behavioural disorder. Also, in adults CH remains unrecognised or misdiagnosed in many cases for some years. Photophobia or phonophobia and nausea are in part responsible for this delay. CH can be subdivided into two subtypes: episodic CH (80–90% of the patients) and chronic CH (10–20%).

Paroxysmal Hemicrania is a rare syndrome, that occurs frequently in females and is well responsive to indomethacin. Like CH, pain has a severe intensity, strictly unilateral, associated with autonomic signs, but the attacks are shorter-lasting (2–30 minutes) and more frequent (5–20/day) than CH ones. The rarity of this headache in children is confirmed by the lack of papers in scientific literature. **SUNCT** is a very rare primary headache disorder, with brief, unilateral, severe headache attacks, accompanied by ipsilateral conjunctival injection and lacrimation. The pain has a neuralgic character and the crises are typically short-lasting (5–240 seconds) and very frequent (3–200 per day). SUNCT was described only in three cases in childhood: the first case was an Italian 10-year-old girl,

who suffered from brief painful attacks in the right frontal area, accompanied by ipsilateral conjunctival injection and lacrimation. Indomethacin and NSAIDs were not effective.

Pathophysiology and treatment The TACs pathogenesis is not well known, however recent studies suggest the involvement of subcortical structures (posterior hypothalamus and dorsal nucleus) with subsequent trigeminovascular and autonomic activation. Clinical features, biochemical abnormalities, hypothalamic activity on functional imaging studies observed in patients with TACs, suggest a possible role of hypothalamus both as a generator of headache attacks, and as a possible target for treatment. There are direct hypothalamic-trigeminal connections, and the hypothalamus is known to have a modulatory role on the nociceptive and autonomic pathways, particularly on the trigeminovascular system. The present therapy for each of these syndromes is the following: oxygen, sumatriptan, verapamil, lithium, methysergide in cluster headache, indomethacin in paroxysmal hemicrania, intravenous lidocaine, lamotrigine, and topiramate in SUNCT.

Conclusions TACs are not a very frequent entity. There are also few cases (especially in young subjects) of headache attacks that are believed to be a type of TACs, but they do not meet all diagnostic criteria and are classified as probable (or like) trigeminal autonomic cephalalgias (3.4 ICHD-II, 2004), as reported in the literature and as observed in our Headache Centre. In these patients it is always useful to perform appropriate examinations like neuroimaging (CT, MRI, MR angiography) to exclude the possibility of a secondary headache such as pituitary tumors, parasellar meningioma, cerebral aneurysm, arteriovenous malformations, malignant frontal tumor, and posterior fossa lesions.

ATYPICAL AURAS

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The term “atypical aura” is not included in the second edition of the International Classification of Headache Disorders (ICHD). The previously defined syndromes, migraine with prolonged and migraine with acute onset aura, specifically described in the ICHD first edition, have been abandoned. According to the new classification, they should be coded as probable migraine with aura, specifying the atypical features. The typical aura of migraine is characterized by focal neurological features that usually precede headache but may accompany it or occur in the absence of the headache. Typical aura symptoms develop over ≥ 5 minutes and last no more than 60 minutes, and visual aura is overwhelmingly the most common. Typical visual aura is homonymous, often having a hemianopic distribution and expanding in the shape of a crescent with a bright, ragged edge, which scintillates. Visual auras vary in their complexity. Elementary visual disturbances include scotomata, simple flashes (phosphenes), specks, or geometric forms. They may move across the visual field, sometimes crossing the midline. Shimmering or undulations in the visual field may also occur and may be described by patients as “heat waves”. More complicated auras include teichopsia or fortification spectrum; visual distortions and hallucinations can also be reported. These phenomena are more common in children, and are characterized by a complex disorder of visual perception that may include metamorphopsia, micropsia, macropsia, zoom, or mosaic vision. Non-visual symptoms can occur and include apraxia and agnosia; speech and language disturbances; states of double or multiple consciousness associated with déjà vu or jamais vu; and elaborate dreamy, nightmarish, trance-like, or delirious states. Olfactory hallucinations may also occur. In

all these conditions, a differential diagnosis with partial epilepsy is mandatory. Sensory symptoms occur in about one-third of patients who have migraine with aura. The usual sensory auras are typically cheiro-oral, with paresthesias starting in the hand, migrating up to the arm, and then jumping to involve the face, lips, and tongue. The leg is occasionally involved. Paresthesias may be followed by numbness and, in a few cases, loss of position sense. Sensory auras rarely occur in isolation and usually are associated with a visual aura. Dysphasia may be part of typical aura but motor weakness, symptoms of brain stem dysfunction, and changes in level of consciousness, all of which may occur, signal particular subtypes of migraine with aura (hemiplegic, and basilar-type). Typical aura occurring in the absence of any headache requires a differentiation from transient ischemic attack (TIA). Adequate investigations, especially when this condition first occurs after age 40, are mandatory, especially when negative features (i.e., hemianopia) are predominant or when the aura is of atypical duration. Complex auras, that in many cases pose differential diagnosis challenges, characterize basilar-type migraine. The distinguishing feature of basilar-type migraine is a symptom profile that suggests posterior fossa involvement. Diagnosis requires at least two of the following aura symptoms, all fully reversible: dysarthria, vertigo, tinnitus, decreased hearing, diplopia, visual symptoms simultaneously in both temporal and nasal fields of both eyes, ataxia, decreased level of consciousness, and simultaneously bilateral paresthesias. Basilar-type migraine should be diagnosed only when weakness is absent, because about 60% of patients with hemiplegic migraine have basilar-type symptoms. Another atypical and rare headache disorder is retinal migraine. This entity has been classified independently of migraine with aura in the ICHD-II edition, being coded as an autonomous migraine disorder. It is characterized by recurrent attacks of fully reversible scintillations, scotomata, or blindness, affecting one eye only, that are accompanied or followed within 1 hour by migrainous headache. Other causes of monocular visual loss, including TIA, optic neuropathy, and retinal detachment must be ruled out by appropriate investigation.

OSMOPHOBIA IN MIGRAINE AND TENSION-TYPE HEADACHE: A PROSPECTIVE STUDY

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Introduction In the second edition of the International Classification of Headache Disorders (ICHD-II), osmophobia has been proposed in the Appendix within the associated symptoms for the diagnosis of migraine without aura (MO). Following our retrospective investigations in primary and secondary headaches [1–3], we report detailed results of our clinical prospective study about the presence and the role of osmophobia in patients affected by migraine (M), without (MO) and with aura (MA), by episodic tension-type headache (ETTH), or both, and we further evaluated possible relationships between osmophobia and other features of M.

Materials and methods We analyzed a consecutive series of patients referred to our Headache Centre from January 2008 to February 2009, with a diagnosis of M (MO and MA), ETTH, or both, in accordance to the ICHD-II criteria. At the end of the visit, patients received a semi-structured questionnaire to evaluate the possible presence of osmophobia in four consecutive attacks, with further specifications about the clinical features.

Results We recruited from our Headache Centre 103 patients (75 females; 28 males; age 37.9 ± 11.5), of whom 75 were MO, 3 MA, 18 ETTH and 7 MO+ETTH. We analyzed 412 headache attacks.

Among MO patients 65.3% (49/75) reported osmophobia in at least one attack; none among ETTH patients suffered this symptom. Among MO+ETTH patients osmophobia was reported only during M attacks, specifically in 43.8% of the patients. Osmophobia specificity for migraine diagnosis resulted 100%.

MO attacks with osmophobia distinguished themselves from those without osmophobia by a stronger presence of pain: unilateral (83% in osmophobic attacks vs. 52% in non-osmophobic), throbbing (65% vs. 47%), severe (58% vs. 27%), and aggravated by routine physical activity (87% vs. 71%). Among patients with MO, osmophobia was present in 4/4 attacks in 42%. At the start of the algic phase in 38% of attacks, during the first 10 minutes in 51% and before the start in 11%. The symptom stopped before the end of the algic phase in 40% of attacks, with the algic phase in 55% and persisted longer (less than 10 minutes) in 5%. Osmophobia was reported for a single category of smells in 28% of attacks, for 2 categories in 41.3%, for 3 in 27.4%, and for 4 in 2.9%. The odours most frequently involved were scents (71% of attacks), cigarette smoke (58.6% of attacks) and foods (55.4% of attacks). Furthermore, olfactory stimulus triggers attacks in 22.3% (11/49) of osmophobic patients; in 2 of them it triggered 4/4 attacks.

Discussion and conclusions This study confirms that osmophobia is a very specific marker to discriminate adequately between M and ETTH. Attacks characterized by the presence of osmophobia present more associated symptoms and a more typical migrainous pattern of the headache.

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Clinical aspects and headache management in adults

FUTURE DRUGS FOR HEADACHES

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Migraine is a complex neurovascular disorder in which genetic and environmental factors interact. At present, frontline therapies in migraine's acute treatment include the use of non steroidal anti-inflammatory drugs (NSAIDs) and triptans.

Recent evidence indicates Calcitonin Gene Related Peptide (CGRP) playing a fundamental role in migraine mechanics. CGRP is a strong vasodilatory neuropeptide released from activated trigeminal sensory nerves.

The development of CGRP antagonists has also been driven by the fact that triptans are vasoconstrictive and cannot be used in patients with vascular risk factors.

Oliceridine is the first CGRP antagonist for the treatment of migraine which has been tested in clinical trials, but its principal limitation is that BIBN4096 presents low oral bioavailability and has only been tested through intravenous formulation. The first oral non-peptide CGRP antagonist Telcagepant has recently been shown to be highly effective in the treatment of migraine attacks. This development can be considered the most important pharmacological breakthrough for migraine treatment since the introduction of sumatriptan in the early 1990s. These results are important since they confirm the current pathophysiological concept of migraine.

The pipeline of future compounds for the treatment of acute migraine include TPRV1 antagonists, EP4 receptor antagonists, Serotonin 1F receptor agonists and Nitric Oxide synthase inhibitors.

The near future of preventative treatment of migraine is well represented by botulinum toxin type-A, glutamate receptor antagonists, tonabersat, candesartan and occipital nerve stimulation procedures for completely refractory headaches.

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LESSONS FROM TRIPTANS IN MIGRAINE TREATMENT

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Research for a new antimigraine compound started at Glaxo in 1972 and led to the discovery of the first triptan drug, sumatriptan, a 5-HT₁-like receptor agonist with an indolic structure identical to the neurotransmitter 5-HT.

On November 14th, 1991, SISC organised in some Italian Headache Centres a "Migraine Day", officially starting the sumatriptan "revolution", followed by the "age of triptans". The availability of sumatriptan, a specific analgesic for migraine pain, had opened new prospects for migraine treatment, which up to then had only used non-specific analgesics, such as FANS, paracetamol, and ergotamine, an agonist drug of various receptors, with important side effects and contraindications. Research was immediately directed towards the synthesis of triptans with better pharmacokinetic and pharmacodynamic characteristics and less side effects. Six triptans were synthesized, 5 of which had the same indolic structure as sumatriptan and were therefore defined as "me-too", while one had a carbazolic structure.

Like all revolutions, the triptans' was a complete one. The congresses, courses, and conferences were practically all about the research of the triptan with the highest therapeutic index.

However, the physiopathology of migraine pain implies, besides 5-HT, noradrenaline, the formation of NO, GABA, enkephalins, and the release of neurotransmitters (SP and CGRP) and neuropeptides. Proof that an antagonist of the CGRP receptor is effective in migraine pain treatment when taken by mouth opens new prospects. If, different types of antimigraine drugs and their associations are available, subtypes of patients shall be identified, according to the different treatments or associations they need.

The methodological elements which can be deduced from research on the clinical efficacy of triptans, opening new prospects of research about the physiopathology and clinical aspects of migraine, are the following: 1) detecting premonitory symptoms that may increase the awareness of migraine; 2) detecting the onset time of migraine aura and its signs and symptoms; 3) deciding when the drug must be administered in clinical trials; and 4) detecting pain intensity (light, moderate, or severe) and the possible autonomic symptoms when administering the drug and afterwards, after established periods of time, and assessing the following primary end points: - pain relief and pain free after 30 and 60 minutes; - pain free after 2 hours (not pain relief); - sustained pain free after 24 hours; - sustained pain free and no side effects after 24 hours; and the following secondary end points: - presence and intensity of possible other symptoms (osmophobia, phonophobia, photophobia, nausea, vomiting); - recurrence after 24 hours; - disability time per treated attack; - consistency across multiple attacks.

The criteria of inclusion of migraine patients in clinical trials must consider the severity of migraine, assessing the progress and char-

acteristics of the last 5–10 attacks, in order to divide the subjects included in the studies into groups. The efficacy of a drug is different in episodic migraine patients with attacks lasting 3–4 hours and in patients with attacks lasting 4–8 hours or previously treated with drugs causing pain relief for a few hours, with the reappearance of pain, for example, after 4–6 hours.

Patients' selection contributes to the disparity between clinical trials and clinical practice; it is fundamental that patients in clinical trials are as similar as possible to the patients who are then going to take the drugs in clinical practice.

Drugs should be used as research tools and clinical records should be created on these bases, in order to know more about the mechanism of pain generation subsequent to the activation of the trigeminal vascular system and about the role played by vasodilatation and plasma protein extravasation.

TOPIRAMATE WEIGHT LOSS IN MIGRAINE PATIENTS

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Introduction Topiramate (TPM) is generally recognized efficacious and safe in migraine prevention [1]. A significant proportion of patients undergoing topiramate may show weight loss. We aimed to study whether common clinical determinants may be associated to topiramate weight loss in migraine patients.

Patients and methods Fifty-one patients who met international criteria for migraine prophylaxis were consecutively enrolled. The patients gradually reached the full dosage of 100 mg/day of topiramate in four weeks. Weight was assessed before taking topiramate. Four months after initiating therapy an interview was performed in order to assess: changes in food intake and weight. Body Mass Index (BMI) was calculated.

Results Thirty-seven percent of the patients reported changes in weight with a mean loss of 5.1 kg in four months. No differences between men and women were found. No differences in initial BMI between patients without weight loss (BMI 23.4+/-2.4, 95% CI 22.51–24.32) and patients with weight loss (BMI=25.0+/-4.5, 95% CI 22.75–27.24) were found. No differences were found in terms of TPM associated weight loss, when patients were sub-grouped on the basis of BMI <25 (kg=1.6+/-2.7, 95% CI=0.60–2.61) or BMI>25 (kg=2.3+/-3.1, 95% CI 0.77–3.88), respectively ($p=0.11$). The proportion of patients who presented a favorable response to migraine prevention to TPM was similar to what has been reported in controlled trials.

Conclusions In the present study we showed that 37% of migraine patients under TPM therapy lost weight in four months time. The mean weight loss was similar to what has already been reported in previous studies [2, 3], although the proportion of migraineurs who reported weight loss was lower than the percentage observed in other conditions, including obesity and epilepsy. Conversely, to the findings demonstrated in epileptic individuals, in our migraine patients statistical analyses excluded any relevant correlation between high initial BMI and weight loss, and therefore high BMI could not be considered as a predictor of weight loss under TPM treatment. We also performed further statistical calculations dividing patients according to BMI<25 or BMI>=25: non significant differences were found, further suggesting that a high initial BMI was not a predictor of weight loss. We may argue that different pathogenetic mechanisms between the two diseases may explain the result. The mechanism by which TPM leads to weight loss still needs to be completely understood. It has been hypothesized that

TPM might enhance mitochondria energy metabolism. The present study has some limitations mainly due to the small sample size and to the self-reported assessment of weight changes. Based on our results, we may conclude that unknown genetic and environmental factors may influence the course of weight loss under TPM therapy. Further studies are needed to clarify these issues.

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HEADACHE PREVENTION IN THE COMMUNITY: RESEARCH RESULTS AND FUTURE PERSPECTIVES

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Objectives Previous studies have shown that a cognitive and exercise instruction program reduces the frequency of headache, neck and shoulder pain and drug assumption in a working population [1] and that the benefits remain stable for a considerable time following intervention [2]. This study was aimed at examining the effects of the same program in a very extensive community.

Methods One thousand eight hundred and ninety-six employees of the city of Turin were randomized and distributed into two groups: group 1 ($n=918$) and group 2 ($n=978$). They were given a diary in October 2007 (month 1), in April 2008 (month 7) and in October 2008 (month 13) to record daily frequency and severity of the headache, neck and shoulder pain episodes and drug assumption. At month 2 a program of shoulder, neck and relaxation exercises and instructions of how to reduce muscle hyperfunction was administered to group 1. The instructions were reiterated after 2 and 4 months. At the beginning of month 8 (beginning of the second phase of the study), the same instruction program was administered to group 2 while no further instructions were given to group 1. For each subject, the frequency of headache, cervical pain and drug assumption between months 1, 7 and 13 were calculated, and the mean group frequencies and the differences between groups at months 1, 7, and 13 were statistically compared with Student *t*-test.

Results Mean headache days at months 1, 7, 13 for group 1 were 7.29, 4.98 and 4.79, respectively; for group 2, 7.24, 6.45, and 5.13. Mean days of cervical pain for group 1 were 11.28, 8.06, and 7.46; for group 2, 10.69, 10.13, and 8.13. Mean days of drug assumption for group 1 were 2.95, 2.12, and 1.89; and for group 2, 2.91, 2.53, and 2.00. At month 1 there was no statistically significant difference between the two groups; at month 7 group 1 in respect to group 2 had a significantly lower frequency of headache ($p<.0001$), cervical pain ($p<.0001$) and drug assumption ($p<.05$); at month 3 data remained stable for group 1 and improved for group 2 and no statistically significant difference was present between the groups at this point.

Conclusions The data at hand show that the administration of a cognitive and exercise instruction program can significantly decrease the prevalence of headache, cervical pain and drug

assumption in large population samples and that the benefits may remain stable for a considerable time following intervention.

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Primary headache: chronicity and chronification

CHRONIC MIGRAINE

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The term chronic daily headache (CDH) is usually largely used without a specific codification, and refers to a heterogeneous group of headaches disorders (migraine without aura, tension-type headache, hemicrania continua, new daily persistent headache), which occurs in patients daily or almost daily. Currently CDH is not defined by the 2nd Edition of The International Classification of Headache Disorders (ICHD-II, 2004) [1], which distinctly defines these different types of headache.

Some patients with migraine without aura have a progressive disorder characterized by attacks of increasing frequency, at times leading to headaches more days than not, which was defined by Silberstein et al. in 1994 as transformed migraine (TM). Silberstein's proposed diagnostic criteria were accepted by many authors, although not by ICHD-II, which codified this form as chronic migraine (CM) in the chapter of Complications of migraine. CM is described as a headache which fulfils the diagnostic criteria for migraine without aura, occurs on 15 or more days per month for more than 3 months, in the absence of medication overuse. In 2006 these criteria were revised, by an Ad Hoc Committee, for a broader concept of chronic migraine: at least 15 headache days per month in which at least 8 headache days meet criteria for migraine without aura or respond to migraine specific treatment. The diagnostic criteria of medication-overuse headache (MOH) are described in the chapter of Headache attributed to a substance or its withdrawal.

CDH affects up to 4% to 5% of the general population. The prevalence of CM is not well known, because many studies were performed before the ICHD-II, and because many authors use the terms of CDH, TM and CM despite ICHD-II criteria. In a large population study in the USA the rate of new onset of TM/CM was determined to be 2.5% per year. Although the ICDH-II does not include medication overuse in the definition of CM, this condition is often associated with drug overuse, as well as depression and other psychiatric disorders. Risk factors in transforming episodic migraine into CM were analysed in several studies: the "nonmodifiable" risk factors were age and gender, the "not readily modifiable" were low education, socioeconomic status, and history of head injury. Easily modifiable risk factors resulted in headache frequency, acute medication overuse, depression, stressful life events, sleep disturbances (i.e., snoring and sleep apnoea) and obesity [2]. CM is often refractory and difficult to treat. In a recent study Mathew [3] reviewed the main therapeutic strategies. The non-pharmacologic treatment included physical techniques and behavioural therapy, such as stress management, counselling, relaxation and biofeedback. The pharmacologic therapies were gabapentin,

tizanidina, fluoxetine, amitriptyline, valproate, topiramate, and botulinum toxin type A. Controlled trials evidenced a higher efficacy with topiramate and botulinum toxin type A. Occipital nerve stimulation, vagal nerve stimulation and patent foramen ovale closure are not suggested as treatments at the moment, because clinical trials are in the preliminary stages. If medication overuse is present, the only proven effective treatment is withdrawal of the symptomatic drugs before starting with the prophylaxis.

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TENSION-TYPE HEADACHE

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Tension-type headache (TTH) is the most frequent type of headache in the general population, since more than 80% of individuals experience this kind of headache at least once in their lifetime. Pain is typically bilateral, mild to moderate, pressing or tightening and not worsening with routine physical activity. There is no nausea but photophobia or phonophobia may occur. Patients consider this kind of headache as a bother with which to live occasionally. When headache frequency becomes too high and that bother becomes unbearable, patients ask for medical aid. The International Headache Society has provided a smarting classification of TTH based upon headache frequency to better define its individual and social impact [1]. TTH may be associated with pericranial tenderness so the clinical examination must be completed with manual palpation of pericranial muscles which is a useful guide to treatment strategies. Another clinical feature to be considered is the frequent coexistence of chronic TTH with migraine. In these cases clinicians should educate their patients to distinguish one from the other kind of headache and to treat each episode with specific drugs. Frequent and chronic tension-type headache are often comorbid with psychopathological and psychiatric disorders. An Italian study carried out on patients referring to tertiary headache centres demonstrated that chronic TTH patients have a significant higher prevalence of anxiety, depression and somatoform disorders than migraine patients [2]. The psychiatric comorbidity of TTH is another important factor to be considered in the evaluation of the patient and in the consequent therapeutic choice. In the past years TTH was considered as a psychogenic headache but new advances in the knowledge of this kind of headache enhance the role of biochemical and neurophysiologic factors as pathogenetic mechanisms. Simple analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstays of treatment of episodic tension-type headache. Combination of analgesics or NSAIDs with caffeine have shown to be also more effective but have to be prescribed under medical control to avoid excessive use and abuse. These symptomatic drugs should be assumed also to treat residual episodes during preventive treatment. The tricyclic antidepressant amitriptyline is the drug of choice in the preventive treatment of chronic tension-type headache. Amitriptyline is the most documented and widely used prophylactic drug for chronic tension-type headache (CTTH). Its efficacy in preventing TTH attacks seems to be independent of its antidepressant activity. It is not fully clarified whether the serotonin (5-HT) reuptake inhibition plays a major role

for the analgesic effect of amitriptyline. Also, other antidepressants have proved to be as effective such as amitriptyline in the treatment of CTTH. Central and peripheral myorelaxants like tizanidine are effective, particularly in the cases with pericranial tenderness. Benzodiazepines should be considered especially when anxiety is comorbid. Another drug which has recently been introduced in the treatment of chronic TTH is topiramate. Beneficial effect of botulinum toxin on tension-type headache was reported in open-label studies but further scientifically rigorous clinical studies are lacking. It has been demonstrated that inhibition of nitric oxide is effective in chronic tension-type headache. These interesting data indicate that more specific and effective treatment possibilities will emerge in the future.

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CHRONIC CLUSTER HEADACHE

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Cluster headache (CH), considering the most painful primary headache disorder, is part of the so-called trigeminal autonomic cephalalgias. In the second edition of the International Classification of Headache Disorders (ICHD-II), chronic cluster headache (CCH) is characterized by attacks of strictly unilateral pain lasting from 15 minutes to 3 hours, associated with ipsilateral autonomic signs (e.g. lacrimation, nasal congestion or rhinorrhea), occurring for more than 1 year without remission or with remission lasting less than 1 month (ICHD-II, 3.1.2). CCH may evolve from the episodic subtype or may arise *de novo* in about 10% of the patients. In one study, about one-tenth of patients with episodic cluster headache evolved into the chronic form and this conversion seems to be related to a long duration of the disease and to a late age of onset. However, in about one-third of patients, CCH shifted to episodic cluster headache and the chronic form persisted only in 47% of patients with a disease course >20 years.

The diagnosis of cluster headache is based on an accurate description of headache and associated symptoms and does not usually require laboratory examinations. Differential diagnoses including other primary headaches and the presence of atypical features (persistent or worsening pain, abnormal signs on neurological examination) deserve neuroimaging studies. Also the chronic form of the disorders, for its refractory periods could necessitate more investigation into the differential diagnosis, particularly to detected secondary cases (Tolosa-Hunt syndrome, temporal arteritis sinusitis, occipital arteriovenous malformation, pituitary adenoma, upper cervical meningioma, vertebral artery aneurysm or dissection). The clear aetiology of CH is unknown but the strongest hypothesis suggests a disorder of the central nervous system, involving the hypothalamic-limbic pathway.

Effective acute treatments for cluster headache attacks are injectable or intranasal triptans and oxygen inhalation, whereas for the preventive therapies the choice depends on the episodic or chronic form of the disease. The calcium-channel blockers vera-

pamil remains the main treatment of episodic and chronic cluster headache, while steroids are limited to a very short and intensive course in the episodic form or they can also be given for a short time when chronic cluster attacks become intolerable. Lithium is a valid alternative used in the chronic form, whereas methysergide, valproic acid and other anti-epileptic drugs, have shown some effects in cluster prophylaxis and may be used as a second line therapy. In severe chronic cases, a combination of verapamil, lithium and other drugs may be required, but the potential for toxicity is obviously high.

A small proportion of chronic cluster headache patients, about 1%, are resistant to medical therapy and thus dramatically disabled. Traumatic procedures that interrupted trigeminal sensory or autonomic pathways have been used in these refractory cases without lasting success and with serious complications (permanent neurological deficits or even death).

In recent years, deep brain stimulation of the ventro-posterior hypothalamus, the activated brain area during spontaneous or nitroglycerin induced cluster attacks, has been introduced with encouraging results [1] and criteria for the selection of these patients were proposed. Stimulation is usually well tolerated, however, is not free from risk.

Recently, the occipital-nerve stimulation (ONS), used in the treatment of other headache forms, and considering the success of occipital nerve blockade in cluster headache, has been proposed as a new treatment option for these resistant patients. Results from two recent studies [2, 3] are only partially promising because ONS does not induce definitive long-lasting remission, and data are insufficient for deep brain stimulation to indicate the these procedures are effective.

Chronic cluster headache, and its drug-resistant subform, are disabling disorders and further research on their pathophysiological mechanisms is needed to improve their treatment and management.

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MEDICATION-OVERUSE HEADACHE

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Medication-overuse headaches were first detected in the '80s and since then considerable knowledge has been acquired about them. An important tool for this progress has been the introduction of the classification of the International Headache Society, which has included Medication-Overuse Headache (MOH) among secondary headache forms in the 2nd edition of 2004 [1]. Furthermore, the severity of medication-overuse headaches has decreased over the years, also as a consequence of the new drugs available for acute headache treatment. At the end of the '80s, the most used drugs by patients coming to the Headache Centre of Modena were combinations of caffeine, butalbital, and ergotamine (Cafergot PB); amobarbital, paracetamol, and codeine (Lonarid); caffeine, metamizole, codeine, and chlormezanone (Eblimon); caffeine, propyphenazone, and ethylmorphine (Mindol Merck); caffeine, aminophenazone, and ergotamine (Virdex). All these analgesic combinations con-

tained active principles which could often cause both overuse/abuse, as in the case of barbiturates, and organic damages, as in the case of ergot derivatives. Today it is much rarer to have patients using every day large and toxic quantities of analgesic combinations. The most common case is instead frequent or daily use of therapeutic dosages of triptans [2]. Even if it has been remarked that triptan overuse may increase migraine frequency sooner than other medications [3], in our experience, these drugs are often the only effective ones for acute treatment in chronic migraine patients. The present real cases of overuse concern almost only analgesic combinations still containing barbiturates or the combination of indomethacin, prochlorperazine, and caffeine.

In spite of progress, there are still various sectors to improve and goals to reach. We think that the first one is prevention. In order to fully achieve it, we need first of all more effective and tolerated prophylactic treatments, specific for these patients. The second one is optimal ways of handling the most critical patients suffering from chronic headache, analgesic overuse, comorbidity, and organic complications. There are no guidelines to manage these patients, since studies published in literature are so heterogeneous that they do not allow comparing results and coming to strictly evidence-based conclusions. In this situation, recommendations based on experts' consensus should at least be given, stressing that also minimal goals are important in the treatment of critical patients, such as: reducing the risks of organic damages deriving from analgesic overuse, reducing the frequency of use and/or the quantity overused, and hindering progressive worsening by periodic hospitalization. The intervention of experts could also make hospitalization easier for these patients. The hospitalization of patients with chronic headache and analgesic overuse is often fundamental, but hindered by hospital chief executives, since deriving DRG are not very remunerative. Finally, we must consider the growing attention paid to chronic pain and that people are more conscious of the disability associated to migraine. In this context, the conditions of a large number of patients that we are not able to treat should at least be recognised as disabling.

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PSYCHIATRIC COMORBIDITY IN PATIENTS WITH CHRONIC DAILY HEADACHE AND MIGRAINE

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Studies on the prevalence and impact of psychiatric disorders among headache patients have yielded findings that have clarified the relationship between migraine and major affective disorders, anxiety, illicit drug abuse, nicotine dependence, and suicide attempts. Studies in both clinical and community-based settings have demonstrated an association between migraine and a number of specific psychiatric disorders. In large-scale population based studies, persons with migraine are from 2.2 to 4.0 times more likely to have depression. In longitudinal studies, the evidence supports

a bidirectional relationship between migraine and depression, with each disorder increasing the risk of the other disorder. Although a strong association has been demonstrated consistently for migraine and major depression, especially for migraine with aura, there has been less systematic research on the links between migraine and bipolar disorder. Short-term pharmaceutical care intervention improves the patients' mental health, but it does not significantly change the number and severity of headaches. The increase in self-efficacy and mental health associated with pharmaceutical care may be instrumental in improving the long-term pharmacotherapy of patients with migraine and headache.

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LONG-TERM RESULTS OF A WITHDRAWAL PROTOCOL IN A GROUP OF PATIENTS WITH MEDICATION-OVERUSE HEADACHE (MOH)

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Introduction Medication-overuse headache (MOH) is a growing problem worldwide: its prevalence in the general population is approximately 1–2%, being higher in women. More than 15 days/month with headache, developed or markedly worsened during medication-overuse, associated with regular overuse for more than 3 months of one or more symptomatic drugs, are diagnostic criteria (IHS). Withdrawal programmes are the only treatment for this disorder and a clear restriction of symptomatic drugs intake is the crucial requirement for any kind of preventive treatment. Behavioural treatments have an important role too, because of the implication of many psychological issues (anticipatory fear of pain, intolerance or difficulty dealing with pain, psychiatric comorbidities). The aim of our study was to analyse the outcome of a group of patients enrolled in “The Care Protocol”¹ and to identify risk factors for relapse into overuse.

Methods Fifty-two patients (7 males, 45 females; mean age 47 years) with a diagnosis of probable MOH (p-MOH) according to the revised ICHD-II criteria for this condition, were enrolled. All patients underwent a standard withdrawal protocol for 5 days during Day Hospital hospitalization. At discharge a prophylactic therapy and a symptomatic drug were prescribed. The patients enrolled in the study were observed after 6 months for the evaluation of the efficacy of treatments.

An ad hoc data sheet including personal and family history, psychological evaluation, headache history (number of attacks, headache duration) and the profile of drugs used, comorbidity, was administered. Statistical analysis was performed using the Pearson Chi-Square and ANOVA tests.

Results The mean duration of chronic headache was 79 months and the mean duration of symptomatic drug overuse was 39 months. Forty-one patients (78.8%) returned to the Centre for the follow-up evaluation at 6 months, 21.2% were lost at follow-up. Prophylactic therapy and the prescriptions of symptomatic drugs were correctly followed on average by 60% of patients. MOH diagnosis was still present in 51.3% of patients who were still overusing symptomatic drugs, whereas the remaining subjects had reverted to an episodic headache. No significant associations between the epidemiological and demographic data (sex, age, smoke, qualifications, family unit, job type, feeding, insomnia, snoring, etc.) and the relapse into overuse. Familiarity for headache, overuse of symptomatic drugs,

comorbidities, and the psychological profile were not related to the negative outcome. According to this follow-up study, there is a significant relation between stress at work and the relapse into overuse; another identifiable risk factor is the duration of chronic headache.

Conclusions It has been confirmed in the literature that drug withdrawal is the first therapeutic step and some studies have reported relapse rates of 22–44% during the first year of follow-up. We must improve our strategy of care and the intractable patients should be better studied in the context of a global approach because a little more than half of our patients had failed to improve or had relapsed at 6 months. Non-pharmacological treatments, self-help groups and psychological support should be useful to reduce the risk of relapse and improve the outcome of our therapy.

Nota

¹A course of in-patient therapy and after-care that takes into consideration both the medical and the psychological needs of patients.

CHRONIC DAILY HEADACHE IN CHILDREN AND ADOLESCENTS: A 10-YEAR FOLLOW-UP STUDY

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Introduction Chronic daily headache (CDH) with onset in children and adolescents represents a challenge in diagnosis, etiopathogenesis and therapy. The prevalence of CDH in childhood and adolescence ranges from 0.2 to 0.9% in the general population, rising to 20–30% of all patients referring to third level centres both in adult and paediatric age.

Objective To analyse the clinical evolution of CDH in a ten-year follow-up.

Material and methods In 1998, we enrolled 81 CDH patients (54 F, 27 M; m.a. 11.6, SD=2.58). In 2008, we interviewed 37 (25 F, 12 M; m.a. 21.8, SD=2.96) of them, according to the ICHD-II criteria.

Results We found an overall improvement in 86.5% (32/37), a worsening in 8.1% (3/37), and unchanged in 5.4% (2/37). Sixteen patients were headache-free (43.2%), 8 (21.6%) had frequent episodic tension-type headache, 7 (18.9%) infrequent episodic tension-type headache, 5 (13.5%) chronic tension-type headache, and 1 (2.7%) had migraine without aura. Most of the patients improved or remitted within one-year from the first referral. None of the patients had been diagnosed with medication overuse in 1998 and 2008.

Discussion and conclusions CDH with onset in children and adolescents has an overall good prognosis in the short period following the first visit in third level centres, with a low relapsing rate over a period of ten years. Many factors may explain the good trend over time: from the type of global intervention (medical and psychological) characterising our centre to a better prognosis for chronic headache with onset in childhood than adulthood. Further studies are compelling to look for risk factors of headache chronification and the implementation of the best treatment for these patients. The role of medication overuse needs to be clarified, because of the different role it plays in the young compared to adults.

Headache management: economics and surveillance

DIAGNOSTIC AND THERAPEUTIC APPROPRIATENESS

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Introduction The improvement in people's health education and the necessity for safety, leads patients to greater demands for med-

ical interventions; on the other hand, the National Health Care System needs to save resources in order to reduce health care costs but, at the same time, requests from physicians effective and cost-effective care (appropriateness).

A clinical organizational appropriateness could be obtained through Diagnostic Therapeutic Pathways (D.T.P.) according to guidelines.

Discussion Unfortunately, the guidelines have become a jungle: if we think of the approximately 2400 guidelines of the National Guideline Clearinghouse, produced by 285 various organizations and to these we must also consider those of other scientific organizations.

In Italy, the most diffuse headache guidelines are the Guidelines of the Italian Society for the Study of Headache [1], the ICHD-II classification [2], and the more recent WHO/EHF - AIDS for management of common headache in primary care [3].

Even though there is a vast offer, primary care physicians and specialists do not use these guidelines frequently: the Rand Corporation has found that only in 54.9% of patients do physicians base treatment on guidelines. This problem, in part, is related to the physicians personal opinions.

Physicians, for example, judge the guidelines, as documents based on evidence of efficacy as impersonal, objective and the conclusions are inevitable. The guidelines, in fact, refer to "an unreal patient", and not to that "specific patient" that doctors must, concretely treat in their clinical context, and therefore, may not have an effective value in the single case, even if they are important in estimating the appropriateness and reducing the variability of medical decisions.

According to this vision, the guidelines could reduce professional autonomy and the variety of the professional actions, limiting them to a medium level, instead of an optimal level.

Sometimes, this is a precise criticism: the guidelines produced by the European Headache Federation (EHF) and the World Health Organization (WHO) (AIDS for management of common headache in primary care), to help primary care physicians, recommend stepped-management for acute migraine (step-1: analgesic-drugs, step-2: triptans) to get the most effective and cost-effective individualised care. There are, instead, other evidence-based strategies (stratified-care) which, in patients with high disability, prefer triptans to get better treatment results.

The EHF/WHO guidelines seem to limit the choices of the professional and the quality of the treatment.

Another diffuse opinion, is that the guidelines, often, are not instruments which really can be used by the physician, who must decide which are the best examinations/tests and treatments for the patient. Others think that the guidelines reflect only the opinion of the expert who, also, could be conditioned by personal interest. Such negative opinions are diffuse between the Italian physicians, according to the results of a study of the CeVEAS.

Against the acceptance of these guidelines, is the worry of their eventual legal applications. A negative role is also played by jurisprudence, in fact, even if there is no specific law that considers it a duty to faithfully and dogmatically apply these guidelines, it requests that the physician be able to adjust his/her decisions, according to the best scientific evidence and the patient's interest. Thus, when a physician does not follow the indications of the guidelines, he/she must be able to justify his/her choices.

A question arises: should the ability to adjust one's decision according to the guidelines be the same for all physicians? For example, should the family physician be able to diagnose headaches according to the ICHD-II criteria at all levels (levels: 1 to 4)?

The ICHD-II classification states that the family physician should be able to diagnose to levels 1–2: but in this case, according to the law and to the appropriateness, is this ability sufficient?

Conclusions The guidelines because of these problems are gradually being used as a starting-point for the realization of local documents prepared with the health care professionals who will have to apply them: D.T.P. of the local network of specialists, family physicians and pediatricians of the single hospitals, etc. We hope that, finally, an effectively useful document for clinical practice will reach the physician.

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THE COSTS OF HEADACHE DISORDERS

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In a world of limited resources for healthcare services and health related research, documentation of the impact of different diseases, both on the individual and on society, is crucial for a rational distribution of means. As recently evidenced [1], migraine costs the European society €27 billion per year. No precise data could be given for other headache types due to insufficient studies, but it has been suggested that the cost is at least equal to that of migraine. Therefore, headache disorders, as well as dementia or stroke, could cost the European society more than €50 billion per year. Worldwide, on average, migraine affects 14% and chronic daily headache 4% of the population, also predominantly involving young women during their peak years of productivity and vitality. In recent years several attempts have been launched to raise the awareness that headache entails widespread suffering and loss of opportunities for patients and their families [2], such as the Global Campaign against Headache disorders, “Lifting the Burden”, promoted in 2004 jointly by the World Health Organization (WHO), the International Headache Society (IHS), the World Headache Alliance and the European Headache Federation [3]. Severe migraine is considered by the WHO as among the most disabling illnesses, comparable to dementia, quadriplegia and active psychosis, and it has been included in the top 20 causes of disability worldwide (World Health Report, 2001). Nonetheless, funding of headache research is extremely low, in particular from public agencies, where migraine is the least publicly funded among all the neurological diseases, i.e., 0.025% [1]. No public or private funding was identified for non-migraine headaches [1]. Moreover, funding for anxiety and mood disorders, the two most comorbidities of migraine, are very similar to that of migraine [1] with a cumulative effect in reducing the possibilities of research development. This neglect for headache disorders is widespread, being present in Italy, but with some differences, also in the other European countries and in the USA [1]. Besides the need of increasing research funding, a big problem still remains in the underdiagnosis of primary headaches, even though it is often a clinical diagnosis, without the necessity of instrumental exams, and it is well classifiable with the international criteria formulated by IHS. This lack of correct and early diagnosis causes a consequent poor management and general malpractice with an increase in costs. In particular, for migraine, despite the evidence of efficacy and use-

fulness in reducing costs, it is well known that a low percentage of triptans are administered for acute attacks (about 5%), there is a low and delayed introduction of prophylactic therapies (12%), and an underdiagnosis and treatment of conditions in comorbidity with migraine, e.g. anxiety, mood disorders or dysfunction of the cervical spine. The complications of migraine, e.g. pharmacological abuse, chronification of headache or admission to the Emergency Department, represent the principal part of this burden, that better management can reduce. Making patients and especially general practitioners (GPs) more aware of these disorders, with continued education about diagnoses and treatments, is fundamental in achieving a better management, because GPs are the physicians who first and foremost see the patients. The headache centres should be connected with GPs and also try to have a multidisciplinary approach, because headache disorders have several comorbidities that increase their disability. In conclusion, only a more appropriate distribution of public funding and a better utilization of available resources could improve the management of headache sufferers and finally conduce to less disability.

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BIOLOGICAL COSTS OF PHARMACOLOGIC AND NON-PHARMACOLOGIC TREATMENTS

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Traditionally the study of the management of disease from an economic point of view considers direct costs, related to medical care, and indirect costs, related to absenteeism (lost workdays) and presenteeism (lost productivity) in the workplace.

Little attention has been paid to the so-called “intangible costs” which by their nature are non-monetary, elude quantifying and therefore have been omitted from many pharmacoeconomic studies. Intangible costs include the patient's pain, suffering, depression, anxiety, loss of sleep, and fatigue as well as the family's and/or caregiver's distress.

Furthermore for many non-employed individuals (housewives, elderly, school-children...) the indirect economic burden of illness cannot be measured in terms of lost wages or lost workdays.

Using a terminology mediated from biological science, intangible costs can be considered a function of “biological costs”, that is, the costs that headache imposes on the fitness of patients.

Biological costs are inversely proportional to the choice of adequate treatments and adequate therapeutic strategies for the management of headache: the more correct the choice the less burdensome the costs.

Approaches to prevention include education, lifestyle modification, as well as acute medications to address the immediate need for relief during an attack and preventive medications to reduce frequency, intensity, and duration of the attacks.

Unfortunately, in the busy daily clinical practice, non-pharmacological approaches are frequently neglected thus missing those inexpensive strategies that could minimize headache-related disability, improve health-related quality of life, and avoid headache escalation and medication misuse.

Symptomatic medication misuse and overuse may entail side effects (chronic kidney failure for combination analgesics, gastrointestinal ulcers for NSAIDs, or ergotism) that persist also after the discontinuation, or the development of chronic daily headache. The establishment of preventive therapy requires that clinicians and patients work together to develop a treatment plan based on the needs and preferences of the patient. The choice of preventive therapy should be customized for each patient, paying attention to or not to the comorbidities etiological links (e.g. depression) in order to identify “the best possible” treatment to avoid not only unwanted side effects and drug interactions but also the failure of the treatment which in turn will increase the patient’s lack of self-confidence and becomes the gateway to self-medication and drug overuse.

Also the identification of a correct therapeutic strategy has a pivotal role in the management of headache. Clinical approaches to the patient with migraine include step care, whereby all patients begin on a simple or nonspecific treatment, stepping up to the next level of therapy if treatment is unsuccessful; or stratified care, whereby first-line therapy is tailored to the severity of the patient’s pattern of headache. Studies have demonstrated that for most disabled headache patients, the stratified-care approach results in a more robust headache response with less disability and greater cost-effectiveness than step care avoiding that a lot of people leave therapy (*lapsed consulters*).

While cost alone should not be the determining factor in medical care, the current healthcare environment demands attention to economic issues. In a world of limited resources for healthcare services and health related research, reliable data on the individual and societal impact of different disorders are crucial for a rational distribution of means.

There is a need for up-to-date and comprehensive population-based studies to evaluate from a different perspective the burden of headaches thus considering the biological costs, which are the costs that the patient bears on him or her self, as the most important determinant of the socio-economic impact of the disease.

GENERIC DRUGS AND BIO-AVAILABILITY

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At a time in which health spending is being reduced, the Regions are incentivating the prescription of generic drugs. In this regard, two important issues need to be kept in mind.

The first issue is research spending. In Italy a large part of pharmaceutical research is conducted by multinational or Italian companies. This considerably reduces costs for the Italian National Health Service in the drug research field. This opportunity is possible thanks to a “drug patent”, which, until recently, lasted 20 years. This time period was barely long enough for the drug Company owning the patent to recuperate the costs of the research carried out. The new laws have reduced this period to 10 years, which can in some cases be extended to 15 years, introducing at the same time the use of generic drugs, copies of tested branded drugs whose patent has expired, in order to cut health spending.

The second issue concerns the bio-equivalence of the generic drugs. A drug is considered equivalent if its bio-availability falls within a range of $\pm 20\%$ compared with the equivalent branded drug. This means that if one first administers a generic drug whose bio-availability is $+20\%$ and then one administers another generic drug whose bio-availability is -20% , the difference in bio-availability between these two drugs would be 40% , which is a significant difference especially for some neurological drugs. This new laws should therefore be reviewed in the light of these considerations.

PRIMARY CARE PHYSICIAN CONSULTATIONS FOR HEADACHE IN THE REGION OF CALABRIA: MIGRAINE CARE SCHEME

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Introduction The basic tenet of clinical practice guidelines is systematically to combine scientific evidence and clinical judgement to produce clinically valid operational recommendations for appropriate care. These can then be used to persuade clinicians, patients, and others to change their practices in ways that will lead to better healthcare outcomes and lower healthcare costs. The concept of clinical practice guidelines has often been met with enthusiasm. This has stimulated cross-fertilization of ideas between medical specialties, which prevents the process from being dominated by groups with narrow interests. Domination by one group can result in conflicting guidelines that are not always suitable for use in primary care. Reduced physician autonomy and primary physicians concerned with cost-containment are other problems. If clinical practice guidelines are not evidence based or validated, they could lead to ineffective or even inappropriate recommendations.

Materials and methods The study explores the awareness of technical terms used in EBM and manner of treating patients with migraine among a random of 500 general practitioners. A mailed questionnaire included questions on GPs’ demographic and practice characteristics; awareness of EBM; sources of information about migraine and EBM; and patient’s treatment behaviour.

Results Only 27.2% of GPs agreed that clinical trials are needed to evaluate the efficacy of treatments and this awareness was higher in those who learned about migraine from scientific journals or continuing education courses and who attended a course on EBM. For two-thirds of GPs, disability is equivalent to illness diagnosis, and this behaviour was more prevalent in those who agreed that clinical trials are needed to evaluate the efficacy of preventive or curative treatments of migraine and that the clinical approach to migraine required an evaluation of clinical effectiveness. Most GPs (93.15%) felt that it is important to integrate clinical practice with the best evidence available. This behaviour was more frequent in those who agreed that the clinical approach to migraine requires a clinical effectiveness evaluation and that clinical trials are needed to evaluate the efficacy of migraine treatments and in those who attended EBM courses. However, this is in contrast with the result that when scientific evidence indicates that a current treatment is less efficacious or more expensive than the new treatment, respectively, only 145 GPs (3.1%) would modify the treatment.

Discussion Despite an overall positive attitude toward evidence-based diagnosis, the GPs participating in this study were not aware that guidelines were the most favoured approach for moving from opinion-based medicine to EBM. Less than half of the GPs (46.7%) modify the treatment when and if new scientific evidence indicates that it is less efficacious than the new one. Education alone may not be enough, monitoring physician behaviour against practice guidelines may be an answer.

ECONOMIC IMPACT OF EMERGENCY DEPARTMENT HEADACHE: A STUDY ON COSTS OF LOST PRODUCTIVITY

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Background Headache is one of the most common chief complaints in the Emergency Department (ED) accounting for 0.8–4.5% of all admissions. Migraine is often underdiagnosed in the ED setting, rarely referred to a Headache Centre, and represents a major cause of lost work-time and reduced work efficiency.

Objective To determine loss of productivity in employees with migraine referring to the ED.

Methods A six-month prospective study of all consecutive patients referring to the ED for headache and afterwards evaluated in the Acute Headache Centre (AHC) of the University of Trieste was performed. Patients with a diagnosis of migraine (IHS criteria) were enrolled. Unemployed and self-employed workers were excluded. Demographic and clinical characteristics, missed work-days (MW) and workdays with reduced production capacity (RPCW) over the preceding three months (MIDAS scale), the daily costs of migraine-related absenteeism and pre-absenteeism quantified by mean daily wage of each professional employee (National Statistical Institute wage data) were analyzed with SPSS 13.0. Patients were treated in the AHC with a proper therapy and a three-month follow-up visit was planned.

Results Out of a total of 144 patients admitted in the AHC, 69 patients were enrolled, 58 F (84.1%) and 11 M (15.9%), mean age 38 ± 8 years. The diagnosis after AHC evaluation was migraine without aura (MO) in 42 patients (60.9%), migraine with aura (MA) in 4 patients (5.8%), MO plus MA in 15 patients (21.7%), and MA plus tension-type headache in 8 patients (11.6%). The total number of MW and RPCW over the preceding three months were 404 (mean 5 days/person) and 658 (mean 9 days/person), respectively. The total wage loss estimated per year due to migraine-related absenteeism and pre-absenteeism was € 346,211,28. We evaluated 24 patients (34.8%) at three-month follow-up visit and a reduction of 68.2% of MW and 43.4% of RPCW was found. The wage savings estimated per year due to the specific treatment administered in the AHC was € 210,720,67.

Conclusions Wage losses in employees with migraine referring to the ED are elevated. An Acute Headache Centre dedicated to the ED headache is effective in reducing the social and economic costs in terms of loss of productivity caused by migraine.

Management of primary headache and related disorders in childhood and adolescence

GUIDELINES AND NEW PHARMACOLOGICAL AGENTS

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Acute pharmacological treatments represent the mainstay of migraine management. The goal of this strategy is to abort quickly all the headache symptoms with return to normal activity and without relapse. All migraineurs usually require an acute treatment regimen and can benefit with adjustments of lifestyle habits, including sleep regulation, diet modifications, regular physical exercise, stress management and relaxation exercises.

Once all these measures have been addressed, but headache still occurs more than three times per month and is still disabling after abortive medication, then preventive therapy could be considered with the goal of minimizing the impact of the headache by reducing the number of attacks.

Until some years ago, the treatment of migraine in childhood and adolescence was based on few randomized and placebo controlled trials. According to the literature, only acetaminophen (15 mg/Kg) or

ibuprofen (7.5–10 mg/Kg) - for children under 12 years, and sumatriptan nasal spray (10–20 mg) - for adolescents, as acute therapy, and flunarizine (5 mg/day) as prophylactic treatment were effective in childhood and adolescence migraine [1]. Besides being effective, these drugs are safe in the paediatric population, therefore these substances are the only ones recommended as first-line drugs for the acute and prevention treatment of juvenile migraine in relevant reviews and guidelines [1–3].

A recent review reported conflicting results regarding the efficacy of propranolol, no clinical improvement with nimodipine, clonidine, L-5HTP, trazodone and papaverine, and insufficient data for timolol, pizotifen and magnesium oxide [2].

Many possible explanations of the differences in therapeutic response between adult and paediatric migraines have been proposed. A main factor responsible for the inefficacy of drugs in both acute and prophylactic migraine treatment trials is the higher placebo-responders rate in paediatric studies. Moreover, in the new criteria of the ICHD-II 2004, the duration of migraine attacks in children is briefer (i.e., 1 to 72 hours).

In recent years encouraging data in children and adolescents regarding either acute treatment with oral triptans (such as rizatriptan, zolmitriptan, almotriptan) and zolmitriptan in the nasal spray form or preventive therapy with antiepileptic drugs (such as topiramate, sodium divalproate and levetiracetam) have been reported, reducing the need to extrapolate this information from studies in the adult population.

Efforts are needed to develop protocol studies designed for symptomatic and prophylactic therapy of migraine in children and adolescents, using high-quality research, standardized criteria for the diagnosis and response to treatment and new outcome measures (i.e., quality of life and satisfaction of child or parents) [3].

In this review, general principles for the management of migraine in children and adolescents are examined and guidelines for the use of selected drugs for acute and prevention treatment are reviewed. The therapeutic options of juvenile migraine, including a combinations of biobehavioural interventions and specific drugs for the acute and prevention treatment are discussed on the basis of the foremost reviews and guidelines.

New data about the acute treatment of juvenile migraine (such as the recent approval for use of almotriptan in adolescents by the Food and Drug Administration), and encouraging results on preventive strategies are emerging.

In conclusion the overall management of the juvenile migraineurs should take into account the comorbid conditions and must be individually tailored.

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NON-DRUG TREATMENT IN CHILDREN AND ADOLESCENTS

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Taking a careful history in a patient presenting with headache is the prerequisite for further diagnostic and therapeutic manage-

ment. The family history, the patient's previous history, and the psychosocial, environmental and emotional context (e.g. family, housing conditions, school, leisure activities and peer relationships) should be assessed as the first step of a complete therapy planning. Non-drug treatment begins with exploring factors precipitating, exacerbating or alleviating the headache. The patient and the parents should be informed of the nature of the headache and advised to maintain a sound rhythm in daily life, which includes regular meals, sufficient physical exercise and sleep. An appropriate treatment requires an individually tailored strategy giving due consideration to both non-pharmacologic and pharmacologic measures in the context of the degree of disability and/or by the possible comorbidities (e.g. psychiatric). There is very good evidence that psychological treatments, principally relaxation and cognitive behavioural therapy, are effective in reducing the severity and frequency of chronic headache in children and adolescents [1].

In a recent systematic review, Damen et al. (2005) [2] selected controlled trials reporting the effects of non-pharmacological prophylactic treatments in children with migraine. The analysis of the results showed that relaxation, relaxation + biofeedback, relaxation + biofeedback + cognitive behavioural treatment were more effective compared with waiting list controls. The authors concluded that a few non-pharmacological treatments such as relaxation may be effective as prophylactic treatment for migraine in children. Nevertheless, they also suggested that, because of the small number of studies and the methodological shortcomings, conclusions on effectiveness have to be drawn with caution.

Starting from the consideration that children and adolescents with headache show greater indices of psychopathology and show higher risk of developing psychological disorders in adulthood than healthy controls, different psychotherapeutic approaches are sometimes provided in clinical practice. Relaxation and cognitive-behavioural techniques have been found to reduce the intensity and frequency of headache in children and adolescents.

Similar conclusions are still lacking in relation to psychodynamic psychotherapy. We think that rigorous studies, conducted in accordance with the principles of evidence-based medicine, should be performed also in this field.

The parents of headache children often do not consult their physician, but have recourse directly to alternative therapies (e.g. acupuncture, chiropractic manipulation, homeopathy, phytotherapy) which are frequently more economical, seem safer, and whose practitioners often adopt a holistic approach to the care of the patient. However, the scientific proof of their effectiveness is often lacking or obtained in small cohort studies, sometimes no placebo controlled studies. This is a key point: the role of placebo needs to be clarified when we deal with headache patients in children and adults as well. The topic is very critical, because of the risk of considering efficacious every kind of treatment, so high is the placebo response in children and adolescents. In synthesis, we conclude that evidence exists of the efficacy of psychological treatments in children and adolescents and success can at least be maintained for up to one year, but shows a trend towards a further increased improvement [3].

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SLEEP BREATHING DISORDERS IN CHILDHOOD HEADACHE

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Introduction Sleep breathing disorders (SBD) are a spectrum of disorders ranging in severity from primary snoring to obstructive sleep apnea syndrome, they are as frequent in children as headache. Few studies have pinpointed the relationship between sleep disorders and headache in childhood and have shown a higher frequency of sleep disturbances (i.e., sleep quality, night awakening) and daytime sleepiness in children with headache than controls. Aim of this study was to assess the prevalence of SBD in headache in the children sample.

Materials and methods Forty-seven school-aged children (21 F), consecutively referred for headache to the Centre for Headache in Childhood of the Second University of Naples and 52 healthy children (23 F), performed an overnight polysomnography (PSG).

According to international criteria, apnea was defined as complete cessation of airflow lasting 10s or more; hypopnea was defined as either a >50% reduction in airflow for 10s or more or less than 50% but discernible reduction in airflow accompanied either by a decrease in oxyhemoglobin saturation of >3% or an arousal.

Apnea-Hypopnea Index (AHI) was used to evaluate the severity of SDB and we selected three categories: minimum ($1 \leq \text{AHI} \leq 3$), moderate ($3 \leq \text{AHI} \leq 5$) and severe ($\text{AHI} \geq 5$). In our study we considered only moderate and severe SDB ($\text{AHI} \geq 3$). Chi-Square test was performed to verify the different prevalence of SBD in both groups.

Results Headache frequency distribution was as follows: 82.97% MO, 2.12% MA, and 14.89% TTH. The groups were matched for age and sex distribution. SBD ($\text{AHI} \geq 3$) was found in 33 headache children (70.21%) and 2 healthy children (3.84%) (Chi-Square 44.716, $p < 0.001$).

Discussion It is well known that a strong relationship between headache and sleep disorders exists, but there is no evidence of correlation between headache and SBD moderate-severe grade. Our study suggests to improve diagnostic quality and efficiency in clinical practice of headache encouraging the sleep breathing recognition in childhood headache.

Conclusions SDB are more prevalent in headache children than in the control group.

ANALYSIS OF COMORBIDITY BETWEEN HEADACHE AND EPILEPSY IN A PAEDIATRIC HEADACHE CENTRE

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Introduction The primary headaches (PH), in particular migraine (M) and tension-type headache (TTH), are frequent disorders in paediatric age. Currently, it is considered that M occurs in individuals with an hereditary vulnerability and an hyperexcitable cerebral cortex. Several epidemiological studies suggest a non-random association between M and epilepsy, but this relationship is not completely understood. The answer may lie in the disorder of membrane channels or channelopathies.

Objective To analyse the relationship between PH (in particular M) and asymptomatic epilepsy in children.

Materials and methods This is a retrospective study of 1,795 cases diagnosed at the Headache Centre of the Department of Paediatrics of Padua between 1995 and 2008; cases having the following inclu-

sion criteria were selected: a) diagnosis of primary headache (ICHD-II 2004), and b) diagnosis of idiopathic or cryptogenic epilepsy (ILAE 1981). A longitudinal follow-up was undertaken in 2008.

Results Comorbidity between headache and epilepsy was found in 56 subjects (20 males, 36 females; mean age at PH onset 8.6 years). Migraine (82%) was more frequent than TTH (18%) and the risk of M was 4.5% more frequent than TTH. The prevalence of epilepsy was 3.1% and prevailed in M (5.4%) than in the TTH (1.8%) group. The ratio between migraine with aura (MA) and migraine without aura (MO) was 1:5.6.

Considering the diagnosis of epilepsy, we found that partial epilepsies (77%) and cryptogenic epilepsies (57%) prevailed in patients with comorbidity. In migraineurs with cryptogenic partial epilepsy (CPE), temporo-occipital lobes were more frequently affected than frontal lobes, differently from TTH subjects in whom frontal cryptogenic epilepsy prevailed. In migraineurs, rolandic benign epilepsy was more frequent than occipital idiopathic epilepsy. A family history for epilepsy was reported by 39% of our probands.

Discussion Our data show a strong association between asymptomatic epilepsy and migraine, mainly MA, in children. There was a statistically significant association between M and temporo-occipital cryptogenic epilepsies differently from TTH, and in migraineurs rolandic benign epilepsy prevailed between idiopathic epilepsies. Our data support an association between migraine and different epileptic syndromes; it is likely that behind this association there are multiple genetic predisposing factors common to both disorders.

The study of comorbidity between M and epilepsy, by selecting a more homogenous population both from the clinical and genetic point of view, could contribute to understanding the pathogenetic mechanisms of both disorders.

THE PREVALENCE OF RED EAR SYNDROME IN JUVENILE PRIMARY HEADACHES

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Introduction In the Red Ear Syndrome (RES), first described by Lance, there are recurrent attacks of unilateral ear discomfort or burning pain associated to erythema of the ipsilateral ear. Since that description, approximately 59 patients have been described in the literature associated to primary headaches or to secondary pathologies. The possible association with primary headache disorders characterized by the activation of cranial autonomic pathways suggested a similar underlying pathogenesis.

We were the first to describe a link between RES and paediatric migraine, where RES might be a specific feature of the clinic phenotype in migraine. For this reason in preliminary data we showed that the RES was not a rare symptom, in a similar manner as other symptoms like allodynia or osmophobia that are actually considered important features of migraine episodes in children and adults.

Objective To determine the frequency, the sensibility/specificity and the possible association with other clinical migrainous features of clinical Red Ear Syndrome in a young population visited in our Centre for Diagnosis and Treatment of Headache in Youth.

Methods Medical records of the children admitted for headache between 1st December 2004 and 30st November 2005, were consecutively studied. A semi-structured interview based on the main features of headache attacks was always administered by the same two doctors. General and neurological examinations were carried out on all the children. A short supplementary questionnaire aimed at finding out the prevalence and some characteristics of RES (presence of red ear syndrome, localization, duration and relation to the

migraine attacks) was utilized. The children, affected by headache, were classified according to the IHS criteria (2004).

Results We visited 226 children (115 males, 111 females) with headache in our Headache Centre in the study period. The age range was 6–18 years, the mean age was ten years. According to the IHS criteria, we classified migraine in 172 children (76.5%), and other primary headaches (primary stabbing headache, episodic and chronic tension-type headache) in 54 children (23.5%). The prevalence of RES was found in 42 headache cases (18.5%). It occurred in 40 (23%) migrainous children and in only two cases (3.6%), respectively in the other headache group. The RES in migrainous cases was bilateral in about 70% and unilateral in 20%, the duration was usually about 30–120 minutes and in 20% of the subjects the red ear started before the onset of the painful attack. The discomfort was often defined moderate or sometimes severe (the mothers applied a cold pack to the children's ears). RES resulted as a symptom with poor sensitivity but high specificity. The migraine group with RES had a significantly higher rate of males, phonophobia, vomiting and pulsating pain.

Discussion To our knowledge this is the first study that observed the RES in a large population of primary paediatric headaches. Our study showed that RES is not infrequent in migraine, reporting a similar prevalence as reported for osmophobia and allodynia in paediatric migraine. It may be a useful clinical marker in the diagnosis of paediatric migraine, and also in affected children and can probably help to distinguish different migraineur subgroups. It is not possible to suggest an univocal physiopathological explanation for RES (an antidromic local assonal reflex with the release of vasodilator peptides or trigeminovascular activation has been considered regarding the RES associated to migraine). However, our data suggest a role of brainstem structures to provoke RES in migraine.

Lectures

“Alessandro Agnoli” Lecture

INNOCENT PAIN

THE EXPERIENCE OF PAIN IN METAPHYSICS, PHE- NOMENOLOGY AND NEUROPHILOSOPHY

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The concept of “innocent pain” was introduced into the metaphysical sphere to explore the mystery of the “evil” in the world, whereas in the sphere of the neurosciences, it refers to idiopathic pain experiences. In migraine, as in other primary, non-symptomatic cephalalgias (such as tension-type headache, cluster headache/TACs and other central pain syndromes), we are confronted with cephalic or systemic pain spectrum syndromes in which the relationship (causal) between the “disease” and the aetiological agent is not immediately identifiable, in such a way that the pain apparently occurs “without a reason” (*sine causa*).

After a short historical excursus on the ontology of pain as mankind's destiny (a biblical view) or as a (post-Renaissance) idea of pain as an individual, “medical” problem, the meaning of pain is considered from an evolutionary perspective as a communicational interface between the internal (*milieu interieur*) and external environment (*habitat*).

Pain is a complex phenomenon which, having many categories of attributes, demands distinct levels of psycho-biological research. As an original biological phenomenon, pain is present at all levels of the evolutionary scale, but there is nevertheless something in Man's way of experiencing pain that is not found in animals. In particular, in the

long-term memory circuits of the human brain, pain becomes an “existential” experience, a question on the meaning of suffering (why did it happen to me?). Cases observed in psychiatric clinical practice, in particular, fall into this context, and range from the extremely broad field of psychalgia, panalgia, somatoform disturbances, chronic strain and delusional headache to the “pain of the soul”, which includes angst. This reference to angst leads us on to the concept of pain as a symptom of distress that is not provoked by an injured body part, but rather linked directly to a wounded whole. After all, physical pain, separated from its emotional dimension, loses its specifically human quality (this is the thinking behind leucotomy, yoga, transcendental meditation, and other Oriental techniques).

Looking at the phenomenological, neurophysiological and neuroanatomical bases of pain, we must focus, in particular, on issues linking the two main aspects of the origin of “pain consciousness”: the sensory and “evaluative” aspects, the stimulus and its contextualisation. Like, for example, a symphony, a scent, or a colour (all phenomena that belong to the “subjective” sphere, and which no physical instrument could ever record or consciously hear, see or smell), pain is today considered and studied as a *qualia* of consciousness – in the sense, of course, of phenomena belonging to Gerald M. Edelman’s “**Second Nature**”.

After these general considerations, the lecture will deal with the following topics:

- *Pain, time, space.* As well as external and/or internal stimuli (triggers), there also exist “mental stimuli”, evoked by memory. The pain of memory is not only the painful recollection of an event often forgotten, removed (and thus, for the consciousness, *sine causa*); it is also nostalgia, the pain that is caused by the simple passing of time, by the impossibility of going back (*nostos*), of reuniting, and which can also express itself in a spatial sense (pain projected outside the body, into extra-personal, even remote, distal spaces).

- *Pain as a metaphor.* This section deals with symptoms considered the effects of a “conversion phenomenon”, that is, symptoms reflecting a physical response to moral or mental distress.

In this context, the body and parts of the body are thought to function as “organs of memory” expressing, in the language of pain, a traumatic memory. Recollection is, by nature, a “synthesising” experience and single acts of recollection constitute an ongoing existence-reinforcing process. Every memory, even the most innocent, contains a small element of suffering, distance and loss. In every act of recollection, the living system becomes a whole, even though it is having to acknowledge the renunciation of something that time has taken away. This is the pain we call “melancholy”.

- *Chaos and migraine.* The problems that arise when studying complex diseases like migraine and central pain phenomena (wherein the concept of *sine causa* is actually related more to the intervention of fractalic, non-linear causality) are probably best explored through recourse to new, more sophisticated instruments of investigation, such as the theory of chaotic systems and fuzzy logic. In this new context, the meaning of pain alters and becomes part of a more complicated framework of exchanges: interactions between organisms that belong to the natural (physical) world and a series of factors relating to social and cultural models; habits, environment (geophysical) and lifestyle; epigenetic transmissibility (archetypal continuity), plasticity phenomena and new, more advanced hierarchies of values and behaviours. Even though pain is, essentially, a “signal”, it has been studied very little from the perspective of the “theory of signals” (now part of the theory of chaotic systems). And the physics of chaos starts from the assumption that the more complex a system is, the less it can be understood using causalism-based approaches.

Although there is still not enough material to allow the construction of a “general theory of central pain”, there exists evidence that the genesis of migraine may derive in part from deficiencies of coher-

ence between synchronised neural subsystems. In particular, we can hypothesise a loss of coherence between the mesencephalic network, which is responsible for the integration of cortical sensory inputs (lights, smells, sounds, expectations, etc.), and inhibitory control filters, which, through **habituation** processes, are responsible for reducing, adequately and in a synchronous manner, the overload of environmental stimuli. The migraine attack is associated with a behavioural response whose effect is to reduce the level of sensory inputs; this leads to a reduction of the work of the sensory integration system, and in turn to resolution of the migraine attack.

Conclusions In order to rise to the challenge presented by the concept of innocent pain, the neurosciences must be open to the indeterministic view of nature that has already been formulated scientifically in the sphere of contemporary physics. Taking as our starting point the moral (theological) concept of innocent pain, we have come to believe that at the “heart” of nature, there are very probably a great many more “innocent, chaotic free processes” at work than deterministic, Newtonian science has thus far led us to believe.

“Federigo Sicuteri” Lecture

CALCITONIN GENE-RELATED PEPTIDE: FROM MOLECULE TO MIGRAINE THERAPY

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Background Calcitonin gene-related peptide (CGRP) is expressed throughout the central and peripheral nervous systems, consistent with control of vasodilatation, nociception, motor function, secretion, and olfaction. CGRP is prominently localized in primary afferent C and A fibres of spinal and trigeminal ganglia, verified by selective antidromic tracing.

Purpose We have shown that the activation of the trigeminovascular pathway results in the release of CGRP both in animal and man. The trigeminal nerve activation results in antidromic release of CGRP, acting via the CGRP receptor, which is located both in intracranial vessels and in the trigeminal nuclear complex in the brain stem. CGRP receptors are localized in the vascular smooth muscle cells, both in meningeal and cerebral arteries; antagonists that reduce signalling in the trigeminovascular pathway putatively act at multiple sites inside the blood-brain barrier. Here we will discuss recent developments in our understanding of the role of CGRP and its receptor in the cranial circulation related to migraine. A central question is “where do the new CGRP antagonists act?” [1]. The recent development in therapy is the specific CGRP receptor blockers olcegepant and telcagepant; these have added important information on the role of CGRP in migraine as well as indicating the site of antimigraine target. Other ways of interacting with CGRP mechanisms have appeared; limiting the availability of CGRP in the circulation with a specific CGRP antibody or a CGRP-binding RNA-Spiegelmer. Either way reduces neurogenic inflammation and attenuates signaling within the trigeminovascular pathway, however, they are limited in effect by the blood-brain barrier. Specific CGRP receptor blockade has been shown to reduce the effect of released CGRP and to abort acute migraine attacks [2].

Conclusions Although the triptans produce relief for many people, a substantial number of affected individuals are unsuited due to cardiovascular co-morbidity or simply not responding to these compounds. The new class of antimigraine drugs may provide some hope of relief.

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BRAIN CONSEQUENCES OF CHRONIFIED MIGRAINE: A 9-YEAR MRI FOLLOW-UP STUDY IN MIGRAINEURS FROM THE DUTCH GENERAL POPULATION

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Background We previously reported that migraineurs from the general population are at increased risk of cerebellar infarcts and white matter hyperintensities (WML) (CAMERA-I study). A higher risk in those with higher attack frequency suggested a causal relationship. In order to establish a causal relationship, progression of both the number of patients with lesions and the amount of lesion load per patient need to be confirmed in a follow up study.

Methods All participants (n=435) of the initial population-based CAMERA-I were re-invited 9-years later for re-scanning of the brain using the same MRI systems (1.0T and 1.5T) and protocol including thin slice (3mm) T2 and FLAIR pulse sequences. Brain infarcts are independently rated by two neuroradiologists, who are blinded for diagnosis, to assess presence and/or progression of infarcts in follow-up vs baseline MRI-scans. In case of discrepancies, a consensus is reached. 3D-WML-volume is independently quantified in both baseline and follow-up scans, using validated software. Progression of lesions will be correlated to migraine-diagnosis and migraine-characteristics, controlling for cardiovascular risk factors, and correlated to cognitive and cerebellar function.

Results Of the 435 baseline-participants, n=324 (74%) could be recruited for this follow-up study (127 migraineurs with aura; 102 without aura, 95 controls). All underwent a structured interview and extensive cerebellar function testing, n=285 (66%) had a brain MRI, n=283 cognitive testing, and 285 physical/neurological examination. Longitudinal MRI comparison was completed in June 2009.

Discussion This population-based MRI follow-up study will clarify the relationship between migraine and brain lesions and whether these lesions also have functional consequences.

Premio Franco Michele Puca 2007

AN ACUTE REDUCTION OF THE ENDOCANNABINOID-HYDROLASE FAAH IS COUPLED WITH AN IMPROVEMENT OF THE FACILITATION OF THE PAIN PROCESSING AT SPINAL LEVEL IN MEDICATION-OVERUSE HEADACHE

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Objectives Our study was aimed to investigate: 1) a possible relationship between the functional activity of the endocannabinoid system (ES) and the facilitation of pain processing in migraine patients with medication-overuse headache (MOH); and 2) the effect of the withdrawal treatment (WT) on both the ES metabolism and the pain processing.

Background The ES has been demonstrated to play a role in the antinociception also by the prevention of the central sensitization processes of nociceptive pathways. The sensitization of cephalic and extracephalic pain pathways, expressed as a facilitation of the tem-

poral summation of pain, has been demonstrated to play a pivotal role in the development and maintaining of the chronic form of migraine, including MOH [1]. In MOH patients, a defective functioning of the ES expressed as a down-regulation of the biochemical mechanisms degrading endocannabinoids has recently emerged [2].

Methods We used the temporal summation threshold (TST) of the nociceptive withdrawal reflex (NWR) as an objective method to explore the spinal cord pain processing and the platelet activity of the enzyme fatty acid amide hydrolase (FAAH) to detect the functional state of the ES.

In 21 (12 F, 9 M; mean age: 42.8±12.0) MOH patients and 8 (5 F, 3 M; mean age: 41.4±12.9) healthy subjects the TST of the NWR, the subjective painful sensation and the FAAH activity were measured, before and after 7 and 60 days after a standard withdrawal treatment (WT).

Results Both a significant facilitation in pain processing (reduced TST and increased painful sensation) and a reduction in FAAH activity were found in MOH before WT when compared to controls. A significant FAAH activity reduction coupled with a significant improvement in facilitation of spinal cord pain processing (increased TST and reduced pain sensation) was found in MOH patients before WT when compared to MOH patients 7 and 60 days after WT.

Conclusions We hypothesized a chronic reduction in endocannabinoid tone in MOH patients before WT when compared to controls as a consequence of an adaptive response induced by chronic pain and which could act in favour of a facilitation of the pain processing. Furthermore, the acute reduction of the FAAH activity coupled with an improvement of the facilitation in pain processing immediately after WT and its persistence 60 days after WT could represent the consequence of a mechanism devoted to acutely reduce the degradation of endocannabinoids and aimed to increase the activity of the ES which results in an anti-nociceptive effect.

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Premio Franco Michele Puca 2008

SATELLITE GLIAL CELLS OF TRIGEMINAL GANGLION: NEW TARGETS FOR MIGRAINE THERAPY. EVIDENCE FROM AN *IN VITRO* MODEL OF RAT TRIGEMINAL CELL CULTURES

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Introduction Recent data focused on the role of trigeminal satellite glial cells (SGC) in participating in pain transmission.

Objectives The aim of our study was to characterize primary cultures of rat trigeminal satellite cells, as a model to study the direct effects of different pro-inflammatory stimuli on glial activation and neuron-glia interactions.

Methods Primary cultures of both trigeminal neurons and satellite cells were prepared according to our previously described protocol, with some modifications [1]. Briefly, after tissues collection and enzymatic digestion, cells were pre-plated on 25 cm² flask. After 2 h of controlled incubation, we were able to separate neurons floating in the culture medium from SGC that adhered to the bottom of the uncoated flask. SGC were cultured until reaching almost complete confluence. At this time, cells were detached from the flask, resuspended in fresh complete culture medium, and plated on 96-

well plates for functional experiments, 24-well plates for the preparation of conditioned media and 6-well plates for COX mRNA and protein analysis. Finally, for immunocytochemistry analysis, cells were seeded on glass coverslips. Neurons were cultured on coated 24-well plates under appropriate conditions (NGF) and 7 day after seeding reached complete maturation.

CGRP was assessed by radioimmunoassay. COX mRNA and protein analysis were performed using RT-PCR and Western immunoblot, respectively.

Results On the basis of immunocytochemistry, we found that the most abundant SGC were highly positive for GFAP and Glutamine Synthase, with a small cell body and an elongated shape. Subsequently, in functional experiments, we found that SGC release sizable amount of prostaglandin E₂ (PGE₂) under basal conditions. However, we found that prostanoid release could be further increased by pro-inflammatory stimuli. In particular, we found that IL-1 β and the NO donor DETA-NO significantly increased PGE₂ release in a time- and dose-dependent manner. However, these stimuli showed different profiles of action, suggesting different underlying mechanisms. In fact, we found, using appropriate pharmacological tools, that DETA-NO increased PGE₂ release acting on soluble guanylyl cyclase. As suggested by mRNA analysis, the stimulatory effect of IL-1 β on PGE₂ release was mainly due to increased expression of COX2 enzyme, which was significantly upregulated after 4h incubation, while no stimulatory effects were observed on the steady state levels of COX1 mRNA. With respect to NO, we did not observe any induction of COX2 mRNA levels. In support of this hypothesis, we measured by Western blot increased amount of COX2 protein in the lysates of cells treated with IL-1 β for 4h, while no effects were observed in cells treated with DETA-NO. Subsequently, we performed experiments to obtain conditioned media without any direct influence of applied stimuli used to activate SGC. In these experiments named "stimuli-consistency experiments" we demonstrated that it was possible to activate SGC with a short exposure to both pro-inflammatory stimuli. Indeed, when medium containing stimuli was removed and plain medium was added to SGC cultures, we measured a significant release of PGE₂ after 24 h. The collected medium was a "conditioned" medium. We tested conditioned media from activated SGC on trigeminal neurons. We studied the effects on neuronal CGRP release evoked by different depolarizing agents after a short term (30 minutes) or a long term exposure (from 2 to 24 h) to conditioned media. Conditioned medium was able to further increase evoked CGRP release, and after long term exposure it was able to increase basal CGRP release. In these experimental models of neuronal sensitization, we studied the effects of sumatriptan and a CGRP antagonist.

Discussion Here we propose a simplified model to study neuron-glia interaction into trigeminal ganglion. Our data demonstrate that SGC are deeply involved in trigeminal sensory processing and may constitute a new target of treatment in pain syndrome such as migraine.

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THE PATHOPHYSIOLOGY OF HEADACHE FROM INTRACRANIAL HYPOTENSION

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The orthostatic headache is the main symptom of the intracranial hypotension syndrome. The headache occurs or worsens within 15 minutes after sitting or standing and improves in recumbent position, according to ICHD 2004 criteria. It can occur after lumbar puncture, myelography, spinal anaesthesia, ventriculoatrial or ventriculoperitoneal shunts overdraining, or spontaneously. The most frequent cause of headache from intracranial hypotension is the lumbar puncture. The headache usually occurs after about 48 hours after the execution of lumbar puncture, but may appear even up to 12 days later. It occurs in approximately 30% of cases, it regresses spontaneously with bed rest, in about 70% of cases, within 7 days from onset, and rarely lasts for 2 weeks.

The dull pain is usually located in the occipital-frontal-nucal side. Often it is associated with nausea, vomiting, dizziness, tinnitus, photo/phonophobia, and rarely diplopia. These symptoms usually resolve after a few days, and can sometimes persist for several weeks.

The pathophysiology of lumbar puncture headache (LPH) is still unclear [1]. There is evidence that leakage of cerebrospinal fluid (CSF) leads to CSF hypotension, which causes dilation of intracranial veins, resulting in LPH. In normal adults, free drainage of approximately 10% of the CSF through a lumbar needle regularly causes orthostatic headache. The incidence and severity of LPH increase with the size of the lumbar puncture needle and, therefore, with the size of the hole in the dura. Several pathogenetic mechanisms are suggested.

It is often stated that the CSF cushions the brain and that loss of CSF, by diminishing the upward buoyant force on the brain, allows the force of gravity to cause the brain to sag when the patient is erect. The sag increases tension on the veins that anchor the brain to the dural venous sinuses. The stretching of the brain anchorage veins could cause LPH headache.

Another often cited mechanism for LPH is distension of the venous sinuses and their tributary veins. Loss of CSF results in lower CSF pressure, without a similar decrease in intravenous pressure. The pressure difference across the thin, flexible walls of the intracranial veins increases and the veins dilate. There is considerable experimental and clinical evidence for the venous distension hypothesis. Forbes and Nason observing the pial vessels of the anaesthetized cat through a transparent cranial window, reported dilation of the pial veins with removal of CSF from the cisterna magna. Jugular venous compression, which increases the transmural pressure of intracranial veins and causes them to dilate, increases the intensity of LPH. MRIs of patients with LPH may show a thickened, contrast-enhanced dura and dilation of the dural sinuses. A similar MRI picture has been reported in patients with spontaneous spinal CSF leaks [2] and in patients with ventriculoatrial or ventriculoperitoneal shunts, both conditions where orthostatic headache may be a prominent symptom. Biopsy of the enhancing dura has shown venous dilation. There is also evidence that acute distension of the venous sinuses and their tributaries produces pain.

Another proposed mechanism is that of an altered distribution of craniospinal elasticity. Lumbar puncture may increase the compliance of the caudal spinal portion of the CSF space relative to the rostral intracranial portion. This increase in caudal compliance changes the distribution of hydrostatic pressure in the CSF, causing an abnormally low intracranial CSF pressure in the erect position. As a result, there is acute intracranial venous dilation while sitting or standing, causing LPH. The heart of this hypothesis is the hydrostatic effects of altered distensibility of the CSF space.

In conclusion, we believe that all the physiopathological mechanisms described may together contribute to cause headache from intracranial hypotension.

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TREATMENT OF POST-DURAL PUNCTURE HEADACHE

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Background Post-dural puncture headache (PDPH) has been defined as a bilateral headache that develops within 7 days after dural puncture and disappears within 14 days [1]. PDPH is the most common complication of procedures in which the dura is penetrated, such as diagnostic lumbar puncture, myelograms, spinal anaesthesia, and unintentional dural puncture during attempted epidural anaesthesia. The introduction of fine gauge pencil-point needles since the 1950s have led to a significant reduction in the incidence of PDPH, which varies from 2% or less after spinal anaesthesia to as much as 70% after diagnostic lumbar puncture [2]. Multiple treatment regimens have been advocated with varying degrees of success and risk, including conservative measures, pharmacological treatments, and epidural blood patches [3].

Methods A search of MEDLINE was performed using various combinations of the keywords “post-dural puncture headache”, “bed rest”, “hydration”, “epidural blood patch”, “acetaminophen”, “caffeine”, “methylxanthine”, “cortisone”, and “sumatriptan” for the period January 1980 to May 2009.

Results Conservative measures include bed rest and hydration. A meta-analysis that evaluated the use of bed rest to prevent PDPH found no difference in incidence of PDPH for those with immediate mobilization vs. bed rest for up to 24 hours. Thus, bed rest has no role in PDPH prevention. Increased hydration after dural puncture has been advocated to minimize PDPH occurrence, possibly by increasing the rate of cerebral spinal fluid (CSF) production to replace the fluid lost from leakage. However, the only study that has examined this issue showed that the incidence of PDPH is independent of daily fluid intake. Methylxanthine derivatives have been recommended for the treatment of PDPH. Intravenous caffeine (500 mg in 1L of i.v. fluid over 1 hour) and aminophylline (5–6mg/kg over 20 min) have been reported to be effective in alleviating PDPH in up to 90% of patients. Oral caffeine has been shown to provide a significant better pain relief than placebo for PDPH. The association acetaminophen/caffeine (1000 mg/130 mg) has been shown to be significantly more effective than placebo and non-inferior to naproxen sodium (550 mg) for the treatment of tension-type headache. Data on the efficacy of this combination in the treatment of PDPH are not available yet. Sumatriptan has been widely used for migraines, however evidence is conflicting on its efficacy in the treatment of PDPH. Intravenous hydrocortisone (200 mg first, then 100 mg TID for 48 hours) significantly reduced mean headache intensity after 24 and 48 hours, compared with conventional therapy (bed rest, hydration, acetaminophen, and pethidine) in women who underwent cesarean section and developed PDPH. Epidural blood patch is generally considered the definitive treatment for PDPH, especially for severe and debilitating cases, 15–30 mL of the patient’s blood are injected into the epidural space

through a Tuoy epidural needle to form a blood clot that prevents further leakage of CSF. Success rates are usually up to 98% of patients. Prophylactic patching has been dismissed as ineffective. Concerns about the potential danger of this technique led to the hypothesis that an epidural injection of saline or Dextran 40 would produce the same mass effect and restore normal CSF dynamics, without the risks of autologous blood patch. Many case reports have been described, but the paucity of evidence failed to support the use of epidural saline or Dextran 40 to treat PDPH.

Discussion and conclusions Treatment of mild, non-debilitating PDPH is usually accomplished with conservative measures, analgesics, and caffeine. In the majority of cases PDPH will resolve spontaneously. If symptoms are severe and debilitating, epidural blood patch may be considered. Unfortunately, the literature regarding the treatment of PDPH often involves small numbers of patients, or uses inappropriate statistical analysis. Therefore unequivocal conclusions cannot be drawn.

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CRANIAL NEURALGIA: CLINICAL ASPECTS

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As defined by the IASP, cranial neuralgias (CN) may be defined as painful disorders of the neck and face having as distinctive feature a strict distribution of pain along the territory of the affected nerve. Both major trunks and terminal branch divisions of cranial nerve conveying pain sensitivity may be affected.

Several European authors, as well as, the authors of the IHS classification of the headache disorders, considered other clinical features such as the pain quality (lancinating, electric-shock like, etc.), severity (intense), duration (short), time pattern (abrupt in onset and termination, recurring in paroxysms, refractory period) and the presence of trigger factors as additional distinctive features of CN. If, in practice, this pattern of pain characteristics is typical of most CN (as recognized by the IHS criteria for the different clinical entities), these features are distinctive but not specific of neuropathic pain and recognize specific pathophysiological mechanisms, etiology and therapeutic approach.

The IHS classification of headache disorders have included cranial neuralgias (trigeminal neuralgia, glossopharyngeal neuralgia, intermedius neuralgia, occipital neuralgia etc.) in part 3, chapter 13 “Cranial neuralgias and central causes of facial pain”. In this chapter the authors have used a mixed clinical/etiological classification criterion that appears rather weak and aspecific.

An alternative clinical classification identifying four clinical groups a) neuralgia, b) facial pain associated with cranial nerve symptoms and signs, c) TACs, and d) pure facial pain appears more effective in facilitating the diagnostic process of facial pain.

Biological, genetic, neuroradiological and neurophysiological markers

THE RELATIONSHIP BETWEEN NITROGLYCERIN-INDUCED HYPERALGESIA AND LEVELS OF SPINAL ENDOCANNABINOIDS: THE ROLE OF INHIBITORY HYDROLASES

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Endocannabinoids are present in most tissues and, in some pain states, their levels are elevated at key sites involved in pain processing. Endocannabinoids are hydrolysed by specific enzymes: fatty acid amide hydrolase (FAAH) is an intracellular hydrolase that catalyzes the cleavage of bioactive of several endogenous fatty acid amides, such as anandamide (AEA), while the hydrolysis of 2-arachidonoylglycerol (2-AG), another important endocannabinoid, is mainly catalysed by the monoacylglycerol lipase (MAGL). Recent studies have reported that inhibition of FAAH produces analgesia and reduces inflammation in models of acute-inflammatory pain. The development of MAGL inhibitors could offer an opportunity to study the anti-inflammatory and anti-nociceptive role of 2-AG, which have not yet been elucidated. In this study we evaluated whether systemic inhibition of FAAH and MAGL, may alter nociceptive responses in a well-known animal model of migraine based on the hyperalgesia induced by nitroglycerin administration at the tail flick test. The test was performed in male Sprague-Dawley rats that were pre-treated with nitroglycerin (10 mg/kg, i.p.) or saline (4 hours before) and treated with URB597 (a FAAH inhibitor, 2 mg/Kg, i.p.) or URB602 (a MAGL inhibitor, 2 mg/Kg, i.p.) 60 minutes before the tail flick test. URB597 induced significant analgesia already in baseline condition and it abolished nitroglycerin-induced hyperalgesia. URB602 did not show any analgesic effect per se, but it inhibited nitroglycerin-induced hyperalgesia. The present data suggest that inhibition of FAAH and MAGL activities, with the theoretical consequent increase in spinal content of AEA and 2-AG, may modulate pain perception in a specific animal model of migraine, therefore prompting new targets for the development of symptomatic/prophylactic drugs for migraine.

GENOTYPE INFLUENCES TYPE OF DRUG OVERUSED IN MEDICATION-OVERUSE HEADACHE

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Introduction Medication-overuse headache (MOH), a chronic headache condition due to symptomatic drug overuse, is a borderline disease between severe headache and substance dependence

disorder. In a previous report on some genetic polymorphisms (wolframin (WFS1) H611R (R/R and non-R/R)), BDNF G196A (G/G and non-G/G), and DRD4 120bp tandem duplication (L/L and non-L/L)] involved in dependence behaviour, we detected a role for two of these polymorphisms (WFS1 and BDNF) in MOH patients' monthly drug consumption.

Objectives To look for, in a MOH population, if the choice of the drug overused was influenced by these polymorphisms.

Materials and methods In a tertiary headache clinic, 107 MOH patients were enrolled; all clinical data were recorded and a blood sample collected to perform genetic analysis.

Genetic analyses were performed in order to assess if the three polymorphisms previously related with MOH drug consumption would be able to influence the choice of the drug overused by patients. Patients were segregated into four groups in order of the drug overused: triptans, NSAIDs, association of different type of drugs, and drugs in combination. Two-way ANCOVA, and Bonferroni as post hoc test, were performed to find associations.

Results As previously shown, WFS1 and BDNF polymorphisms resulted to be associated with higher drug consumption. At Bonferroni test, significant differences emerged within the group of drugs in combination, and a trend emerged within the group of patients that associated different types of drugs. No differences emerged analyzing DRD4 polymorphism.

Discussion All drugs in combination used by our patients contained caffeine, whose psychotropic effect is well-known. All examined polymorphisms were previously related with addictive disorders, while in MOH only WFS1 and BDNF resulted to be related to higher drug consumption. In this study we were able to better observe that WFS1 and BDNF polymorphism were mainly related with caffeine containing drugs, and a slight difference started to emerge within the group of patients that associated more drug types.

Conclusions Reward dependence is a behavioural characteristic typical of patients with drug dependence and could account for the worsening of MOH. The caffeine seeking and the trend to associate different types of drugs is consistent with an addictive disorder in MOH patients carriers of these polymorphism.

INTERICTAL IMPAIRMENT OF TEMPORAL DEVELOPMENT OF THE VISUAL SYSTEM SHORT-RANGE LATERAL INHIBITION IN MIGRAINE WITHOUT AURA PATIENTS

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Background A lack of habituation of transient visual evoked potentials (TR-VEPs) during the repetition of the same stimuli has been observed in migraine patients during the pain-free period.

The exact underlying cause of this phenomenon in migraine is still not known. It has been attributed to increased cortical excitability possibly due to deficient intracortical inhibition or to a reduced ascending aminergic control (i.e., preactivation level) of the visual cortex directly or indirectly via the thalamo-cortical fibres. The latter should affect both excitatory and inhibitory cortical neurons. Which of the former or the latter contributes more to the habituation deficit cannot be determined with the methods commonly used to evoke visual responses.

Refined VEP techniques have shown that it is possible to accentuate the relative contributions that arise from short- and long-range lateral inhibition between neurons through differential temporal modulation of adjacent regions of radial windmill-dartboard (W-D) or partial-windmill (P-W) visual patterns.

In this study, we have chosen to apply these VEP techniques to look at the temporal development of lateral interactions in the visual cortex in an habituation paradigm in both healthy volunteers (HV) and migraine without aura (MO) patients recorded interictally.

Materials and methods Steady-state visual evoked potentials were recorded in 15 MO patients and in 20 age- and gender-matched HV. Two visual stimuli were used: windmill-dartboard and partial-windmill, which are contrast-reversing (~4 Hz). For each stimulus session, 600 sweeps were acquired and off-line partitioned in 6 blocks of 100. Fourier analysis was performed on the averaged signal to extract the amplitude of the fundamental (F1) and the second harmonic components reflecting respectively short- (W-D fundamental harmonic) and long-range (P-W second harmonic) lateral interaction within the visual system.

Results The MO patients group showed different temporal development of the F1 harmonic amplitude response along the six blocks in the W-D condition with respect to HV. In fact, the F1 amplitude in the early blocks tended to be higher in migraineurs than in healthy control subjects. Moreover, during the subsequent blocks, amplitude of F1 component progressively increased in HV, but decreased in MO patients group. The difference between patients and controls proved to be significant at the last block (last vs. 1st F1 amplitude block +30.9% in HV, -25.1% in MO, $p=0.020$). There were no significant differences between groups in the temporal development of the 2nd harmonic amplitude response elicited by P-W visual stimulation.

Discussion Previous data have shown that the generation of the fundamental component in the VEP elicited by the windmill-dartboard stimulation may arise from short-range lateral inhibition, possibly from GABAergic synapses. Therefore, the progressive decrease in amplitude we found in MO patients during the W-D recording session could be related to a time dependent reduction of short-range lateral inhibition; whereas, in HV short-range lateral inhibition developed in the opposite direction, since it increased during the stimulus repetition. There was no significant difference in the time development of the long-range lateral inhibition, studied with P-W visual stimulation, between migraineurs and HV.

We hypothesize that the hypofunctioning serotonergic pathways in migraine may cause a functional disconnection of the thalamus leading to decreased intracortical short- but not long-range lateral inhibition, which could contribute to induce lack of habituation during stimulus repetition.

IS MOTOR CORTICAL FACILITATION IMPAIRED IN MIGRAINE WITH AURA?: EFFECTS OF SHORT TRAINS OF HIGH AND LOW FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

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Introduction Dysfunction of neuronal cortical excitability has been supposed to play an important role in the etiopathogenesis of migraine. Different studies with transcranial magnetic stimulation (TMS) support the view that intracortical inhibition is reduced in migraine [1]. Less is known about the possible role of excitatory intracortical circuits dysfunctions.

Each stimulus of a train of high-frequency rTMS (5 Hz) is able to induce in normal subjects, a gradual increase in size of the muscle pro-

duced by muscle-evoked potentials (MEPs) [2], while low-frequency rTMS (1 Hz) lead to a progressive reduction in MEPs amplitude.

Objective To evaluate these parameters in untreated migraine with aura patients compared with healthy subjects, to get, above all, information on the excitatory intracortical activity.

Methods Five trains of 10 stimuli at 5 Hz and at 1 Hz frequency, with 2 minutes inter-train intervals and at 120% of APB motor threshold intensity, were delivered over the hand motor area. MEPs were recorded over the right APB. We measured the size of MEPs to each magnetic stimulus of the train in 12 healthy subjects and in 12 patients. Statistic analysis was carried out by repeated measures ANOVA.

Results In healthy subjects we found, as expected, a progressive increasing in MEPs size at 5 Hz rTMS, while a progressive reduction in MEPs amplitude was observed at 1 Hz stimulation; we found opposite results in migraineurs, where 5 Hz stimulation was not able to determine an increase in MEPs amplitude, while a significant paradoxical facilitation on MEPs amplitude was induced by 1 Hz stimulation ($p=0.01$).

Conclusions Our results are in agreement with other studies showing dysfunction of cortical excitability in migraineurs and paradoxical responses to high- and low-frequency rTMS [1]. The peculiarity of our study consists in the demonstration of a possible dysfunction of excitatory intracortical circuits in migraine. rTMS delivered at 5 Hz frequency and suprathreshold intensity progressively increases the size of MEPs in normal subjects, probably through the activation of excitatory intracortical circuits. In migraineurs, failure of 5 Hz rTMS to lead to an increase in the MEP size, and paradoxical facilitation at 1 Hz irTMS, is not easy to explain. We could hypothesize a primitive alteration of excitatory circuits or secondary dysfunctions towards the most documented alterations of inhibitory intracortical circuits (functional depletion of hyperactive excitatory circuits at 5 Hz).

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NORMAL MOTOR CORTICAL EXCITABILITY IN MEDICATION-OVERUSE HEADACHE PATIENTS: A STUDY OF CORTICAL SILENT PERIOD IN FACIAL MUSCLES

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Background Evidence has accumulated showing that migraine is a disorder with abnormal monoaminergic (particularly, serotonergic) transmission in the CNS. The brainstem aminergic system represented the state-setting system that is ideally organized to modulate information processing and, therefore, cortical activation. This is why it supposedly plays a pivotal role in the cause of the abnormal cortical information processing that characterizes migraineurs brain interictally (lack of habituation), and also in its behavioural modifications occurring pre-ictally and during the attack.

Moreover, a primary low cortical activation, as happens in migraine, may co-exist with deficient inhibition, since the former can promote the latter via reduction of cortical lateral inhibition. In fact, recently, in a transcranial magnetic stimulation (TMS) study, we found that episodic migraineurs recorded interictally have shortened silent period (SP) in perioral muscles, as a result of

reduced activation of GABA_B-ergic circuits in the motor cortex. Since cortical activation in migraine fluctuates depending on the migraine cycle (interictally-preictally-ictally), it would be of interest to assess cortical motor excitability in migraineurs experiencing clinical evolution from initial episodic to chronic daily headache due to medication overuse, where a condition of persistent ictal phase should be present.

Objectives To study motor cortical inhibition in chronic daily headache with medication-overuse headache (MOH) patients, and compare them with a group of healthy volunteers (HV) and migraine patients recorded interictally (MO).

Materials and methods We recorded SP from perioral muscle by means of TMS in 15 MOH patients and 12 MO patients recorded interictally, and we compared them with 13 HV. Silent period was induced using a figure of eight TMS coil centered over the hot-spot for perioral muscles that delivered high intensity magnetic stimuli during a maximal muscle contraction. Electromyographic responses were recorded from surface electrodes placed over the subjects' perioral muscles bilaterally.

Results Mean SP duration in MOH patients was similar to that of HV (respectively 107.12±48.82 and 108.11±30.11), while in MO patients interictally was significantly shortened (59.99±30.44; $p=0.009$). In MOH patients SP duration correlated positively with monthly tablets intake ($r=0.679$, $p=0.005$).

Discussion These findings provide neurophysiological evidence showing that medication overconsumption induces normalization of the cortical motor inhibitory neurons underactivation found in episodic migraine interictally.

EFFECTS OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION OF THE MOTOR CORTEX ON TRIGEMINAL AND RADIAL LASER EVOKED POTENTIALS IN HEALTHY SUBJECTS AND MIGRAINE PATIENTS

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Background Repetitive transcranial magnetic stimulation (rTMS) of the motor cortex modulates acute and chronic pain perception. It was previously shown that 1 Hz rTMS over the primary motor cortex (M1) facilitated laser evoked potentials.

Objective To investigate the effects of 5-Hz rTMS over the M1 on acute experimental pain and evoked responses induced by CO₂ laser stimuli.

Methods The authors examined whether 5-Hz rTMS over M1 at a targeted cortical region corresponding to the motor threshold of the right abductor pollicis brevis affected laser evoked potentials (LEPs) in 20 migraine without aura patients and 12 normal subjects, using 7.5 watt and 25 msec duration laser stimulation of the right supraorbital zone and dorsum of the hand. The LEPs were recorded by CZ, FZ, PZ, referred to the nose, and T3, referred to FZ. Subjective pain-rating scores and LEPs obtained under three different conditions: rTMS, realistic sham stimulation, and a control condition with no stimulation, were compared.

Results In both patients and normal subjects, the 5-Hz rTMS over the M1 significantly reduced the P2 amplitude and the pain rating at the hand level, without any effect at the trigeminal level.

Conclusions The 5-Hz rTMS facilitatory effect on the motor cortex, may induce an inhibition of specific cortical nociceptive areas generating the later LEPs wave, with a probable somatotopic correspondence. This inhibitory effect on Adelta-fiber-mediated responses, induced by motor cortex activation, evident also in migraine patients, may raise the question of rTMS techniques able to provide aid in migraine treatment.

RECOVERY CYCLE OF BLINK REFLEX AS A MEASURE FOR TRIGEMINAL SENSITIZATION (ALLODYNIA) IN MIGRAINE, CORRELATIONS WITH PAIN EXPERIENCE AND PSYCHIATRIC COMORBIDITY

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Introduction Migraine is a frequent pain disorder that determines relevant disability, affecting quality of life and individual and social functioning. Migraine, especially when chronic, presents psychiatric comorbidity: anxiety and depression. Important neural mechanisms, like central sensitization, could have a role linking pain worsening and chronification to psychic factors and psychiatric comorbidity. Recovery cycle of Blink reflex has been used to explore excitability of trigeminal circuits in migraine [1].

Objective To explore the possible interplay between pain experience, psychological mechanisms (defensive strategies, anxiety), psychiatric comorbidity and central sensitization (allodynia) in patients with migraine, by studying objective measures for trigeminal sensitization like the recovery cycle of blink reflex.

Methods We studied 30 patients affected by migraine (according to IHS criteria), 14 with allodynia (A) and 16 without allodynia (WA) and 10 healthy controls (HC). They were part of a larger series of patients participating in a clinical study assessing allodynia and psychological and psychiatric aspects in migraine. They underwent the following tests: 1) SCID-I, DSM axis II (SCID-II) and State-Trait Anxiety Inventory (STAI) for psychiatric comorbidity; 2) Questionario Italiano del Dolore (QUID) for assessment of pain perception; 3) Defense Mechanisms Inventory (DMI) to explore defensive strategies; and 4) recovery cycle of blink reflex (BR). BR was obtained through paired pulses with interstimulus intervals (ISI) of 150, 300, and 500 ms. The ratio of the area in the R2 of the second to R2 of the first shock was measured for each ISI.

Results Patients in group A showed greater psychiatric comorbidity and defensive strategies and had less suppression of the R2 at the ISI of 150 and 300 ms when compared with the groups of WA patients and HC. R2 suppression was significantly correlated with psychiatric comorbidity and defensive strategies.

Discussion Allodynia is associated with increased pain perception, defensive strategies and psychiatric comorbidity in migraine. Moreover, allodynia is significantly associated with measures of the central trigeminal sensitization like the BR recovery cycle. This could be relevant for prognostic evaluation contributing to the understanding of neural mechanisms underlying chronification of migraine.

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IS PAIN QUALITY ASSOCIATED WITH SPECIFIC PHYSIOPATHOLOGICAL MECHANISMS IN ADOLESCENT MIGRAINE? A COMBINED NEUROPHYSIOLOGICAL AND PSYCHOLOGICAL STUDY

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Introduction Recent studies showed a different efficacy of treatments in migraine, depending on the pain characteristics. In partic-

ular, Jakubowski et al. [1] showed that migraine prophylaxis with Botulinum Toxin Type A is more likely to be active in migraineurs referring imploding pain (IP) than in those with exploding pain (EP). This might suggest different physiopathological mechanisms working in either IP or EP headaches.

Objectives To investigate: 1) whether the level of the somatosensory system excitability in migraine adolescents with EP or IP is different, and 2) whether this may interact with some psychological features concerning anger.

Materials and methods We studied 18 patients with migraine without aura. They were divided into 2 groups on the basis of their type of pain, identified by means of illustrative drawings: 1) 11 patients (mean age 14.5±1.4 years, 4 girls, 7 boys) had a prevalent EP, and 2) 7 patients (mean age 14.1±2.2 years, 5 girls, 2 boys) referred a prevalent IP. The somatosensory evoked potential (SEP) recovery cycle, a tool to assess the somatosensory system's inhibitory mechanisms, was compared between the 2 groups. We calculated the SEP's latency and amplitude modifications after paired electrical stimuli at 5 ms, 20 ms and 40 ms interstimulus intervals (ISIs), comparing it with a single stimulus condition assumed as the baseline. Psychological assessment was performed by means of the State Trait Anger Expression Inventory (STAXI), as a measure of the components of anger.

Results As for the frontal N30 SEP component recovery cycle, there was a significant interaction between the ISI and the group of patients (two-way ANOVA: $F=3.29$, $p=0.04$). Post-hoc analysis showed that the N30 amplitude recovery at 5 ms ISI was higher in IP than in EP patients. Correlation analysis showed that: 1) in EP patients there was a positive correlation ($F=5.51$, $p=0.04$) between the N30 amplitude change at 5 ms ISI and the level of anger directed inward (Anger-In), and 2) in IP patients there was a positive correlation ($F=21.7$, $p=0.003$) between the N30 amplitude change at 5 ms ISI and the anger trait (T-Anger).

Conclusions Our results suggest that the inhibitory mechanisms within the somatosensory cortex are more impaired in IP than in EP patients. Moreover, the observed interaction between the N30 SEP component recovery cycle and some psychological features concerning anger confirms the strict relationship between brain excitability level and psychological factors, already shown in our previous study [2].

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Clinical aspects and headache management in adults

AGE AT ONSET IN MIGRAINE WITHOUT AURA: A PROGNOSTIC FACTOR?

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Introduction Migraine without aura (MO) is a long-lasting disease whose prognosis has not yet been fully investigated. Patients may present complete remission, partial clinical remission, persistence and progression to chronic migraine [1].

Limited evidence exists regarding the identification of risk factors or predictors which might influence migraine prognosis. Age at

onset (AAO) has been proven a useful tool in the investigation of the clinical, biological and genetic characteristics able to influence the prognosis of a number of neuropsychiatric disorders [2]. In migraine, AAO might represent a prognostic factor, since its variations could influence the clinical course of the disease. Therefore, we decided to perform a mixture analysis on AAO in a sample of patients affected by MO, in order to verify the presence of different patient subgroups and compare clinical correlates among them.

Methods This study was conducted at the Headache Centre of the Unit of Clinical Pharmacology of the University Hospital of Cagliari. A sample of 334 patients affected by MO, recruited in a clinical genetic study at our Headache Centre from 2004 to 2008, was enrolled for this study. Diagnosis was made according to the IHS criteria 2004. AAO was defined as the age at which patients experienced their first episodic headache. High-frequency (HF) or low-frequency (LF) of MO was established if patients respectively experienced more than or less than/equal to two attacks per month. AAO distribution in patients was studied using a mixture analysis, a statistical approach that breaks down the empirical AAO distribution observed into a mixture of normal components. Chi-square test was used to compare clinical correlates among identified subgroups. Logistic regression was performed in order to correct for effect of possible confounders.

Results An early-onset, an intermediate-onset and a late-onset group were identified. Patients with high-frequency (HF) of migraine attacks were overrepresented in the early-onset group, while low-frequency (LF) was found in the late-onset group. Chi-square test performed between early- and late-onset groups also revealed a statistically significant difference in terms of frequency (HF vs. LF; $p=0.01$). Considering the frequency of migraine attacks as a main outcome, the regression model confirmed that a higher AAO was associated with LF ($p=0.02$).

Discussion To our knowledge, this is the first study attempting to identify AAO subgroups in MO using the mixture analysis in a population of outpatients from a Headache Centre.

The significant association between AAO and attack frequency found in our study supports the hypothesis that AAO could act as a predictor factor able to influence prognosis and suggests that a later AAO can act as a protective factor against migraine progression. A recent review indicated that attack frequency is an important factor associated with migraine clinical progression, suggesting that increasing frequency could be a marker of headache evolution [1]. In a population-based study of family aggregation, early onset was associated with a higher level of familial aggregation [3].

Conclusions AAO could represent a clinical marker of MO prognosis and a phenotype suitable for identifying MO susceptibility genes.

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IMPAIRED AORTIC COMPLIANCE IN YOUNG SUBJECTS WITH MIGRAINE: A CASE-CONTROL STUDY (“MIGRARTERY”)

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Background Vascular changes associated with migraine are traditionally considered to selectively involve cranial blood vessels, but the following observation challenges the above traditional view: generalized peripheral vasoconstriction during the migraine attack, and migraine associated with coronary artery vasospasm, migraine associated with Raynaud's phenomenon, and migraine as a risk factor for ischemic stroke, mostly in young people [1]. However, the mechanisms which link migraine to cardio- and cerebro-vascular events remain uncertain. In the present case-control study, we hypothesized that aortic stiffness, an independent predictor of stroke and cardiovascular disease [2, 3], may be increased in young migraineurs with no overt cardiovascular diseases or major cardiovascular risk factors.

Patients and methods Forty-one patients with episodic migraine (following the IHS criteria for migraine with and without aura, age 31 ± 8 years) and 41 age- and sex-matched healthy control subjects were examined to investigate carotid-to-femoral pulse wave velocity (PWV), by tonometric method, a state-of-the-art measure of aortic stiffness and an independent predictor of stroke and cardiovascular disease.

Results All subjects were free from overt cardiovascular diseases, diabetes, arterial hypertension and hypercholesterolemia; 24% were smokers and 24% used oral contraceptives. Thirty-eight percent of the patients were under prophylactic treatment (antidepressant drugs), but none of them were taking vasoactive drugs (including β -blockers and Ca^{++} -channel blockers). Eighty-two percent of migraineurs were females (12% migraine with aura, 15% migraine associated with tension-type headache). Aortic pulse wave velocity was significantly higher in migraineurs than in control subjects (7.4 ± 1.2 vs. 6.5 ± 1.1 m/s, $p=0.001$). Age, mean arterial pressure as a measure of distending pressure and the presence of migraine (all $p<0.05$) independently predicted aortic pulse wave velocity when a consistent number of cardiovascular risk factors was simultaneously controlled for.

Discussion Migraine is independently associated with an increased aortic stiffness. This finding, obtained in young subjects without major cardiovascular risk factors, may represent one possible mechanism underlying the increased cardiovascular risk in patients with migraine.

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MIGRAINE, DEAFFERENTATION AND SPONTANEOUS ELECTRICAL ACTIVATION IN SENSORY PATHWAYS – THE PATHOPHYSIOLOGICAL CIRCLE OF NEUROGENIC PAIN

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Background From the 80s, Federigo Sicuteri and I proposed an overlap between neuropathic pain and migraine [1]. The clearer example of neuropathic pain is represented by deafferentation [2]. The parallel between deafferentation and migraine was grounded on both: a) the clinical pattern; and b) the neuro-physiological profile evident in the larger part of migraine headaches. Indeed, deafferentation and migraine shared the following signs: A) Clinical:

super-sensitivity to stimuli, overreaction (as shown by applying our method to test vascular/visceral hyperalgesia/allodynia), therapeutic sensitivity to beta-blockers, barbiturates, tricyclic antidepressant, negative modulators of NMDA transmission, poor responsiveness to opiates, and worsening with climatic changes; B) Electrophysiological spontaneous firing that we indicated as “quasi epileptic foci” since mirroring the ones spreading from brainstem till to the cortex in deafferentation [3].

Objective To verify the possible overlap between deafferentation and migraine pathophysiology, and to evaluate therapy implications that the overlap may imply.

Methods Observation duration 1987–2008. Inclusion criteria: deafferentation due to trauma, cerebral lesions, surgical injuries, and infections. Exclusion criteria: schizophrenic and paranoid disorders diagnosed following DMS III. Comorbidity with migraine established by using the criteria of the IHS Classification 1988. Four consanguineous who were alive were used to obtain family history of primary headache.

Results Deafferentation resulted in severe dysaesthesias or phantom pain when it occurred in the trigeminal area of migraine sufferers. In fact, phantom tooth ($n=408$) occurred in migraine sufferers and its severity parallels the one of migraine. Phantom eye and dysaesthesias ($n=192$) are related to the occurrence of migraine headache and there was a direct relationship with the severity of this primary pain. Breast phantom pain ($n=201$) does not relate significantly ($p>0.2$) to migraine but dysaesthesias had a direct positive relationship ($p>0.05$) with the occurrence of headache in family history ($n=225$). Leg and arm phantom pain ($n=215$) was not significantly higher ($p>0.2$) in migraine, whereas dysaesthesias were frequent ($p>0.005$) in patients with a family history positive for migraine ($n=243$).

Three patient Groups were identified with a different tractability as shown by our longitudinal observation: Group A included migraine sufferers undergoing deafferentation. They gave a positive response to classical prophylactic anti-migraine drugs. The course of deafferentation symptoms parallel the ones of migraine disease. Group B included exempt subjects with no family history for primary headache, and who had a very positive and sharp response to antagonist at the metabotropic NMDA receptor sites (90% amelioration in a 15-day treatment period). A subgroup of these patients ($n=64$) had benefited from using lipoic acid alone (69% amelioration in a 3-month treatment period). Group C included subjects characterized by both deafferentation, free from migraine and a positive family history for headache. Therapy discussed for Group B induced a significant benefit ($p>0.001$), but there was proneness to relapse (11 months duration ± 6.5 SD) following the achieved benefit.

Conclusions and hypothesis regarding epileptic-like pattern in migraine CNS

The link between M and deafferentation seems easily explained should we accept that both the pathologies consist in central neurogenic pain. The response peculiar to consanguineous headache sufferers seemed to indicate an inherited abnormal CNS set up which has also been evidenced by our method underlying the heritability of vascular/visceral allodynia/hyperalgesia. Should we accept the neurogenic nature of deafferentation and migraine, EEG alterations might represent the emerging peak of an altered signalling till to the cortex allowed by a deficit of control systems. The spontaneous on going of epileptic-like foci might represent the link between migraine and epileptic-like conditions, which could pave the way for the application of antiepileptic drugs in migraine prophylaxis.

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LIVING WITH HEADACHE: GRAPHIC REPRESENTATIONS OF DISEASE MADE BY CHRONIC HEADACHE PATIENTS AND THEIR PSYCHOLOGICAL INTERPRETATION

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Introduction Graphic works could be a source of information about the patients' self and disease perception. Graphic and contents analysis could help health care professionals to understand patients' feelings and their satisfaction about headache treatment.

Methods Fifty (45 females) subjects (aged between 25 and 60 years), affected by chronic daily headache, according to the ICHD-II criteria [1] and referring to Villa Maria Teresa Headache Unit (Florence), were given the task of graphically representing their life with headache. The subjects were given standard sized paper, coloured pastels, pens and drawing pens. The graphic works were analysed by a psychologist who explored 4 issues: self, disease, treatment perception, and general feelings and emotions.

Results Self-perception was characterized by the sense of loss of life control and duplicity (headache presence/absence, right/left hemicranium). Disease perception was characterized by the idea of headache as an external pervasive event which, temporarily but hardly, impairs life activities. The treatment, considered as a chronological index of life, was perceived as the sole hope of salvation and Villa Maria Teresa health care professionals were seen as a lifeline, also because of their ability to listen. The general feelings consisted primarily in a sense of loneliness, caused by the patient's isolation during the headache attacks and incomprehension by other people, accompanied by a double vision of one's lifetime, with a depressive past and a hopeful future.

Discussion In our patients, as a whole, life is perceived as double and partial, with deprivation of experiences considered normal by other persons [Figure 1]. The feeling of failure is close to the feel-

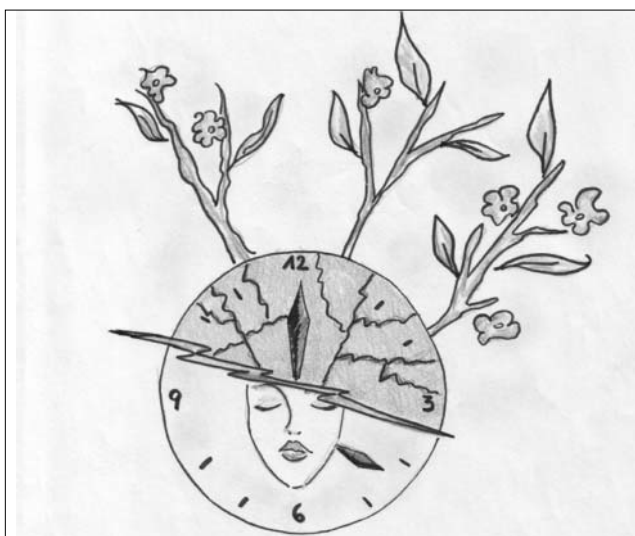


Figure 1 A graphic work representing living with chronic headache

ing of hope in the future, i.e., in the possibility of defeating or controlling the headache. Treatment is the instrument to regain a normal life. The limit of our study is the poor generalization of the results, which are subjectively interpreted and derive from an investigation with an inadequate, non rigorous design.

Conclusions Health care professionals, while caring for patients affected by headache, especially if chronic, should consider and pay attention to the psychological aspects of these patients, who on a daily basis and for a long period of time, have to confront themselves not only with the pain but also with feelings of failure.

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PHARMACOEPIDEMOLOGY OF TRIPTANS IN A HEADACHE CENTRE

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The efficacy and safety of triptans in the absence of contraindications have been proved. Nevertheless, these drugs are not much used in clinical practice [1], while they are the most commonly used class of medication in specialty care [2].

The aims of our study were to: (i) examine the pharmacoepidemiology of triptans in the population of migraine patients treated at a specialist centre; (ii) analyse if there were any differences among patients continuing to use triptans and patients, that after having tried these drugs, discontinued them.

Methods We examined all migraine patients, according to the International Classification of Headache Disorders 2nd edition criteria [3], older than 18, consecutively examined for a follow-up visit at the clinics of the Headache Centre of the University Hospital of Modena from October 2008 to March 2009. Only patients who had used triptans as abortive treatments were included.

A questionnaire with closed and open questions about the use and tolerability of triptans was prepared for the study. The questionnaire was administered in the waiting room by a trained postgraduate student of the School of Clinical Pharmacology, who had never examined the patients before.

Results Three hundred and forty-three migraine patients (F: 75%, M: 25%; mean age 40.4±10.3 years) reported to having used triptans. Migraine without aura ($n=247$, 72%) was the most common diagnosis, followed by chronic migraine ($n=90$, 26%) and migraine with aura ($n=6$, 2%). Globally, 60% ($n=206$) of the sample had tried at least two triptans and 72% ($n=246$) continued to use them habitually.

The patients who had discontinued triptans (97/343, 28%) were significantly younger (mean age 36.8±6 years), had been suffering from migraine for less years (7.6±4), and had less migraine days/month (7.7±6) than those who instead continued to use them (mean age 41.8±1 years; years of migraine 15.5±9; migraine days/month: 13.4±1; $p<0.0001$, Student's *t*-test for unpaired data). More patients among those who had discontinued triptans (89/97, 92%) than among those who continued to use them (139/246, 57%) reported triptan-associated side effects ($p<0.0001$, Fisher's exact test). Most patients who had discontinued triptans (57/97, 59%) had taken this decision precisely because of side effects. The decision to continue to use triptans had instead been taken by most patients because of their efficacy (210/246, 85%).

The most used triptans had been sumatriptan (66%), almotriptan (54%), and rizatriptan (47%). The triptan discontinued by the highest percentage of the patients who had used it (31/37, 84%) had

been sumatriptan 6 mg subcutaneous injection. Rizatriptan 10 mg had been significantly more discontinued (85/113, 75%) than sumatriptan 50 mg (28/71, 39%), almotriptan (84/146, 45%), zolmitriptan (44/78, 56%), and rizatriptan 5 mg (23/49, 47%) ($p < 0.05$, Chi-square test). Significantly more patients reported side effects with sumatriptan 6 mg subcutaneous injection (33/37, 89%) and 100 mg tablet (50/75, 67%) than with any other triptan.

No patient reported serious or unexpected adverse triptan-associated effects. The most common side effects were the so-called "triptan sensations", i.e., a feeling of drowsiness (47%) and of neck or chest tightness (36%).

Conclusions In general, the patient decides to take a given drug depending on the balance between expected benefits and potential risks. Most migraine patients going to a specialist centre continue to use triptans, after having tried them, above all for their efficacy. The minority discontinuing them are younger patients, who have been suffering from less severe migraine and for less time. These younger migraine patients seem inclined to consider the price to pay in terms of worrisome, but non-serious side effects, unacceptable if compared to the benefits of the use of triptans.

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NEW PHARMACEUTICAL PREPARATION OF TRYPTOPHAN, 5-OH-TRYPTOPHAN AND VITAMINS (PP AND B6) IN MIGRAINE PROPHYLAXIS: AN OPEN CLINICAL STUDY

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Introduction Migraine is a disorder frequently observed in the general population (12–14% in western countries), with a higher prevalence in female. When crises are 3 or more per month, prophylaxis is recommended. Tryptophan (TP) and 5-OH-tryptophan (5-OHTP) are precursors of serotonin and represent a significant approach in the treatment of conditions that involve serotonin synthesis and release in the central nervous system (CNS). Pathological conditions associated with serotonin deficiency in the CNS include mood disturbances, depression, fibromyalgia syndrome and migraine-headache as suggested by pathogenetic researches published several years ago [1].

Objectives The aim of this open, non-randomized, clinical trial was to evaluate the efficacy of a new pharmaceutical preparation of TP and 5-OHTP with different controlled release [2].

Materials and methods Forty-six outpatients (14 men, 32 women), mean age 33.65 years (male 18–51, mean age 32.28; female 18–58, mean age 34.25) were visited in our headache centre from December 1st to 31st 2008. Every patient received a diagnosis of episodic (less than 15 days of migraine per month), migraine without aura (according to the IHS 2004 criteria) and was invited to register on a dedicated diary the number of headache attacks for two months without prophylaxis. After, they had to take 1 tablet orally daily for two months, in the morning, with double

strait (blue with fast 5-HTP release, white with retard TP-release) containing L-tryptophan (250 mg), 5-OH-tryptophan (50 mg) (both extracted by *Griffonia simplicifolia*), PP vitamin, that inhibits alternative metabolic pathways to serotonin synthesis and B6 vitamin, that optimizes the action of the enzyme that converts 5-OH-tryptophan in serotonin. Primary efficacy parameter was the change in number of migraine attacks, assessed by comparing values before and after the prophylaxis period.

Results After four months, at the control visit: 8 subjects (7 F, 1 M) had no improvement, 3 (2 F, 1 M) slight improvement (<50% reduction in the number of the attacks), 22 (13 F, 9 M) mild improvement (>50–70%), and 12 (10 F, 2 M) high improvement (>70–100%). Only one subject referred an adverse event (gastric pyrosis), spontaneously resolved in a few days after discontinuing treatment and was excluded from the study.

Discussion and conclusions This new pharmaceutical preparation of TP-5 OHTP (Brioplus®) seems to be effective in prophylactic treatment for episodic migraine, even if in this open label study, only the number of attacks per month was evaluated. This association of serotonin precursors, PP and B6 vitamins is also warranted as demonstrated by the poor incidence of adverse events.

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FACTORS THAT WORSEN MIGRAINE IN THE WORK-PLACE

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Background Migraine is a very common disorder affecting people during the most productive years, and affects employees' ability to work. Factors that worsen migraine impact productivity through reduction of working abilities.

Objective Aim of the study was to investigate the work-related aggravating factors for migraine during working activities.

Methods A six-month prospective analysis of all consecutive patients evaluated in the Headache Centre of the University of Trieste was performed. Patients with migraine were enrolled (ICHD-II criteria). Unemployed subjects were excluded. Migraine-related work-time loss, in terms of absence and reduced productivity over the preceding three months, was evaluated with the validated Italian version of the Migraine Disability Assessment Questionnaire (MIDAS). Demographic information, employment status, MIDAS scores, and the migraine worsening work-related factors were analysed using SPSS 13.0.

Results Sixty-nine patients were enrolled (84.1% F and 15.9% M; mean age 38±8 years). Only 10 patients used specific therapy for migraine before being examined. Sixty-two patients (89.8%) were employees, and 7 (10.2%) were self-employed subjects. The mean of work-missed days and the mean of days with workplace productivity severely reduced over the preceding three months were 5 and 9 days, respectively. Sixty patients (86.9%) reported work-related factors worsening the attacks, most frequently working with the public (76.8%), planning the workplace activities (52.2%), and heavy physical activity (23.2%). Fifteen patients (21.7%) modified

their working activities because of headache, especially if they were employees (29.2% of employees vs. 14.3% of self-employed patients), but it was not related to the type of worsening factors.

Conclusions Worsening work-related factors are frequent in employees. More than one-fifth of patients were forced to modify their working activities because of headache. Our data underline the high disability in migraineurs in the workplace, and confirm the benefit of a specific treatment in order to reduce the pain and the job-related aggravating factors.

EFFICACY OF A TERRITORIAL HEADACHE CENTRE ON THE NUMBER OF ACCESSES FOR HEADACHE IN THE EMERGENCY DEPARTMENT

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Headache and in particular migraine represent a frequent condition in the general population from 12% to 25%. Headache Centres usually have the role to diagnose the type of headache using the standardized ICDH-II criteria and treating it to try and reduce the burden of disease. It is usually very difficult to evaluate efficacy of a headache centre in a specific area, since there are no objective, or quality parameters except the number of patients visited in a certain period.

We tried to evaluate the impact of a new headache centre in a district of Rome, Ostia, that presents the characteristic of being about 40 km from the centre of the city and with a population of more than 350,000 patients referring to only one hospital, the G.B. Grassi Hospital, where in February 2006 a headache unit was activated for the first time. We decided to concentrate our attention in the population of our district, thus, this service was not associated with the Regional Centre for the Reservations of Health Services.

We considered quality parameters as numbers of controls/years and number of accesses to the Emergency Department (ED) for headache.

Considering the number of controls, we started at 40% in 2006 and reached 75% in 2008 with a rapid saturation of the service. Percentage of patients with a previous headache type diagnosis was 15% and 82% of the population was triptan naïve.

The impact of this service, directed by only one neurologist, an expert in the field of headache, was relevant. In fact from a prevalence of 0.66% for headache diagnosis in the ED in 2005, similar to the percentage reported by the Lazio Region 0.77% (data supplied by the Health Public Agency of ASP Lazio) in the period 2005–2008, we obtained a slight reduction of access of 0.5%, while in the Lazio Region the percentage of access increased to 0.87%, and a reduction of frequent user of the ED for headache of 75% was observed.

These data confirm the importance of a strict collaboration between headache centre and the ED to reduce the burden of disease.

HEADACHE IN EMERGENCY, A GROWING PHENOMENON

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Headache is the fifth most common clinical condition leading to Emergency Department (ED) visits, accounting for 0.8–3% of all ED visits. A considerable proportion of these headaches are pri-

mary headaches, but the figures vary largely from one study to another, from 24% to 81%. More recent data on prevalence of headache in the ED in Italy is attributable to the METEOR study by De Carli et al. that showed a prevalence of primary headache in emergency of 0.6% in the year 1994 in 9 Italian Emergency Services.

In collaboration with the Lazio Public Health Agency (ASP Lazio) we conducted a study on the prevalence of headache diagnosis at discharge from all Emergency Services of this Region in the years 2005–2008.

With an average of 2171 million accesses/year in the period under study, data showed a progressive increase of patients using the ED to treat headache. In fact, from a prevalence of 0.87% (17,094 patients) in 2005 the number of patients reach 0.97% (18,568 patients) in 2008 with an increase of 12% in 4 years.

If we consider the severity of the symptoms at access using a triage code, in 2008 we had more than 90% of patients with moderate severe headache. About 2/3 of patients (75.8%) were classified with a green code, 18% with a yellow code, 4.9% with a white code, 0.23% with a red code, and 0.3% were not classified. Considering that reimbursements for emergency interventions are calculated on the basis of the triage code, we can estimate that in 2008 direct costs for emergency access was more than € 3.5 million, with an increase of about 20% in costs from 2005.

Also, the mean time from access to discharge increased, in fact, from a waiting time of 4 hours in 2005, we had reached 6 hours in 2008 with an increase of 20%.

These data globally show that the use of Emergency Services to treat headache has sensibly grown in these years, increasing the length of waiting time for access and direct costs of the disease.

A PICTURE OF MIGRAINE MANAGEMENT IN ITALY

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Since the commercialization of sumatriptan about 20 years ago, scientific societies, pharmaceutical companies and headache specialists have tried to highlight the migraine pathology in the population, arguing that it was underestimated. The migraine prevalence assessed in 1996 in a large sample of the population presenting to their general practitioner (GP) was 11.6%. However, in GP databases, migraine rarely was reported in the list of problems (1.39% of patients). In those years the percentage of migraine patients utilizing specific drugs for migraine, i.e., triptans, was about 3%. Also, in Emergency Departments (ED) the diagnosis of migraine was made in a small percentage of primary headaches.

The low percentage of migraine diagnosis in the GP database and at discharge from ED is in accordance with studies on the low utilization of triptans in the general population. The largest published study was made recently in Italy in a population of more than 5 million which showed a prevalence of 0.6% of users, which correspond to about 6–7% of migraine patients [1]. Even the prevalence of migraine diagnosis in our GP database remained low in 2008 (1.6%); however, about 1/4 of these patients have utilized triptans in the year (Table 1). The generic diagnosis of “headache” was registered in another 2% of patients (5.5% have utilized triptans).

Recently, a study evaluating patients attending 10 headache centres (HC) for the first time confirmed that migraine is still underdiagnosed in Italy and that migraine patients receive a suboptimal medical approach [2]. In particular: 1) only 26.8% of migraine patients had a previous diagnosis of migraine; 2) only 17.2% of migraine patients use triptans; and 3) more than 50% of triptan users were unsatisfied (Migraine-ACT questionnaire) with their usual therapy.

Table 1

	Subjects (Year)		%
Migraine registration in GP database	503849	(2002)	1.39
	42710	(2008)	1.6
Triptan users in the population	5549731	(2006)	0.6
Migraine patients in the GP database utilizing triptans	42710	(2008)	25.5
Triptan users in migraine patients attending for the first time HC	1263	(2006-2007)	17.2
Migraine patients treated with triptans in Emergency Department	50	(2004)	10.0

A study performed in an Emergency Department showed that less than 10% of patients with primary headaches were discharged with a diagnosis of migraine, while the follow-up specialist visits found a prevalence of 74%. Furthermore, only 10% of migraine patients received triptans in the ED.

Obviously, the diagnosis of migraine increases to real prevalence after headache centres consultation, and also the rate of triptans assumption increases substantially. It is possible that close communication between GP, ED physicians and headache specialists will improve migraine diagnosis and management and therefore the utilization of specific migraine drugs. However, we cannot ignore that, despite the great number of HC present in Italy and in the world, a substantial increase in triptans utilization over the years does not emerge. Moreover, a high percentage of new and lapsed users suggesting a high turnover of triptans utilization was recently reported in the Italian population [3]. The reasons why this pathology with high disability is underdiagnosed and undertreated must be further studied.

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PRIMARY HEADACHES IN PATIENTS WITH HEADACHE ATTRIBUTED TO AIRPLANE TRAVEL

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Introduction A new form of headache strictly related to airplane travel has been recently reported and because of this peculiarity, the term “Airplane headache” (AH) was proposed. Considering the fairly stereotyped features of the attacks, we suggested provisional diagnostic criteria for this headache [1], currently not included in the ICHD-II criteria. The onset of pain is strictly related to the flight, mostly during landing; the pain intensity is very severe, located in the frontal-orbital region without side-shift, and lasts up to 30 minutes.

Material and methods Despite the restricted number of cases described, AH does not seem to be so rare. Following our previous paper on the subject, a series of patients required our consultation. They filled in a detailed questionnaire, which was personally analysed by the headache specialist or by a phone structured interview. Up to now, 57 cases have been collected. A specific part of the questionnaire makes it possible to reproduce the diagnosis of migraine without and with aura (MO, MA), episodic and chronic tension-type headache (ETTH, CTTH) and cluster headache (CH).

Results Out of the 57 completely filled in questionnaires, we could

identify 33 cases (57.8%) for which a diagnosis of an associated primary headache was reproducible. A male preponderance was noted (20 males, 13 females). Specifically, 27 patients showed only one form of primary headache, i.e., ETTH ($n=15$, 45.4%; frequent: $n=9$, 27.2%; infrequent: $n=6$, 18.2%), MO ($n=9$, 27.2%), and probable TTH ($n=3$, 9.0%). The concurrence of two different primary headaches was present in 6 patients (18.2%), i.e., MO+TTH in 2 cases (6.0%), and MO+MA, MO+primary stabbing headache, MA+ETTH, and MO+headache attributed to the application of a cold stimulus in the remaining cases. All the patients described the AH attacks as completely different, when compared with their usual headaches; none of them complained of a typical attack during or following their flight.

Conclusions Data from this large series of AH patients confirm the features of the attacks to be fairly stereotyped, and support the specific peculiarity of this form of headache, that should be considered as a distinct nosological entity. The presence of a primary form of headache might represent a predisposing factor for AH.

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MIGRAINE AND HYPNIC HEADACHE: COMORBIDITY OR POSSIBLE EVOLUTION OVER TIME?

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Introduction Hypnic headache (HH) is a primary nocturnal headache, which occurs exclusively during sleep. HH may be either unilateral (in about 40% of cases) or bilateral. The frequency of attacks varies from occasional attacks to a near nightly occurrence. Women appear to be remarkably more commonly affected than men. Many patients have been reported to have coexistent or pre-existent primary headache disorders such as migraine and tension-type headache [1].

Materials and methods For the last 11 years we have observed 33 cases fulfilling ICHD-II criteria for HH. All patients underwent extensive investigations, including brain MRI and Angio-MRI, which resulted unremarkable.

Results We diagnosed 33 patients, 29 females and 4 males with HH. The patients’ mean age at first observation was 64.6 ± 8.7 years (range 51–83), whereas the mean age at onset was 61.8 ± 9.6 years (range 45–82). The pain was bilateral in 23 patients and unilateral without side shift in 10. Twenty patients (18 females and 2 males) had a chronic headache unremitting from onset. The other 13 patients showed an episodic pattern. Up to now 7 subjects had only a single bout which spontaneously remitted, with duration ranging 1 to 8 months. Three patients had a relapsing-remitting course, and the remaining 3 cases showed only sporadic headaches, with frequency

ranging from one attack per month to one attack every 6 months [2]. Interestingly, 18 patients (17 females and 1 male) were affected also by migraine and 3 (2 females and 1 male) by frequent episodic tension-type headache. The prevalence of migraine in our case series of HH patients was 54.5%, significantly higher than that of the general population. Out of the 18 migraine patients, 16 had migraine without aura (all were females, one had also sporadic typical auras without headache) and 2 had migraine with aura (one was male). Among the migraine patients, the headache had completely ceased prior to the onset of HH in 11 patients (one was male, suffering from migraine with aura), whereas in the remaining 7 cases (6 having migraine without aura) the headache was still active and coexisting with HH. It is to be emphasized that in all the HH patients with concomitant migraine, the latter headache had greatly improved as compared to the previous trend, occurring markedly less frequently and with significantly milder severity. We found a strikingly vast majority of female patients in our series (representing 87.9%), much greater than the typical distribution by gender in migraine.

Discussion This case series of HH patients is the largest ever reported in the literature. The pathophysiology of HH remains speculative because there are no experimental studies on its nature. It has been assumed that HH is a spectrum disorder, with an overlap with other primary disorders [3]. The variety of drugs reported to be effective in HH underscores the possibility that the pathophysiology might be heterogeneous. No comorbidity, defined as greater than coincidental association of two conditions in the same individual, has been described for HH up to date. In our case series of HH patients, the prevalence of migraine was 55%, suggesting that migraineurs are more likely to suffer from HH, in particular after the age of 50.

Conclusions We found a high prevalence of migraine in a large series of HH patients. This observation is suggestive of a possible comorbidity between the two conditions. However, due to the fact that for most migraineurs the onset of HH occurs when migraine has already disappeared, it is more intriguing to hypothesize that in a subpopulation of patients, migraine might evolve into HH after its natural course, possibly based on a genetic predisposition.

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FRONTO-TURBINALIS SINUS EXPANSION (FTUSE) HEADACHE: A NOVEL CLINICAL ENTITY

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Introduction The presence of an anatomical variant of the frontal sinus expanded into the pneumatic medium turbinatum (FTUSE or conca bullosa), could be responsible for daily headaches by means of an increase of its pressure not related to an abnormal contact between opposite mucosal surfaces like the well-known contact point headaches [1, 2]. We aimed to: 1) estimate the endo-sinusal

pressure in patients with pneumatic medium turbinatum suffering from daily headaches; 2) describe the histological findings in tissues from the pneumatic medium turbinatum, with a special focus on pain receptors; 3) assess, in these individuals, of the evolution of the headache after lateral laminectomy of the pneumatic medium turbinatum performed using minimal endoscopic sinus surgery.

Methods Twenty consecutive patients (18–65 years) seen at a headache centre in Italy were enrolled. Inclusion criteria were: 1) Moderate-to-severe fronto-supra-orbital daily headache, for at least 12 months; 2) Spontaneous pain, triggered or enhanced by digital compression, in the Ewing’s point and/or the internal orbital corner (Grunwald’s point); 3) Poor acute response to OTC analgesics and NSAIDs; 4) Normal neurological examination, neuroimaging and psychiatric interview; and 5) CT scans of rhino-sinusal region showing frontal sinus expanded into the pneumatic medium turbinatum. Exclusion criteria: septum deformities, polyposis, nasal masses and other abnormal contact between opposite mucosal surfaces.

All patients were submitted to lateral laminectomy of pneumatic medium turbinatum performed using minimal endoscopic sinus surgery.

Results Before the surgery sinus pressure was measured through a device specifically built for this study. Values of endo-cavitary pressure ranged from 1.7–3.3 mbar, with a mean of 2.4 ± 0.4 mbar (significantly higher than the environment pressure). Intra-operative biopsy demonstrated atypical dysembryogenetic pneumatization of medium turbinatum, secondary inflammation and the presence of free nerve endings (functionally pain receptors). All subjects became pain-free within 30 days after surgery and were still pain-free at 12–18–24 months.

Discussion The individualization of the anatomic variant defined as frontal sinus expanded into the pneumatic medium turbinatum, its histological description and the demonstration of a pressure gradient supports the presence of “rhinogenic” headaches not related to an abnormal contact between opposite mucosal surfaces (known as “contact point headaches”) [1]. This condition might represent a novel nosographic entity (“Fronto-Turbinalis Sinus Expansion Headache”). The utilization of nose and sinus endoscopy and high resolution CT allows to better explore peculiar anomalies of the structures of facial maxilla that may be responsible for a phenotype similar to contact point headaches [2, 3], but based on a totally different pathogenic mechanism.

Conclusions The documentation of an endo-sinusal hypertension in patients with FTUSE suffering from daily headaches in which contact points had been excluded, together with the demonstration of pain receptors, support the work hypothesis.

The complete and stable remission of the headache confirms the correctness of the clinical interpretation of the cephalalgic syndrome and the appropriate choice of the surgical procedure.

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MIGRAINE OUTCOME IN POSTMENOPAUSAL WOMEN: ANOTHER POSSIBLE PREDICTIVE FACTOR

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Background The outcome of migraine after menopause is highly unpredictable. It is well known that hormonal factors may play a role in triggering migraine attacks. Throughout women's reproductive life cycle, hormones fluctuations may provoke significant headache changes. All hormonal events (menstruation, pregnancy, oral contraceptives assumption, menopause and hormone replacement therapy) may alleviate or exacerbate migraine. Although migraine prevalence decreases with advancing age, after menopause frequency, severity and duration of migraine attacks can widely vary, in fact, they can either regress or worsen or remain unchanged [1].

The possibility to predict the outcome of the illness in this phase of women's life could be very useful, unfortunately, up to now, no certain data exist predicting the illness' outcome after the onset of menopause.

In previous studies [2, 3] we observed that the outcome of migraine after menopause in the majority of cases follows the one of the patients' mothers and that when migraine attacks are correlated to menstruation during reproductive life, it is more probable that after the onset of menopause migraine improves.

Objective Aim of this study was to identify the existence of other factors influencing the outcome of the illness. In order to find them, we studied the course of pre- and postmenopausal migraine in a number of postmenopausal patients, focalising our attention on the existence of a link between the evolution of migraine after menopause and the presence of dysmenorrhea during reproductive life, the number of pregnancies and the assumption of combined oral contraceptives (COCs).

Methods One hundred and seventy-eight women who experienced a natural menopause (at least 12 months of amenorrhea - age 35–78 yrs) suffering from migraine according to the ICHD-II criteria, referring for the first time to the Turin Headache Centre in the years 2003–2005, were studied. They were asked if and how the characteristics of migraine changed after menopause, if they had ever suffered from dysmenorrhea, if they had ever used COCs, if they had pregnancies and their eventual number. The data were statistically analyzed using the χ^2 test.

Results In 30 (16.85%) patients migraine improved after menopause, in 108 (60.67%) it worsened, while in the remaining 40 (22.47%) migraine remained unchanged.

Twenty-two (73.33%) of the 30 patients whose migraine improved after menopause had suffered from dysmenorrhea, while only 64 (59.25%) of the 108 patients whose migraine worsened after menopause and 22 (55.0%) of the 40 patients whose migraine remained unchanged showed this correlation (p:ns).

The number of pregnancies and the use of COCs did not show any link with the outcome of migraine after menopause.

Conclusions On the basis of these and previous data, it seems more probable that when migraine attacks are correlated with menstruation, after the onset of menopause migraine improves and in the majority of cases daughters' migraine seem to follow their mothers' pattern. Dysmenorrhea seems to be more frequent in the patients whose migraine improved after menopause than in others, while the number of pregnancies and the use of COCs do not influence the outcome of migraine after menopause.

Since, at present, there are little or no data on this particular aspect of the illness, more studies are needed to assess this tendency. If these data will be confirmed this will be a very useful indication for many women approaching the menopausal period.

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EFFECTIVENESS OF THE TELEPHONIC-CASE-MANAGEMENT OF THE HEADACHE PATIENT

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Introduction Headache is among the most diffuse medical conditions, its disabling nature has notable repercussions on the quality of life of the affected patients, and on the costs for the health care system and the society at large. Headache is mostly managed through outpatient care, with continuation of the therapy at home. The global therapeutic programme for this condition is, however, complex and of long duration and its success greatly depends on the continuity of care throughout the treatment period. This continuity is often not sufficiently guaranteed by the standard management approach, in which the patient is not regularly and strictly monitored by the health care personnel during the home period of treatment. In particular, the role of nurse assistance in the therapeutic plan has not yet been assessed. Based on these premises, this study evaluated the efficacy of a structured programme of assistance to the headache patient during home treatment, termed "telephonic-case-management" (TCM), coordinated by nurse personnel, vs. a standard management approach. The primary aim was to assess the effects on patients' adherence to the therapeutic regimen, quality of life and hospitalization rate. The secondary aim was to verify possible effects on pain symptoms.

Methods We evaluated 62 patients, 48 women and 14 men, aged 20–62 years, all affected with headache as diagnosed for the first time at the Headache Centre of the G. D'Annunzio University of Chieti. After receiving the diagnosis and therapy prescription, they were randomly assigned to 2 groups of 31 patients each to enter into either a standard programme of assistance (placebo group) or a "telephonic-case-management" programme (experimental group) for a period of three months. The standard programme involved a control visit at the Centre after the 3-month period, while the TCM, coordinated by a nurse, consisted of a structured programme of weekly phone contacts with the patient and a counseling service available throughout the treatment period. In both groups, the following were evaluated: subjective perception of physical and mental well-being (SWB) through the "SF 12 STANDARD V1" questionnaire at the beginning and end of the study; adherence to the therapeutic programme through compilation of an ad hoc "patient form"; number of hospitalizations; headache pain through weekly recording of the intensity (VAS scale) and number of attacks in a diary. The comparison of the parameters evaluated in the 2 groups was performed through the Student's *t*-test and chi-square test. The level of significance was established at $p < 0.05$.

Results In basal conditions, the two groups of patients were comparable with regards to mean age, life-style variables, headache characteristics, and subjective perception of their well-being. After treatment, in the experimental group the SWB became significantly higher than in the placebo group (score: 47.74 vs. 41.93; $p < 0.007$ for physical SWB; 45.5 vs. 34.87, $p < 0.002$ for mental SWB). Adherence to the therapeutic regimen was also higher in the experimental vs. placebo group throughout the treatment period, with a significant difference during the last weeks (8^{th} – 12^{th} ; $0.009 < p < 0.04$). No hospitalizations were recorded in the experimental group vs. 2 hospitalizations in the placebo group. Headache symptoms improved more in the experimental than placebo group, though the difference was not significant.

Conclusions A programme of assistance to the headache patient based on a structured system of phone counseling is able to improve the level of adherence of the patient to the therapeutic regimen. It is also effective in enhancing the patient's perception of

his/her physical and mental well-being, reducing the rate of hospitalizations in the phases of intense headache pain, with a consequent reduction of costs for the health care system.

A PATIENT PREFERENCE STUDY OF FROVATRIPTAN VERSUS RIZATRIPTAN FOR THE ACUTE TREATMENT OF MIGRAINE

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Introduction The objective of this double-blind, randomised, cross-over trial was to evaluate the preference of migraine patients to frovatriptan (F) and rizatriptan (R).

Materials and methods One hundred and forty-eight subjects with a history of migraine with or without aura (IHS criteria), with 1 to 6 migraine attacks per month in the 6 months preceding the study, were enrolled in 15 Italian headache centres. Subjects were randomised to either F 2.5 mg or R 10 mg and encouraged to treat 1 to 3 attacks for a maximum period of six months. At the end of the study patients were asked to assign preference to one of the treatments according to a questionnaire with a preference score graded from 0 (no preference) to 5 (strong preference): this was the primary study endpoint. Secondary study endpoints were: the number of pain free episodes at 2 hours, number of recurrent episodes within 48 hours, pain relief episodes at 2 hours, sustained pain free episodes within 48 hours, and headache intensity at 2, 4, 24 and 48 hours post-dose.

Results Data are shown for the intention-to-treat (ITT, patients having treated at least one episode of migraine with each medication and who expressed a preference) and for the per-protocol population (PP, patients having treated all three episodes without major protocol violations). As shown in the table there was no significant difference between the two treatments for patient preference. Rate of pain free, pain relief and sustained pain free episodes were similar (no significant difference), while the rate of recurrences was significantly lower under F, reduction of headache intensity, not different between the two drugs at 2 and 4 hours, was significantly ($p < 0.01$) lower with F after 24 and 48 hours.

Conclusions Most of the patients expressed a preference for a triptan: interestingly this preference was not uniquely related to a traditional end-point such as pain free at 2 hours, but also to other end-points like recurrence and sustained pain free that cover the

migraine attack during the 48 hours. These results are probably explained by the different pharmacological characteristics of F and R, in particular by the longer half-life of F that ensures its long lasting effect and results in a greater efficacy in preventing recurrent episodes than R. According to our results, the patient preference model seems to be a better hard end-point for the evaluation of triptans efficacy in migraine patients.

REVIEW ON THE MANAGEMENT OF MEDICATION-OVERUSE HEADACHE: THE STEEP ROAD FROM EXPERIENCE TO EVIDENCE

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Background Management of medication-overuse headache (MOH) is essentially based on the withdrawal of the overused drug. Drug withdrawal, however, is performed in very different ways and therapeutic recommendations for the acute phase of detoxification vary considerably among studies. Basically, the aims of MOH management are: a) to withdraw the overused drug; b) to alleviate withdrawal symptoms by means of a bridging programme, including pharmacological and non-pharmacological support, designed to help the patients to tolerate the withdrawal process; and c) to prevent relapse. Many questions regarding the strategies to achieve these goals are under extensive debate.

Methods The authors provide the best evidence available to the following questions: Should medication withdrawal be done abruptly or slowly? Should the patient receive replacement therapy? Which are the most effective therapeutic programmes for controlling withdrawal symptoms? Should replacement therapy be administered regularly or as rescue therapy? Should preventive treatment be started before, during or after withdrawal? Which are the most effective preventive treatments? Should patients be withdrawn in an in-patient or in an outpatient therapeutic setting? Which is the best approach to prevent the relapse?

Results and conclusions Treatment of MOH is difficult but very rewarding. High quality studies providing evidence-based answers to the multiple, specific questions pertaining to the treatment of MOH are still lacking. However, neurologists have to know that by combining education with a rationale use of the few therapeutic strategies may help people with chronic headache to greatly relieve their sufferings.

Table

	ITT (n=125)			PP (n=96)		
	F	R	P	F	R	p
Overall patients with no preference	(n, %)	21 (17)		14 (15)		
Overall patients with preference	(n, %)	104 (83)		82 (85)		
Patients with preference (n, %)	48 (38)	56 (45)	NS	42 (44)	40 (42)	NS
Average score (SD)	2.9 (1.3)	3.2 (1.1)	NS	2.9 (1.3)	3.2 (1.1)	NS
Pain free episodes at 2h (n, %)	117 (33)	141 (39)	NS	107 (37)	116 (40)	NS
Recurrent episodes (n, %)	77 (22)	117 (32)	<0.01	61 (21)	91 (32)	<0.01
Pain relief episodes at 2h (n, %)	155 (55)	166 (62)	NS	129 (61)	134 (60)	NS
Sustained pain free episodes (n, %)	95 (27)	93 (26)	NS	-	-	-

Comorbidity

PREDICTORS OF MIGRAINE DISABILITY SCORE IN THE MORE SEVERE SUBGROUP OF PATIENTS: A ROLE FOR DEPRESSIVE SYMPTOMS

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Introduction A close relationship between migraine and psychiatric disorders is well known [1], suggesting that a biological pathway, may be serotonin-driven, sustains this association [2].

Interestingly, in migraineurs, depression seems to be predicted by a more disabling headache picture [3].

Objectives To define predictors of migraine-related disability within the subgroup of more severe headache patients, focusing on psychiatric comorbidity and personality characteristics.

Materials and methods Patients (>18 y.o.) with diagnosis of migraine were enrolled. Exclusion criteria was co-occurrence of other types of headache. All clinical data were recorded by a well-trained neurologist that also completed a Migraine Disability Assessment (MIDAS) questionnaire. Psychiatric and psychometric characteristics were assessed by the Structured Clinical Interview for DSM-IV-TR (SCID), to investigate axis I disorders, and by a panel of self-report questionnaires: the Beck Depression Inventory (BDI); the Trait Anger subscale of the State-Trait Anger Scale (STAS-T); and the State-Trait Anxiety Inventory Form Y2 (STAI-Y2).

Results Three hundred and sixty-seven patients were recruited. The MIDAS mean score was 22.54±22.50. Class IV MIDAS subjects were 141, with a MIDAS mean score of 43.34±23.73. Age, sex, educational level, occupational condition, years of migraine duration, age at migraine onset, monthly attack frequency, monthly days with headache, attack duration, pain severity, presence of psychiatric comorbidity, BDI, STAS-T and STAI-Y2 were considered as independent variables for the analysis. On overall, population predictors of MIDAS were: monthly days with headache, pain severity, BDI score, sex, occupational condition, age at onset, STAS-T, monthly attack frequency and educational level. The model was highly significant ($p<0.0001$) and accounted for 35% of variance. In particular, BDI accounted for 5.5% of MIDAS mean score variance. When only patients belonging to IV MIDAS score were considered, results changed. Predictors of MIDAS score resulted to be: BDI, attack duration, monthly days with headache, years of migraine duration and sex. Model was highly significant ($p<0.0001$) and predicted 29.5% of MIDAS variance; BDI accounted for 11.5%.

Since depressive symptoms emerged as the main MIDAS predictor within patients belonging to the more severe group, we decided to detect predictors of BDI scores in the whole sample and, in particular, in the MIDAS IV subgroup. Predictors of BDI in the whole sample were: STAI-Y2, STAS-T, educational level, presence of psychiatric comorbidity and MIDAS total score. The model was highly significant ($p<0.0001$) and accounted for 67.4% of variance. In particular, MIDAS total score accounted for 0.8% of BDI variance. Predictors of BDI in MIDAS IV subgroup were only STAI-Y2, STAS-T. The model was highly significant ($p<0.0001$) and accounted for 65.4% of variance.

Discussion In our sample, we identified predictors of MIDAS score among clinical, socio-demographic and psychometric variables. Analysis was performed both on the whole population, and the severer subgroup (MIDAS IV group), to better understand if higher disability scores were related to the same predictors found in the lower scores.

Interestingly, the role of depression emerged in our analysis: a minor predictor in the general sample, but the main predictor in the MIDAS IV group, suggesting that depressive mood could be typical of severer forms of migraine. Shared serotonergic pathways could account for this observation. Besides, when predictors of BDI in the MIDAS IV group were searched, MIDAS score did not emerge as a predictor. In other words, in the fourth MIDAS group, depressed patients are likely to have higher MIDAS score, but patients with higher MIDAS score are not necessarily more depressed than others.

Conclusions Depression had a role in determination of the self-reported disability score in migraineurs; this association in not reciprocal and suggests the importance to evaluate (and eventually treat) the mood state in migraineur patients with higher MIDAS score.

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PSYCHOLOGICAL FEATURES AND POSSIBLE THERAPEUTIC FAILURE IN CHILDREN WITH CHRONIC MIGRAINE

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Objective To investigate the association between response to therapies versus psychological distress (anxiety, depression and somatic symptoms), as well as, versus social desirability.

Methods The investigation was conducted on 235 outpatients, 12–16 years of age, with a complaint of chronic migraine of at least 8 months duration. Parents were also interviewed by trainees. Children's Somatization Inventory, including 35 non-specific symptoms as "weakness", Children's Depression Inventory, containing 27 self-report items representing depressive symptoms, Revised Children Manifest Anxiety Scale, a 37-items questionnaire, and Lie Scales, as indicators of desirability influence, were administered. Clinical evaluation by trainees was also performed during an interview with the patients and their parents. Pharmacological therapy was prescribed and further evaluation was carried out after 3, 6, 12 months, following psychometric tests and interviews which were carefully performed.

Results The results of r in the Lie Scales were compared with a telephone sample of Group 1 which included 121 young adults suffering from chronic migraine (mean age 26 years ± 3.8 SD). Group 2 included the above mentioned 235 patients suffering from chronic migraine in development age. In this sample r value was 0.33. The difference between adults and children was clearly significant ($p>0.001$). Interviews with parents indicated that they believed in what the child suggested as being "true". Pearson correlation evidenced a correlation ($p>0.001$) between social desirability and pain variables. Social desirability was unrelated to basic demographic data or pain score. Clinical evaluation by trainees indicated a presence of depression and/or anxiety in all cases prevalently ($p>0.01$) higher than from psychometric tests. The battery of tests and the clinical interview were carried out during the first visit, before planning a therapy, which was independent of the results obtained with the psychometric tests. Therapy was evaluated after 3, 6, 12 months following the first visit. At the follow-up times, there was

no significant improvement in the young sufferers with abnormal score in social desirability neither by using beta-blockers nor tricyclic antidepressants.

Conclusions and speculation regarding relationship with therapeutic approaches Correlation between desirability and incongruity in clinical and test results regarding depression/anxiety was achieved as an attempt by the children “to appear normal” or to “fake good” in non-peer related activities; in other words, the very young sufferers sought to compensate for “loss of health and performance” by promoting themselves as having other virtues. Family behaviour can increase this abnormal self-reference and further alter the abnormal behaviour. In our study the high social desirability was associated to a clinical diagnosis of depressive/anxiety disturbance, thus the indices of well-being were opposite to the neuro-behavioural disturbance resulting in a bad therapeutic result regarding migraine. An intervention on the psychological disturbances was followed with success in a further pharmacological therapy.

MIGRAINE COMORBIDITY: A FALSE MYTH?

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Introduction Comorbidity is defined as an illness that occurs more frequently in association with a specific disorder than as a coincidental association found in the general population.

The common illnesses that are associated with migraine and influence its management include comorbid conditions such as depression, anxiety disorders, epilepsy, sleep disorders, and stroke and concomitant illnesses such as hypertension and obesity. Both comorbid and concomitant medical conditions impact migraine treatment. Psychiatric disorders that are comorbid with migraine include depression, anxiety, and bipolar disorder.

Discussion Understanding how to design treatment plans that address migraine in patients with other medical conditions is the focus of the classical pharmacological approach to treatment. Since comorbid medical and psychological illnesses are prevalent in migraine patients, one must consider comorbidity when choosing preventive drugs. Drug therapy may be beneficial for both disorders; however, it is also a potential confounder of optimal treatment of either.

A migraine patient tends to identify him/herself with the category of migraineurs, as in the associations of patients, because as Lacan said “*The symptom appears in the place of the subject’s name. The symptom is a metaphor of the subject*”.

When a symptom is a medical problem, an organic problem, we have to use pharmacology or surgery.

When a symptom is present in a repetitive mode associated to the same “comorbid” symptoms (depression, anxiety etc.), when they leave a “mark” in the subject, we are in the field of psychoanalysis. The meaning of the symptoms is always unknown to the patient, which led Freud to a stronger statement: “In order for the symptom to be produced, it is necessary that it be unconscious”. In other words, symptoms are not formed from conscious processes. This led Lacan to consider the meaning that was repressed in the symptom.

We have to investigate in the “*varieté*” of the symptom, an expression that refers at the same time to ‘truth’ and ‘variety’. There is always a link for Lacan between symptom and truth.

We should not consider if the migraine is “true” but if it is a symptom of something else, something that gives us the “*truth of the subject*”.

Conclusions Freud at the beginning of his studies said as a deduction from the principle “The symptom disappears when one suc-

ceeds in making its meaning conscious. Symptoms disappear as soon as their meaning is known.” In a certain way the economic factor of libido had not yet been imposed for Freud. It would be interesting to study how Freud formulated this principle, and then stated “it is not exactly like this...”. The principle is excellent, but the symptoms do not know it”.

We have to consider the fact that psychoanalysis is not the solution in any migraine, but we have to consider an integrated approach to the patient with migraine, not to consider him/her as “detached pieces”, using an expression of Jacques Alain Miller.

We cannot consider depression different from anxiety, from migraine and, so on, but we have to consider the patient as a suffering subject and for this reason psychoanalysis is a possible instrument.

The analytic discourse is intimately interwoven with that of science. Psychoanalysis does not fear the development of science, on the contrary, it is united with it, and offers to re-open what science forecloses: the subject understood as the subject of the unconscious who suffers.

ALEXITHYMIA IN EPISODIC AND MEDICATION-OVER-USE HEADACHE: A CONTROLLED STUDY WITH CELIAC DISORDER

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Introduction Alexithymia is a term used to describe a disorder where patients have difficulty in expressing their own feelings in words. It was initially used to denote an adaptive style creating a tendency to develop psychosomatic symptoms. However, a specific correlation between alexithymia and somatization could not be satisfactorily established. Alexithymia is poorly studied in headache disorders, but alexithymic traits have been evidenced both in migraine [1, 2] and medication-overuse headache (MOH) [3]. However, the link with headache is not clear. Alexithymia has been stated as both a primary and stable personality construct and a secondary state that is created as a reaction to medical illnesses.

Objectives To compare episodic headache, MOH and celiac disorder (CD) patients vs. healthy controls in order to understand the role of alexithymia in primary and secondary disorders.

Material and methods Four groups were enrolled: 50 episodic headache patients (38 f, 12 m; m.a. 40.39±10.65: MO and/or MA plus ETTH), and 164 MOH (127 f, 37 m; m.a. 45.53±12.12) according to the ICHD-II criteria; 80 CD (48/32; m.a. 37.55±9.97); and 100 healthy controls (60 f, 40 m; 37.34±10.61). The Toronto Alexithymic Scale (TAS-20) was self-administered. Data analysis was performed considering the three factors of the TAS (Factor 1: Difficulties in identifying feelings; Factor 2: Difficulties in describing feelings; Factor 3: Outside oriented thought;) plus the total scores. Data was analysed by Student *t*-test for independent data calculated among the parameter values assessed in all groups of patients. The *p* values ≤0.05 were considered significant.

Results Table 1 describes the main findings. Headache patients were statistically different by normal controls for each of the TAS factors, but they showed higher scores than CD only in Factor 3. We did not find differences between EH and MOH.

Table 1 Analysis of TAS factors in clinical samples and healthy controls

Patients	Factor 1	Factor 2	Factor 3	Total
MOH (<i>n</i> =164)	16.30±6.88*°	14.57±3.90*°	27.35±4.69*°	58.17±11.39*°
EH (<i>n</i> =50)	16.38±6.32*°	13.90±3.64*°	27.80±4.01°	57.84±11.86°
CD (<i>n</i> =80)	22.05±10.10°	17.78±6.24°	24.88±9.44°	64.51±23.93°
NCs (<i>n</i> =100)	10.96±3.73	10.35±3.82	11.64±4.80	33.16±8.84

Legend: *MOH* medication-overuse headache, *EH* episodic headache, *CD* celiac disease, *NCs* normal controls

All data are expressed as mean value ± standard deviation. The symbols refer to Student *t*-test for independent data calculated.

Significant differences: Factor 1: * *p*<0.001 vs. CD; ° *p*<0.001 vs. NCs; Factor 2: * *p*<0.001 vs. CD; ° *p*<0.001 vs. NCs; Factor 3: * *p*=0.007 vs. CD; ° *p*<0.001 vs. NCs; ^ *p*=0.040 vs. CD; Total: * *p*=0.005 vs. CD; ° *p*<0.001 vs. NCs

Discussion and conclusions Both EH and MOH patients showed significant alexithymic traits, but with a lower level than CD. The well-known organic basis of CD opens intriguing questions on the differences with headache and the possibility that alexithymia may be a psychological reaction to chronic CD. Of interest, the role of Factor 3 in headache patients that may suggest a primary personality characteristics: the tendency to be more prone toward external stimuli than internal ones. Alexithymia seems an important psychological factor involved in EH and chronic headache.

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STRUCTURAL ANATOMICAL VARIATIONS OF THE INTRACRANIAL ARTERIAL CIRCULATION IN MIGRAINE PATIENTS

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Introduction Epidemiological studies suggest that migraine may be a risk factor for stroke; the relationship between migraine, aura and stroke is complex and mechanisms other than a direct cause/effect relationship are hypothesised. Migraine aura may be the consequence, rather than the cause, of cerebral ischaemia. Several mechanisms are currently thought to contribute to migraine pathogenesis, but mechanistic concepts are unable to fully explain, either migraine susceptibility in individual patients or the well documented association between cerebrovascular disease and migraine, especially migraine with aura. As recently pointed out [1], the identification of structural anatomical variations in the cerebral vasculature in migraine patients would have important pathophysiological and clinical implications.

Materials and methods We retrospectively analysed the records of 248 outpatients, consecutively seen at the Headache Unit of the C. Mondino Institute of Neurology in Pavia between September 2006 and July 2008 and underwent magnetic resonance angiography (MRA). The patients were divided into two groups according to their primary headache, diagnosed in accordance with the criteria

of the International Classification of Headache Disorders, second edition (ICHD-II) [2].

Ninety-eight (98) patients were affected by migraine with aura (MA; Group 1) and 150 experienced only migraine without aura (MO; Group 2). Magnetic Resonance imaging was performed with the aid of a 1.5-tesla superconductive system and MRA was performed using time-of-flight technique.

Results Statistically significant differences (*p*<0.001) emerged between the two groups in the presence of structural anatomical variations in the intracranial arterial circulation.

In Group 1 (MA), 39 (40%) patients had an anatomical variations of intracranial arterial circulation: 25 (26%) showed variants in the posterior circulation, only 4 (4%) patients showed anatomical variations in the anterior part of the circle, while 10 (10%) subjects presented variants in both parts of the intracranial circulation.

Of the patients in Group 2 (MO), only 17 (11%) showed anatomical variations in the intracranial arterial circulation: 11 (7%) in the posterior circulation, 2 (1%) in the anterior circulation, and 4 (3%) in both the anterior and posterior parts of the circle.

Discussion and conclusions Given that aura and migraine are thought to be caused by cortical spreading depression, and taking into account the prevalence of structural anatomical variations in the posterior arterial cerebral circulation (also described as sex-linked) and the prevalence of infarcts in the posterior circulation territory in migraine [3], we suggest that the cerebral vascularisation could be linked to migraine/stroke and to susceptibility to aura symptoms.

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PREVALENCE AND CLINICAL CHARACTERISTICS OF MIGRAINE IN ELDERLY PATIENTS WITH CEREBROVASCULAR DISEASE

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Background Migraine is a disease with a presumed vascular mechanism that affects about 12% of the adult population in western countries [1]. Migraine and cerebrovascular disease often can co-exist in the elderly. It is unclear whether migraine and cerebrovascular disease are linked, the relationship between them is an ongoing matter of debate.

Objective The aim of the present study was to determine one-year prevalence of migraine in elderly patients with cerebrovascular disease compared with a control group with no vascular disease to better study the relationship between the two clinical conditions.

Materials and methods Patients referring to our Centre were given a questionnaire, based on the IHS criteria. Patients were included in the study if they met the following criteria: an established diagnosis of migraine as defined by the IHS criteria; a MMSE score >24; an educational level of ≥ 5 ; ability to recognize a migraine headache while intensity was mild. Exclusion criteria included: a history of basilar, ophthalmoplegic or hemiplegic migraine headache; a history of other potentially serious neurological conditions associated with headache; frequent non-migraine headaches; and a medical or psychiatric condition that could interfere with data collection. Cerebrovascular patients were compared to a control group with no vascular disease. One-year migraine prevalence rates were reported as cases per 100 subjects.

Results We identified 146 patients (80 females, 54.8%; 66 males, 45.2%) with cerebrovascular disease, aged 58–80 years (mean 69 years) and 154 controls (88 females, 57.1%, 66 males, 42.9%), aged 57–79 years (mean 68 years). The two groups were well balanced with respect to demographic and migraine characteristics. One-year prevalence rate was 8.2% (12/146) in patients with cerebrovascular disease and 8.3% (12/144) in controls. Prevalence rates were higher in women than in men for both patients with cerebrovascular disease (4.8% vs. 3.4%) and controls (4.8% vs. 3.5%). Age-onset of pain was under 65 years in 66.7% (8/12), whereas it was over 65 in the remaining 33.3% (4/12). In controls it was 75% (9/12) under 65 years and 25% (3/12) over 65 years. Intensity of pain was moderate in 50.0% (6/12), severe in 16.7% (2/12) and low in 33.3% (4/12) of patients with cerebrovascular disease; while in controls it was moderate in 58.3% (7/12), severe in 8.3% (1/12), and low in 33.3% (4/12). The type of pain was throbbing in the two groups. The duration of pain was over 4 hours in all migraineurs.

Discussion From our results, it appears that frequency and clinical characteristics of migraine did not differ significantly between the two groups. These prevalence rates indicate that many people at this age experience migraine, supporting the high socioeconomic impact of this kind of headache. We found a higher frequency in women than in men, but the female/male ratio was lower than those reported in younger patients [2]. Nevertheless, the gender characteristic should be taken into consideration in migraine treatment design also in the elderly. Migraine age-onset was higher under 65 years and it decreased slightly with age; than the role of migraine as a risk factor for cerebrovascular disease loses significance with increasing age [3].

Conclusions It was concluded that migraine is a common health problem among elderly patients with cerebrovascular disease but, according to the literature, it seems it is not strictly associated with this vascular disease. Differential diagnosis between the two conditions remains an important issue, because some types of migraine can mimic cerebrovascular disease. Further clinical studies including a large number of patients are needed to better examine this complex relationship between migraine and cerebrovascular disease, to define health care planning and for implementation of correct preventive and treatment measures.

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PATIENTS WITH MIGRAINE AND IRRITABLE BOWEL SYNDROME PRESENT AN ABNORMAL POSTPRANDIAL TONIC AND PHASIC RECTO-SIGMOID MOTOR ACTIVITY

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Background and objectives We have recently shown that in patients with migraine and functional dyspepsia an alteration of postprandial gastric sensorimotor function is evident [1, 2]. Alterations of both visceral sensitivity and motor activity are also described in IBS due to alterations of the serotonergic pathways. There is also an association between irritable bowel syndrome and migraine and alterations of serotonin receptors in the pathophysiology of migraine. We therefore evaluated recto-sigmoid sensorimotor activity in IBS patients with and without migraine.

Patients and methods Twelve patients with migraine without aura (ICHD-II criteria) and IBS (39±10 yrs, range 28–60, 11 females, 5 constipated), 18 patients with IBS (42±13 yrs, range 29–72, 14 females, 7 constipated) and 10 healthy volunteers (28±6 yrs, 9 females) underwent the recto-sigmoid barostat test as previously described [3]. IBS diagnosis was made according to the Rome III criteria. After an overnight fast, a double lumen polyvinyl tube with an adherent, infinitely compliant plastic bag (1200 ml capacity), finely folded, was inserted through the anus as far as the recto-sigmoid junction. The perception and discomfort thresholds were investigated during fasting and the postprandial period (200 Kcal, 200 ml liquid meal) through a series of rectosigmoid distentions; at the end of each distention, patients were asked to assess the sensation using a standardized scale from 0 (no sensation) to 6 (pain), were 1=perception and 5=discomfort. During the test, we evaluated modification of rectosigmoid tone, as the difference between mean 60-min post-prandial volume and mean 30-min fasting volume; rectosigmoid phasic activity was quantified using a motility index during three 30-min periods: fasting period, first and second 30-min period after administration of the meal. A baseline reconstruction was performed using a computerised algorithm and a motility index was calculated as the area between the signal and the baseline normalised over time.

Results Results are expressed as 25th to 75th percentile. As expected, in IBS patients the discomfort threshold was significantly lower than in HV, but no difference was found between patients with and without migraine.

IBS patients with migraine (+12% to +33%) and without migraine (0% to +12%) showed a postprandial rectosigmoid tone modification significantly different when compared to healthy volunteers (-84% to -12%; $p < 0.05$). Postprandial rectosigmoid tone modification was more profoundly impaired in IBS patients with migraine than patients without migraine ($p < 0.05$).

IBS patients with migraine (+30 to +70%) and without migraine (-57% to +1%) showed a postprandial modification of motility index significantly different from healthy volunteers (+1 to +40%; $p < 0.05$). IBS patients with migraine showed a postprandial modification of motility index significantly different from patients without migraine ($p < 0.005$).

Conclusions IBS patients with migraine suffer from an alteration of postprandial rectosigmoid motor function.

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THE PSYCHIATRIC COMORBIDITY OF PRIMARY HEADACHES IN A NEUROLOGICAL TERRITORIAL CENTRE: PRELIMINARY DATA OBTAINED BY THE MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

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Introduction Psychiatric comorbidity of headaches is a clinically relevant phenomenon, needing further systematic research especially in regards to the use of standardized screening procedures which consent uniformity in the identification and assessment of psychiatric disorders in primary headache patients [1].

Objectives To assess the prevalence and types of Mood and Anxiety DSM-IV Disorders in a sample of 175 ICHD-II primary headache patients, 32 males (18.3%) and 143 females (81.7%), aged between 16 and 65 years (mean 38.4) consecutively referred to a headache territorial centre.

Methods The sample included 71 patients with Migraine (40.5%), 82 with Tension-type headache (46.4%), 9 with Cluster headache (5.1%), and 14 with Daily chronic headache (8%).

All subjects were administered the Mini International Neuropsychiatric Interview (MINI), a structured diagnostic interview developed in 1990 for DSM-IV and ICD-10 psychiatric disorders [2], opportunely modified for assessment of only mood disorders (Major Depression, Dysthymia, Bipolar disorder II) and anxiety disorders (Panic Disorder, GAD, OCD). The administration time was approximately 15 min. All interviews were performed by our group, 1 neuro-psychiatrist and 4 clinical psychologists trained and experienced in the use of MINI.

Results Ninety-eight (56%) headache patients assessed with MINI-plus received a lifetime Axis I DSM-IV disorder: in particular, 58.1% ($n=57$) met criteria for one MINI disorder, 41.9% ($n=41$) for two or more disorders.

Regarding the prevalence of Mood disorders in migraineurs, data showed the highest percentage of lifetime Depressive Episodes in Chronic migraine (50%) respect to Migraine without aura (21%) and with aura (12%).

Anxiety disorders present the highest percentage in Migraine without aura: in particular Panic Disorder - current or past - was found in 23.7% of the patients in respect to 20% of Migraine with aura and 12.5% of Chronic migraine patients.

Conclusions The results of this preliminary study show the high frequency of psychiatric disorders among recurrent headache patients.

Next steps consist in increasing the size of the sample and organizing a comparison group of healthy controls without a personal history of headache, matched by age and sex.

The use of MINI associated to a psycho-clinical approach can constitute a valid instrument for the identification of headache patients with psychopathological syndromes and can consent to evaluate the impact of psychiatric disorders on headache symptoms and to identify optimal pharmacologic, behavioural, and psychological treatment strategies.

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Case Reports

THE ROLE OF HOSPITALIZATION IN THE TREATMENT OF CHRONIC DAILY HEADACHE

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Introduction Idiopathic headache can be characterized by psychiatric comorbidity or emotional and behavioural aspects that need comprehension in order to make recovery possible and lasting. As in adults, also in childhood, the literature highlights psychiatric comorbidity among the purposes leading to in-patient treatment and the significant role of emotional factors in headache [1, 2]. A study of ours, about children with newly diagnosed and disabling headache, both migraine and tension-type headache, confirmed the benefit of a more complete assessment and a psychological support provided by hospitalization [3]. Moreover, headache children and their parents deal with headache with great concern because of a possible organic cause, making psychological factors even more significant. We report the cases of two headache children, managed in an in-patient setting, to underline the role that hospitalization offers in performing instrumental exams and promoting comprehension and management of emotional and psychological aspects.

Case Histories Case 1: (N. 13-year-old). Positive headache history on the mother's side of the family. Uneventful personal history. Headache onset (tension-type headache) at twelve years of age with progressive course (i.e., higher frequency and longer duration of headache attacks over time). Symptomatic therapy: FANS, with partial benefit. At admission, N. had been suffering from daily headache for three weeks.

Case 2: (M. 13-year-old). Positive headache history on the mother's side of the family. History of growing pains. Headache onset (migraine without aura) at eleven years of age with progressive course. Different symptomatic and prophylactic drugs without benefit. At admission, M. had been suffering from chronic daily headache for the past six months.

Assessment and treatment Both patients were hospitalized. Interviews highlighted both children's and parents' concern about a possible underlying serious disease. Neurological examinations were normal and a secondary headache was excluded by means of brain MRI and ophthalmological assessment. Clinical observation and emotional/behavioural questionnaires (SAFA, CBCL) did not point out a major psychiatric comorbidity, but highlighted emotional problems in the role of headache pathogenesis and, in one case, a significant life event. Psychological approach allowed a better integration of physical and psychological aspects and management of underlying psychological factors

Case 1: N. showed a moderate introspection character, difficulties in coping with anxious situations, ambivalence regarding the separation-individuation process and a high IQ (144). His parents confirmed the same troubled areas and showed their own difficulties in favouring the child's growth process (e.g. father's push for success and mother's regressive care attitude). Both N. and his parents

showed a good inclination to think over their behavioural and emotional attitudes. During hospitalization, headache intensity and frequency improved, and, after one month, the child was headache free.

Case 2: Interviews revealed that a violent familial event had happened when M. was a small child. Our patient was still unable to cope with and elaborate the memory of that traumatic event. The event itself changed the family's dynamics: the father became submissive and detached, the mother became unable to keep the right distance from the child, interfering with the separation-individuation process. During hospitalization, it was possible to help the patient and his parents to think about the traumatic event and the subsequent emotional difficulties. A prophylactic treatment was started (flunarizine 5 mg/day) and, at two-month follow-up after discharge, the child was headache free.

Discussion and conclusions Our cases show that psychological factors have a role in chronic daily headache, even in the absence of evident psychiatric comorbidity. A comprehensive approach during hospitalization, allows to better understand patients' psychological functioning, unsolved life-events and troubled circumstances and favors the child's and parents' acquisition of a more adaptive way of thinking and a more empathic attitude. Finally, in our experience, the effectiveness of prophylactic drug treatment may be influenced by a comprehensive approach, taking into consideration the patient as a whole.

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PAINFUL OPHTHALMOPLÉGIA IN A PATIENT WITH MENINGIOMA: A CASE REPORT

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Background Ophthalmoplegic migraine is a rare disorder characterized by recurrent episodes of migraine-like headaches associated with cranial nerve palsy (especially the third cranial nerve) in the absence of intracranial lesions [1]. The cranial nerve palsy develops together with headache or in the following four days. Painful ophthalmoplegia can be caused more frequently by an aneurysm, a tumour or an inflammatory granulomatous process of the cavernous sinus or orbit [2].

Clinical case We report a case of a 46-year-old man with a long history of ophthalmoplegic migraine. The patient had a family history of migraine (father and grandfather). No other diseases were referred. The first attack presented at 16 years of age with unilateral pulsatile pain associated with right ptosis, diplopia and extrinsic ocular musculature palsy prolonged for 15–20 days; he, therefore, underwent a CT scan, carotidography and EEG: all were normal. At the age of 41 he presented rare attacks of migraine associated with ophthalmoplegia. He underwent brain MRI and he repeated EEG: both were normal.

At 43 he came to our observation for a new episode of ophthalmoplegic headache on the right side: he was admitted to our Department. The neurological exam showed: right ptosis, diplopia in all directions, left lateral and up and downward gaze and reduced right pupil reflex. We performed brain MRI and angiMRI which

were negative. Transcranial Doppler showed a little right to left shunt, not confirmed by transesophageal echocardiography.

In the following three years he also developed frequent attacks of migraine without other signs, and therefore he took different types of prophylactic drugs (e.g. topiramate) with improvement of headache in terms of reduced frequency and intensity.

At 46 he was admitted again to our Department for a new episode of ophthalmoplegic headache with the same sign and symptoms but at this time the pain associated to diplopia and ptosis were more prolonged (occurred 35 days before and currently present) and more evident with right pupil reflex absent.

Brain MRI was performed again: it showed an expansive process which left an impression on midbrain on the right side, on the third cranial nerve due to a small meningioma.

Conclusions Ophthalmoplegic migraine is an extremely rare disorder and therefore it is necessary to exclude alternative aetiology of headache with palsy, especially when the patient has a long history of headache.

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SECONDARY SUNCT SYNDROME CAUSED BY VERTEBRAL ARTERY OCCLUSION

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We report the case of a 90-year-old woman without familial nor personal history of headache. No hypertension nor diabetes nor smoking in anamnesis.

At the age of 87, she suffered from an ischaemic stroke in the territory of the vertebral artery conditioning dysarthria, dysphagia, hypoesthesia on the left side of the face and in right limbs, and left-sided dysmetria. A CT scan showed hyperintensity of the left vertebral artery suggesting a recent occlusion, confirmed by the successive MRI brain scan, which also revealed multiple ischaemic lesions especially in the posterior fossa involving both the cerebellar hemispheres and the medulla oblongata on the left side.

One month later, the patient began to refer recurrent episodes characterized by intermittent and short-lasting pain localized in the left hemiface associated with conjunctival injection and tearing. These attacks lasted about 30–40 seconds with a frequency of about 30 attacks/day. We do not know the response to lamotrigine because the patient refused this therapy. Pregabalin was ineffective.

This clinical picture is compatible with SUNCT according to the IHS criteria but because of the temporal relationship between vertebro-basilar stroke and headache onset, we define it a SUNCT syndrome secondary to posterior fossa ischaemia (headache attributed to ischaemic stroke according to the IHS classification 6.1.1); there are some reports in the literature about SUNCT secondary to fossa posterior lesions (tumours [1], vascular anomalies [2], etc.) but none regarding post vertebro-basilar stroke.

The other peculiarity of this case is the patient's age at the onset of the symptomatology; in the literature only one case of primary SUNCT with onset at the age of 88 years [3] has been reported.

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HEMICRANIA CONTINUA AND CONCOMITANT EPISODIC CLUSTER HEADACHE: REPORT OF TWO CASES

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Introduction Hemicrania continua (HC) is a rare, indomethacin-responsive headache disorder characterized by a continuous unilateral headache that varies in intensity, waxing and waning without disappearing completely. Exacerbation of pain is often associated with autonomic disturbances. HC was included in chapter IV “Other primary headaches” in the second edition of the International Classification of Headache Disorders (ICHD-II). Some authors deem it should more properly be classified among the trigeminal autonomic cephalalgias (TACs). In two case reports [1, 2] HC was observed in patients with a concomitant history of cluster headache (CH).

Materials and methods We report two cases fulfilling the ICHD-II criteria both for HC and for CH. They were males, 38 and 35 years old, respectively. In the first patient (case 1) HC started earlier and was right-sided, while the onset of CH occurred 4 years later, contralaterally. In the second patient (case 2), CH started earlier and was left-sided, and when he began to suffer from HC the pain was ipsilateral. Both patients underwent extensive investigations, including brain MRI and Angio-MRI, which did not reveal abnormalities.

Results Case 1: This patient started suffering from a daily right-sided headache since the age of 24. The clinical features were thoroughly consistent with a HC diagnosis, and the absolute response to indomethacin confirmed it. He could maintain a pain-free status by taking 25–50 mg/day of this drug. When he was 28 a contralateral headache started, fulfilling the ICHD-II criteria for episodic CH. The response to treatment, including subcutaneous sumatriptan acutely and verapamil prophylactically, was excellent. **Case 2:** This patient developed a typical picture of episodic CH when he was 21. The attacks came in bouts of nearly 30 days with intervening breaks of 10–14 months. The response to subcutaneous sumatriptan for attacks and to verapamil 480 mg/day as prevention was extremely good. At the age of 33 he started complaining of ipsilateral continuous hemicranial headaches. The pain was usually mild to moderate but one to two times a month the patient experienced exacerbations which lasted up to 24–36 h, characterized by severe periorbital pain accompanied by ipsilateral lacrimation and nasal congestion. Following a tentative diagnosis of HC, the patient was commenced on indomethacin 200 mg/day. The headaches promptly disappeared, but two months later the drug was discontinued due to severe gastric ache and subsequent endoscopic evidence of ulcerative gastritis. Thereafter, the patient was started on pregabalin with progressive titration up to the dose of 300 mg daily, when he reported a complete pain-free condition.

Discussion The coexistence of different strictly unilateral headaches in the same patient has been previously reported in a few cases. The commonest association was noted between CH and paroxysmal hemicrania (PH). More recently, we published the first case of HC with contralateral episodic CH [1], and later a second case with the same clinical features was documented [2]. We observed a third patient with concomitant HC and CH, but unlike the other two cases, the headaches were ipsilateral. In a further patient an evolution from CH into HC was noted [3]. From these clinical evaluations, even if sporadic, it could be argued that HC and CH might share some pathophysiological aspects. Actually,

recent positron emission tomography (PET) imaging studies have shed some light on the possible pathophysiology of HC, showing the activation in the contralateral posterior hypothalamic gray.

Conclusions The most recent functional brain imaging studies have shown the activation of posterior hypothalamus in CH, PH, SUNCT and HC, thus there seems to be a unifying biological argument to group these disorders. These findings, in association with the above reported case reports, would suggest to bring HC into the TACs.

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PROPHYLAXIS OF HEMICRANIA CONTINUA: TWO CASES EFFECTIVELY TREATED WITH PREGABALIN

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Introduction Hemicrania continua (HC) is an uncommon primary headache disorder characterized by a continuous, strictly unilateral headache of low-grade intensity with superimposed exacerbation periods of increased pain intensity and associated autonomic symptoms. HC is one of the indomethacin-responsive headache disorders. We report two cases fulfilling the International Classification of Headache Disorders second edition (ICHD-II) criteria for HC; one of the two patients suffered also from ipsilateral episodic cluster headache. Indomethacin was effective in both cases, but was poorly tolerated and its efficacy was not sustained, thus it had to be tapered off. Both patients afterwards had a complete and prolonged response to pregabalin.

Materials and methods We have prospectively followed-up two male patients, 35 and 48 years old, respectively, suffering from HC. At the onset of headache, the patients underwent extensive investigations, including brain MRI and Angio-MRI, which resulted normal.

Results The 48-year-old patient first presented when he was 45 with a constant left-sided headache, with exacerbations of severe pain, associated with nasal congestion. He was commenced on oral indomethacin 150 mg/day and the pain promptly subsided. However, 4 months later, his response to indomethacin appeared to fade and gastric discomfort was reported. Indomethacin was replaced with pregabalin, that was titrated up to the dose of 600 mg/day. The patient reported a significant improvement on pregabalin 300 mg/day and became completely headache free with pregabalin 600 mg/day. He has been thereafter followed-up for over 3 years and has remained pain free. Attempts to lower the dosage of pregabalin have resulted in a return of the headache within 14 days. The tolerability of the drug was excellent, since the patient did not report any significant adverse events. The 35-year-old patient began to suffer from episodic left-sided cluster headache at the age of 21. The attacks responded completely to subcutaneous sumatriptan, whereas preventive treatment with verapamil 480 mg/day was quite effective. When he was 33 he started complaining of ipsilateral hemicranial headaches, which were constant, but waxed and waned in severity. The pain was usually mild to moderate but one to two times a month the patient experienced exacerbations which lasted up to 24–36 h, characterized by severe periorbital pain accompanied by ipsilateral lacrimation and nasal congestion. Following a tentative diagnosis of HC, the patient was commenced

on indomethacin 200 mg/day. The headaches promptly disappeared, but two months later the drug was discontinued due to severe gastric ache and subsequent endoscopic evidence of ulcerative gastritis. Thereafter, the patient was started on pregabalin with progressive titration up to the dose of 300 mg daily, when he reported a complete pain-free condition. An attempt to lower the dose to 150 mg resulted in the recurrence of mild continuous headaches. The tolerability of pregabalin was good, since the patient reported only mild dizziness. During the follow-up period he had a bout of cluster headache, which responded to his standardized treatment.

Discussion HC has a prompt and enduring response to indomethacin 25–300 mg/day. The complete response to this medication is a prerequisite for diagnosis by the classification criteria of the ICHD-II. Unfortunately, a significant proportion of treated patients develop gastrointestinal adverse effects that necessitate cessation of treatment. Moreover, sporadic unresponsive cases have also been described. Patients who cannot tolerate indomethacin pose a difficult management challenge, since no evidence-based recommendations for alternative drugs are available.

Conclusions Drugs other than indomethacin have proven to be effective in HC. They include anti-inflammatory agents, such as piroxicam β -cyclodextrin and rofecoxib, verapamil, melatonin and neuromodulators, such as topiramate, gabapentin, and valproate. This is the first report of the responsiveness to pregabalin in the treatment of HC.

HEMICRANIA CONTINUA SECONDARY TO TRANSDERMAL NITROGLYCERINE

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Introduction Hemicrania continua (HC) is a rare form of primary headache included in the fourth chapter of the International Classification of Headache Disorders – 2 edition (ICHD-II; code 4.7). Despite the low prevalence of the primary form, a number of secondary cases have been previously reported.

Material and methods A 66-year-old man presented with a three-month history of a daily strictly unilateral headache, located in the right fronto-parietal region. He described the pain as dull, mild in intensity for the most part of the day but with 2 to 3 severe exacerbations lasting 45–60 min, during which he noted ipsilateral ptosis, lacrimation and nose stuffiness. As for acute treatment acetaminophene, ibuprofen and ketoprofen did not provide any benefit. The clinical history revealed a pre-existing headache fulfilling the ICHD-II criteria for migraine without aura. The patient reported the onset of a completely new headache, strictly associated with the treatment with transdermal nitroglycerine, recommended by a cardiologist for coronary heart disease. The new headache started within 24 hours of the use of transdermal nitroglycerine. As a result of this adverse event, in agreement with the cardiologist, we suggested to withdraw the vasodilator therapy. As a consequence, the headache abated within 24 hours. A direct relationship has been confirmed by the recurrence of the headache 6–12 hours after nitroglycerine reintroduction. This new therapeutic attempt was preventively arranged with the patient.

Discussion Nitric-oxide donor induced headache is a well-known entity; ICHD-II provides the diagnostic criteria for an immediate (code: 8.1.1.1) and a delayed (code 8.1.1.2) form, whose occurrence is more frequent in migraineurs, with features that should resemble migraine without aura attacks. Furthermore, the occurrence of a new headache as a side effect of a drug used for another condition is a well-known entity, and the diagnostic criteria are

specified in the ICHD-II criteria (code 8.1.10). They include the close relationship between the onset and the disappearance of the headache, respectively with the introduction and withdrawal of the drug; no mention about the clinical features of the headache is reported. Although a diagnosis of both nitric-oxide donor induced headache and headache as an acute adverse event attributed to medication used for another indication should be suggested in our patient, as a matter of fact the headache clinical features met the ICHD-II clinical criteria for HC, with the exception of the indomethacin response, which was not tested.

Conclusions To our knowledge, this is the first report of the occurrence of a headache with clinical features of HC related to transdermal nitroglycerine.

SUNCT OR FIRST DIVISION TRIGEMINAL NEURALGIA ASSOCIATED WITH CEREBELLAR HYPOPLASIA: A NEW REPORT RELATED TO A POSTERIOR FOSSA MALFORMATION

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Introduction Short-lasting unilateral neuralgiform headache (SUNCT) is a rare form of trigeminal autonomic cephalgia (TAC) characterized by neuralgiform pain in the territory innervated by the first trigeminal division associated with conjunctival injection and tearing. The diagnosis of SUNCT is often confused with another rare syndrome, the first division trigeminal neuralgia (TN) [1]. Few cases of SUNCT are secondary (symptomatic), mainly associated with either posterior skull or pituitary gland lesions [2, 3], although other sites have been documented. In this report we describe a new case with clinical features resembling SUNCT or TN associated with a posterior fossa abnormality. The few cases of SUNCT or first division TN secondary to pathologies of posterior fossa were reviewed and discussed in support of a unique nosology of these two rare syndromes.

Case report A 54-year-old man (height: 148 cm) for the last fourteen years, at onset in concomitance with a period of stress, presented periods of headache attacks of undefined lengths. The latest episode lasted more than a year without remission. He presented a stabbing daily headache located on the left side of the forehead, with single stabs of 7–8 seconds occurring 12–13 times per hour, even nightly, with ipsilateral conjunctival injection and tearing. His medical history showed a strabismus corrected when he was 4 years old and clavicular and malleolar fractures. Brain magnetic resonance imaging (MRI) with gadolinium showed a small posterior skull and a cerebellar hypoplasia, without dysplasia, and a straight sinus orientated vertically due to the vertical insertion of tentorium. Aspecific subcortical frontal white matter hyperintensities were present bilaterally. Over the years the patient was treated with antidepressant and anxiolytic drugs without efficacy, and various diagnoses of depression, hypochondria, and anxious neurosis were made. In the latest episode, treatment with gabapentin (900 mg/day) was ineffective, while treatment with gabapentin associated with carbamazepine (600 mg/day) was effective in eliminating the stabs apart from those in the awakening period.

Discussion The diagnosis of SUNCT is often confused with TN, particularly in the first division TN. The distinction between first division TN and SUNCT is certainly blurred and there is potential for overlap. There was no clear differences in age of onset, duration of attacks, diurnal variation (also nocturnal presence), autonomic symptoms, cutaneous triggers, treatment response, presence of aberrant vascular loops potentially irritating the trigeminal nerve. Coexistence of SUNCT and trigeminal neuralgia in some patients are also described. The symptoms of the case presented are compat-

ible both with SUNCT or TN. The characteristic of the case is the small posterior skull with a cerebellar hypoplasia. To our knowledge this may be the first case to describe SUNCT associated with cerebellar hypoplasia. It is remarkable that most of the lesions found in association with SUNCT involved the posterior fossa or, in general, the posterior part of the brain. A case of SUNCT associated with osteogenesis imperfecta, characterized by distortion of posterior fossa anatomical relations was previously described. Osteogenesis imperfecta was also associated to second and third division TN. Another case of secondary SUNCT was reported in a patient with cranesynostosis with foreshortened posterior fossa. In addition to the previous bone deformations, vascular malformations close to trigeminal root were described in a few cases of SUNCT. We cannot diagnose exactly the cranial malformation in our case report, because of the lack of other information. Defining and classifying congenital cerebellar abnormalities remains today, difficult and confusing. Some inferences, however, can be drawn. The small posterior skull with cerebellar hypoplasia associated with a short height and the bone fractures could be compatible with a mild form of osteogenesis imperfecta, for example a type IV of the Silience classification. Theoretically our case report may also be compatible with another bone deformation of the posterior skull, the Chiari I malformation. The most likely explanation of Chiari I malformation is in fact a small (hypoplastic) posterior fossa. In addition to few reported cases of TN associated to Chiari I malformation involving the second and third trigeminal division, a case of an isolated first division TN without autonomic features was recently described. The very similar features of SUNCT and first division TN, and the few cases associated with bone deformation of the posterior skull, support a unique nosology of these rare syndromes.

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A SHORT-LASTING UNILATERAL HEADACHE WITH AUTONOMIC SYMPTOMS IN A TWO-YEAR-OLD CHILD: IS IT A SUNCT?

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Introduction Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) is a rare primary headache syndrome first described in 1978.

SUNCT was included in the second edition of the International Headache Classification (2004), as a syndrome characterized by unilateral orbital, supraorbital or temporal, stabbing or pulsating pain, lasting from 5 to 240 sec, with ipsilateral conjunctival injection and lacrimation. The attacks should occur with a frequency of 3–200/day. SUNCT is rarely reported in childhood. To our knowledge, no cases with onset before the age of 5, have been reported. We describe a case of a 2-year-old child who was diagnosed with this syndrome.

Case description A 2-year-old female presented to the Neurological Emergency Room of the Giovanni XXIII General Hospital in Bari, because she had begun to suffer a painful attack in the morning, persisting for 6 hours. The stabbing pain involved the right frontal and periorbital area, with ipsilateral conjunctival injection, swelling of the eyelids and tearing. Except for duration, (from 5 sec to 30 sec.) the attacks were stereotyped including the occurrence and features of autonomic signs. The attacks recurred in a single stab (from 1 to 6 stabs/h), for a total of more than 40 attacks. Painful attacks appeared especially upon awakening in the morning, in the afternoon, and one hour after sleep. She was free from pain at night time, during sleep, unless she got up. The next morning showed only rare attacks concentrated in the first hour after awakening. No evident precipitating mechanisms of the attacks were identified. Her general physical examination was normal including a completely normal neurological examination except for autonomic symptoms during typical attacks. The ocular examination with eye movements was normal without diplopia. EEG performed during a recurrence of attacks was normal. MRI and AngioMRI of the cranium were completely normal without intracranial or orbital abnormalities. Based on the typical clinical findings and the normal MRI, we diagnosed SUNCT syndrome. The spontaneous remission in a few hours did not require prophylactic therapy. At the last follow-up, after three months, the patient was still symptom free.

Conclusions This child suffered from repetitive paroxysmal unilateral pain attacks, associated with ipsilateral conjunctival injection, swelling of the eyelids and tearing. The natural history of SUNCT is poorly understood: generally a periodic pattern has been reported, with active periods erratically alternating to remission phases. In our case, after an active period lasting 2 days, the disease disappeared completely. However, the typical features of the disease (unilateral pain, short duration and high frequency of the attacks, autonomic signs ipsilateral to pain, numbers of attacks) were all present. Furthermore, it is very likely that the active period lasting 2 days could be the expression of the clinical variability of the disease. On the other hand, the diagnostic criteria of the IHS classification for SUNCT did not include the duration of disease.

A prolonged follow-up of this patient with an early onset of the disease may be useful to better understand the natural course of SUNCT, even if the disappearance in a few days could confirm the possibility of good prognosis in childhood.

A CASE OF SHORT-LASTING UNILATERAL NEURALGIFORM HEADACHE WITH CONJUNCTIVAL INJECTION AND TEARING (SUNCT) COEXISTING WITH TRIGEMINAL NEURALGIA

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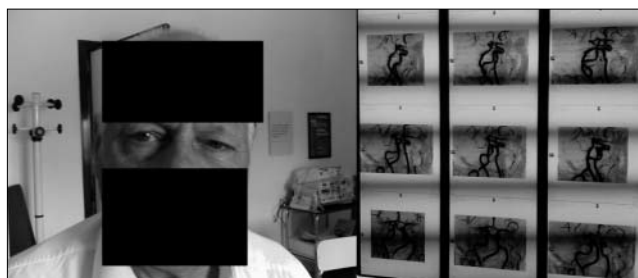
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Case report A 72-year-old man was admitted to our Headache Centre in August 2006 because, since December 2005, he suffered from unilateral (hand) attacks of orbital headache, sometimes with temporal stabbing which irradiated in the nasal zone and palate; pain was almost always triggered by touching small areas in the nasolabial fold and/or palate and trigger areas. Allodynia and hyperalgesia were present in these areas. The pain quality was described as burning, throbbing and brief shock-like. The attacks were extremely frequent (from eight to ten times per day, not during the night) lasting 2–3 min, associated with evident ipsilaterally conjunctival injection and lacrimation, eyelid ptosis and myosis. Between paroxysms, the patient could present a mild burning sensation in the nasolabial area. Magnetic resonance imaging of the brain before and after administration of gadolinium revealed the

presence of a conflict at ponte level between the V cranial nerve and the complex vertebral-basilar artery which occupied the cistern of the angle ponto-cerebellar of the same side of the pain.

Treatment with carbamazepine and amitriptyline has shown no efficacy. New treatment with oxcarbazepine at the dosage of 450 twice daily was effective for seven months and administration of sumatriptan during the attacks decreased the autonomic symptoms and the eye/orbital pain. At the clinical control in the month of May 2007, pain was always triggered by eating and sometimes by speaking; a variety of associations: oxcarbazepine with pregabalin and oxcarbazepine with lamotrigine at the various doses have not shown complete efficacy.

Discussion There is abundant experimental and clinical evidence for close interactions between the nociceptive and autonomic nervous system at all levels of the neuraxis. Pain and the visceral sensation converge at the level of the spinal and trigeminal dorsal horns, brainstem, hypothalamus, amigdala, thalamus and insular cortex. In the case reported, the initial condition was highly suggestive of SUNCT evolving V2 trigeminal neuralgia associated with SUNCT or V2 trigeminal neuralgia with autonomic signs: the onset of attacks together with ocular autonomic symptoms, and the interested trigeminal branch are V2, between paroxysms the patient was never free of pain. In the second stage, the frequency of the pain ranged from two to four crises per day, lasting from 5 to 30 min. Relationship between TN and SUNCT syndrome associated to trigeminal compression is another case reported in the literature raising the interesting question if the association of the two syndromes could be a manifestation of only one form of neuropathic central pain.



CHEATING CLINICAL FEATURES IN SUBARACHNOID HEMORRHAGE

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Introduction Subarachnoid hemorrhage (SAH) is characterized by the sudden onset of a very severe pain, often described as the worst ever experienced, whose intensity rapidly increases and reaches its peak in a very short time, in association with stiff neck and possibly impaired state of consciousness or coma. The picture of SAH is typical and the diagnosis appears to be quite clear in most instances. Nonetheless, some cases can present with an atypical headache pattern or poor neurological signs, and cannot be immediately recognized.

Clinical case A 52-year-old man with no previous headache history complained of a throbbing pain in both frontal-temporal regions, which slowly increased in intensity, reaching the maximum peak in 2–3 hours. Afterwards the pain was described as very severe, and intense phonophobia, photophobia, nausea and vomiting appeared. No relief was obtained by the intake of acetaminophen. During the

following days, he reported a limitation in neck movements, which were painful. Seven days after the onset, since the symptoms were still persistent, the patient was referred to an Emergency Department (ED). Neurological evaluation did not reveal any abnormality; cerebral CT scan resulted normal. Indomethacin given i.v. was temporarily effective, but later on the pain recurred. After being discharged, the patient came back to the ED. Neurological examination and cerebral MRI did not show any abnormal findings. A lumbar puncture was performed, showing a xanthochromic cerebrospinal fluid. The patient underwent a transfemoral cerebral angiography, which did not reveal vascular abnormalities. Since other investigations, among which coagulation parameters and a second cerebral angiography performed two months later resulted normal, the final diagnosis was SAH *sine materia*.

Discussion and conclusions SAH must be excluded when in presence of an incapacitating, very severe and abrupt-onset headache without a previous history, or when facing the “worst headache ever experienced”. The possibility of missing the diagnosis arises when the clinical presentation is atypical, e.g. meningeal signs are not present and the cerebral CT scan results normal. Migraine-like associated symptoms, such as photophobia and phonophobia could accompany the pain, representing an adjunctive confounding element. The most recently developed cerebral CT scans detect up to 97% of SAH but its sensibility decreases over time; if SAH is clinically suspected and the cerebral CT scan is normal, a lumbar puncture is mandatory. Apart from the early, transient presence of blood, xanthochromia appears within 12 hours of SAH onset and lasts for several weeks. Even if most non-traumatic SAH cases are secondary to ruptured saccular aneurysms, in about 10% of cases angiography and other investigations result normal.

THE IMPORTANCE OF CLINICAL FEATURES IN DIFFERENTIAL DIAGNOSIS BETWEEN MIGRAINE AURA AND VISUAL SEIZURES. A CASE REPORT

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Introduction Migraine with aura and epilepsy are neurological disorders that in some cases can be comorbid. Leniger et al. reported that in an epilepsy-referred patient group ($n=103$), 23% had migraine with a risk ratio of 1.9 ($p=0.01$) whereas in a matched migraine-referred group ($n=82$) 11% had epilepsy with a risk ratio of 2.1 ($p=0.05$) [1]. Positive and negative visual symptoms are common both in migraine with aura and in certain forms of epilepsy that is why in some cases one disorder can be misdiagnosed for the other. As suggested by Panayiotopoulos, not always electroencephalographic data are able to differentiate a migraine aura from a visual seizure so a detailed search for clinical features is critically important for diagnosis [2].

Case report A 16-year-old girl came to the Headache Disorder Centre complaining for the past 4 years of recurrent attacks of bilateral, temporal, pulsating headache, moderately disabling, with nausea, photophobia and phonophobia. The duration of the attacks was about 8 hours with a good response to acetaminophen. The initial frequency was 3–4 attacks per month. In the past 6 months, the patient had experienced transient and recurrent loss of vision followed by scintillating scotomata lasting generally 20–30 seconds and occurring just before headache attacks. In some attacks the visual symptoms showed a longer duration (up to 20 minutes). The attacks were daily. Her maternal grandmother was affected by migraine with aura. Her paternal grandmother was instead affected by epilepsy. Since she was 8 years old the patient was under treat-

ment with antiepileptic drugs because of previous episodes of nocturnal generalized seizures but she had not presented any seizure in the last 6 months. An EEG recording showed spikes in fronto-temporal regions. MRI did not show any kind of abnormality. Visual symptoms lasting 20–30 seconds were classified as visual seizures. Visual symptoms lasting 20 minutes were considered as migraine auras. She was diagnosed with “Cryptogenetic Epilepsy, Migraine with and without aura”. Topiramate was added to the current therapy following the standard titration schedule and since reaching the dose of 75 mg the full remission of visual symptoms was obtained with a progressive reduction of headache to complete remission.

Discussion and conclusions In 1999, Panayiotopoulos reported a systematic description of visual seizures and underlined that, less than a minute, elementary visual hallucinations with a daily frequency or more, are more suggestive for visual seizures [2]. Those visual symptoms may be followed by severe headache and vomiting [2]. Visual seizures are generally markedly different from visual aura of migraine, as described by Russell and Olesen [3], although they often trigger migrainous headache, probably by activating trigeminovascular or brainstem mechanisms. Leninger et al. reported that migraine attacks of patients suffering from both migraine and epilepsy are more disabling than migraine attacks of patients suffering from migraine alone. In this case visual seizures were followed by headache alternated with migraine with aura attacks. Diagnosis was obtained by means of a detailed search for clinical features. The same drug was able to control both disorders improving the patient’s quality of life.

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DIFFERENT FORMS OF TRIGEMINAL AUTONOMIC CEPHALGIAS IN THE SAME PATIENT: DESCRIPTION OF A CASE

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Objective To describe the case of a patient presenting three different forms of headache associated with autonomic signs. Transition forms between migraine and some type of trigeminal autonomic cephalgias (TACs), especially chronic paroxysmal migraine or hemicrania continua, have been described. These forms could be important to help in the understanding of common pathophysiological mechanisms favouring also correct taxonomy of these headaches.

Case report Here, we describe the case of a patient, a 45-year-old male, in care since 2003 at our outpatient Headache Centre for episodic cluster headache (CH) who presented 2 other forms of headache associated with autonomic signs in the last year: 1) an episodic unilateral (right orbito-frontal) short-lasting (30–60 sec) neuralgic headache, associated with ipsilateral lacrimation and recurring 20–30 times a day, that began about 1 year ago and was not responsive to the treatment with verapamil (previously prescribed for CH) that the patient started by himself at onset of the symptoms. The patient underwent MRI and MRA scan of the brain that ruled out secondary headaches, thus meeting the clinical picture criteria for SUNCT. The patient was started on lamotrigine at a dosage of 100 mg/day that was able to improve headache after 2 weeks and completely resolved it in 4 weeks; 2) six months later, the patient began to complain of a continuous unilateral mild

headache in the same scalp area, with paroxysms of pain lasting 15–30 min associated with ipsilateral lacrimation resembling the picture of hemicrania continua. The patient then started a trial with indomethacin (100 mg/day) that completely resolved the headache pain in four days.

Discussion and conclusions The case described seems to establish a link between different forms of TACs including hemicrania continua, pointing toward a common pathophysiological mechanism of these headaches.

DRUG RESISTANT CLUSTER HEADACHE: A CHALLENGE FOR CLINICIANS BETWEEN HOPE FOR REMISSION AND WAITING FOR NEW THERAPEUTIC OPTIONS. A CASE REPORT

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Introduction Cluster headache (CH) is the most frequent Trigeminal Autonomic Cephalalgia (TAC) and the most representative of this spectrum of disorders characterized by the association of headache and loco-regional signs and symptoms of facial parasympathetic activation. About 15% of cases suffer from chronic CH and a portion of these do not respond to drugs: these patients are severely debilitated and this represents a major clinical problem.

Case report A 42-year-old man came to our observation in October 2002 reporting a daily severe stabbing headache, supraorbital and fronto-temporal right-sided for 5 months. The pain was associated to ipsilateral tearing, ptosis, conjunctival injection, nasal congestion, rhinorrhea and restlessness. He presented 3–4 attacks/day usually at the same time (1:00 a.m. and 3:00 p.m.) lasting 45–60 minutes. The patient underwent physical and neurological examinations that resulted normal. Brain MRI was normal. The patient received the diagnosis of CH. He was treated first with verapamil 240 mg/day, then with carbolothium 900 mg/day which were both ineffective. Attacks were responsive to sumatriptan 6 mg subcutaneously. Afterwards he was treated with prednisone 60 mg/day obtaining remission only for a week. From 2003 to 2006 he presented a chronic CH with short remission (20 days) only after the oral assumption of steroids and several assumptions of sumatriptan during the day. The administration of verapamil 480 mg/day, lithium 900 mg/day, levetiracetam 1000 mg/day, pregabalin 300 mg/day, topiramate 150 mg/day, valproate 1000 mg/day, and methysergide 5 mg/day did not determine any relief from pain. Melatonin 9 mg/die seemed to control nocturnal attacks. Thus, the patient underwent evaluation for deep brain stimulation (DBS) of the posterior hypothalamus, but 1 month later the headache disappeared spontaneously, for about 1 year. The cluster occurred again from 2007 to 2008 with the same clinical characteristics and pharmacological resistance; the patient was also hospitalized in our clinic presenting hypertensive crisis, dyspnoea, important metabolic unbalance, caused by the excessive self-administration of steroids and sumatriptan. Depression, anxiety and irritability were associated with that important and disabling headache and showed improvement after the assumption of citalopram.

The patient is still presenting periodical pain attacks lasting 1–2 weeks, during which he is unable to work: he continues taking steroids, sumatriptan and SSRI because, as he refers, those are the only efficient drugs. Side effects are: an important edema of lower limbs, dyspnoea and obesity. The pain is currently left-sided. Accordingly to the IHS classification criteria the patient is suffering from episodic CH.

Discussion This case suggests that in CH, characterized by daily attacks and severe disability, the response to prophylactic drugs, also

in combination, may be insufficient. The neurosurgical approach with DBS of the posterior hypothalamus, that seems to be activated during the cluster attacks, can be considered in such cases. DBS can result in complete pain free at least in 50% of patients after more than 1 year. Occipital Nerve Stimulation (ONS) has also shown a certain efficacy against drug-resistant daily chronic headaches suggesting a putative role in CH by means of a non-specific mechanism. For surgical treatment at least 4 inclusion criteria must be considered: complete drug resistance, unilateral pain side, chronicity, and normal psychological profile. This case was drug resistant but did not fit the diagnostic criteria for a chronic form. Pain was not side locked. Moreover, there was a comorbidity with anxiety and depression although these disorders might be consequences of the frequent disabling attacks. Future studies should focus on drug resistant cluster headache, which still remains a challenge for clinicians since neither pharmacological nor surgical therapy are adequate to control them.

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HIGH-ALTITUDE HEADACHE OR SPORT-RELATED HEADACHE? A CASE REPORT

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Introduction Headache is the most common nervous system complication at altitude. High-altitude headaches (HAH) affect about 80% of those who habitually ascent to high altitudes, making it the most common disorder for climbers [1].

To be classified according to the ICHD-II criteria it must have at least two of the following characteristics: bilateral, frontal or fronto-temporal, constrictive quality, mild or medium intensity, aggravated by intense physical activity, movement, effort or coughing [2].

HAH appears to be independent, although patients with migraine tend to describe it as being stronger, but with characteristics similar to their usual migraine attacks.

In addition to HAH, there is another sport-related entity classified as primary headache by physical activity.

Sports associated headaches are common. They can be benign as in primary exertional headache or may signal a serious pathology as in headache associated with traumatic subdural hematoma. Specific sports activities are associated with unique headache conditions such as high-altitude headache. The management of sports-related headaches requires an adequate understanding of its underlying etiology. The mean age at onset for primary headaches provoked by physical exercise and sexual activity begin at the same age (40 years of age), and share clinical characteristics (bilateral, pulsating). Contrary to cough headache, secondary cases are rare and the most frequent etiology is subarachnoid bleeding [3].

The high-altitude headache and sports-related headache are two distinct entities, but with some common features, which sometimes bring into question the differential diagnosis.

Case report A 63-year-old patient, with habitual headache, tension and migraine, came to our attention, after two or three-years of headache attacks, which were constrictive and pulsating, at the top and of high-intensity, occurring while hiking at high altitude and very occasionally during gym exercise, but not during the many other sports that she practiced.

She underwent numerous cardiac, respiratory and vascular investi-

gations, resulting in excellent cardiovascular and respiratory compensation. A brain MRI also with angio sequences was performed, with completely normal findings.

At the end of the investigation, the patient was treated with beta-blockers for prophylaxis of migraine, with a sharp decrease in attacks of HAH, supposing a diagnosis of primary headache by physical activity favored particularly by high altitude.

Conclusions High-altitude headache and sports-related headache are considered as two separate entities, which the international classification distinguishes in two different categories, the first among the forms attributed to secondary disorders of homeostasis and the second among the primary forms.

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A CASE OF TENSION-TYPE HEADACHE IN FIBROMYALGIA

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A 57-year-old woman was admitted to our ward for a daily tension-type headache, non responsive to the usual pharmacological treatment. Five years earlier she had a hysterectomy and after 10 days she had a domestic accident reporting an injury of the pelvis and the spine. Since, she begun to suffer from muscular rigor of the neck and the shoulder girdle, intense constrictive pain localized in the occipital spine, not associated with vomiting and ocular symptoms. She also reported weakness of the upper and lower limbs, tingling, tremors and difficulty in walking and climbing. The patient's medical history reported: Raynaud phenomenon, chronic gastritis and dysphagia, hepatitis C virus infection, hyperhomocysteinaemia, and homozygosis for MTHFR 677C factor. She was also a heavy smoker. She referred widespread pain, unusually severe, above all, in the joints and muscular pain, without any sign of inflammation at clinical examination. The patient underwent a brain and neck CT, a brain angio-MRI, a colour-Doppler examination of the epiaortic and transcranial vessels and blood tests, that resulted normal. Ultrasonography of soft tissues showed fibrosis of the shoulder muscles with involvement of the dermis and hypodermis. Since the headache could be a symptom of a systemic autoimmune disease, we decided to perform several immunological tests that showed positive result for ANA and negative to ENA, anti-dsDNA, AMA, ASMA, APCA, and ANCA. We also performed an electromyography and a muscle and skin biopsy of the deltoid muscle which resulted negative. In addition, the patient was examined by a Neurologist and a Psychiatrist and she underwent a MMPI personality test, which emphasized a state of mild depression. The differential diagnosis of connective tissue (Systemic Sclerosis, Mixed Connectivitis, Polymyositis and Systemic Lupus Erythematosus), were excluded, therefore the most probable diagnosis was tension-type headache in HCV-related to Fibromyalgia [1–3]. The patient has been treated with antidepressants, anxiolytics, and antiepileptic drugs with an improvement of the symptoms.

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MIGRAINE WITH BLADDER DYSFUNCTION: SPINAL-ENCEPHALIC INVOLVEMENT?

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A woman, 45-year-old and suffering from headache without aura for more than 20 years, came to our observation because during her headache attacks, she complained about micturition problems, accompanied with ictal episodes of electric discharges, initially from nuchal and neck, raising then to the head and extending to upper and lower limbs at the same time. MRI showed abnormalities of signal both near the right hippocampal region and the uncus ascribable to gliosis and a small dilation of lateral ventricular temporal horn (these abnormalities were attributed to a variation of mesial temporal sclerosis). MRI with gadolinium of all the spinal cord, SEP (derived from the median and tibial nerve, bilaterally), all cerebrospinal fluid, and haematologic laboratory data and autoimmune screening were normal. EEG showed pointed abnormalities in the inter-temporal regions, bilaterally. Uroflusimetry and urologic evaluation: spontaneous micturition more than once, urine stasis of 700 ml. Abdominal ecography: all intra-abdominal organs and urethra were in order except abnormal relaxation of bladder with post-micturition remnant of 230 ml.

The prophylaxis therapy (VPA 500 mg/die and flunarizine 5 mg /die) gradually improved headache and micturition problems.

To our knowledge there are no data in the literature dealing with primary headache associated to micturition problems during headache attacks.

The neurophysiopathological interpretation of these symptoms could be partially based on an epileptic origin (presence of temporal mesial sclerosis). Nevertheless, the existence of symptoms of exclusively hemispheric character could be due to an involvement of spinal-encephalic structures, such as pontine centre of micturition and periaqueductal grey (this explains the pain and sensitive symptoms just like an electric discharge).

The therapy with valproic acid and flunarizine reduced consistently the recurrence of headache attacks and in particular those associated with "aura".

PSYCHODIAGNOSTIC INVOLVEMENT IN THE BURNING MOUTH SYNDROME: CASE SERIES

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Background Burning Mouth Syndrome (BMS) refers to a chronic orofacial pain disorder usually unaccompanied by mucosal lesions

or other clinical signs of organic disease; it is characterized by both positive (burning pain, dysgeusia and dysesthesia) and negative (loss of taste or altered and paraesthesia) sensory symptoms involving lips and tongue [1, 2].

Objectives To effectively and correctly diagnosis and create a specific picture of the neurological state of Burning Mouth Syndrome (BMS) in patients that have the same symptoms as explained above and to show how there is a neuropathic component involved.

Patients and methods Seven self-report questionnaires were administered to six patients: the Minnesota Multiphasic Personality Inventory-2 for hypochondriasis, depression, hysteria, psychopathic deviation, masculinity-femininity, paranoia, psychasthenia, schizophrenia, hypomania, and social introversion; the DSM IV-R for mental disorders; the Beck Depression Inventory for the severity of depression; the State-Trait Anxiety Inventory for anxiety; the Eating Disorder Inventory-2 for psychological features frequently related to anorexia nervosa or bulimia nervosa; the Eating Attitude Test for a standardized measure about eating disorders; the Body Attitudes Questionnaire that measures six attitudinal dimensions (attractiveness, disparagement, feeling fat, salience, lower body fatness and strength) and a new questionnaire based on the International Classification of Headache Disorders (IHS ICD-II) [3].

Results All the patients replied honestly and clearly to the tests so that we could obtain a personal and complete profile and identify the prototypes of the patients with BMS syndrome.

Conclusions We were able to reach a stereotype of the patient in which the diagnosis of Burning Mouth Syndrome (BMS) was made not just by the painful symptoms and clinical signs but also by the psychological and neurological characteristics. BMS, considered a "symptom" until now, has been an accurate diagnostic criteria in the International Classification of Headache Disorders (ICHD-II). In effect it is classified among cranial neuralgias, in the group of the central causes of orofacial pain.

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HEADACHE ATTRIBUTED TO LANGERHANS CELL HISTIOCYTOSIS OF CRANIAL BONE: A CASE REPORT

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Langerhans cell histiocytosis (LCH) is a sporadic disease, which occurs mainly in children and young adults, involving the cranial vault more often than the skull base. Among the headaches attributed to disorders of the cranial bone, placed at point 11.1 in the second edition of the International Classification of Headache Disorders (ICHD-II), LCH is not considered responsible for this kind of headache, which includes osteomyelitis, multiple myeloma and Paget's disease. We describe a case of an 11-year-old girl whose headache met the diagnostic criteria for disorders of cranial bone.

Case report An 11-year-old girl had been admitted to our Ward with a one-month history of progressive pain in left frontal and

parietal area of the cranial bone. The girl described that the headache was felt exclusively in an oval area of 2 x 3 cm. In the first two weeks both size and shape of pain remained the same as at the onset of symptoms. In the subsequent two weeks the pain features modified. The pain was reported mostly mild to moderate, almost continuous, with sensory disturbance such as hypoesthesia and hyperalgesia. The pain was exacerbated either spontaneously or precipitated by combing hair or touching the area concerned. At the same time, rapidly expanding swelling was reported in the same region. The particular topography associated with sensory disturbance suggested that the pain had a probable epicranial source conveyed by, or originating in, some branches of the cutaneous nerves in the scalp. Personal history was negative for fever and traumas in the last period.

Treatment was generally not necessary. When needed, standard oral doses of paracetamol usually sufficed. Her general, neurological and fundoscopic examinations were otherwise normal. Routine blood laboratory tests were also normal. Cranial X-rays and computed tomography scan showed an osteolytic lesion, which from magnetic resonance imaging appeared hyperintense in both T1- and T2-weighted images with heterogeneous enhancement after gadolinium administration. The confirmation of solitary skull bone lesion after total bone scintigraphy and total body skeletal X-rays required a neurosurgery curettage. The girl was diagnosed with LCH III as unifocal single system disease. At the last follow-up, after three months, the patient was still symptom free.

Conclusions The patient suffered from recurrent headache in strictly localized regions of the scalp that met the diagnostic criteria for disorders of the cranial bone. The osteolytic lesion observed within the cranial bone developed in “close temporal relation to and maximal over the bone lesion” and “the pain resolved within three months after successful surgical treatment of bone lesion”. While LCH is not considered in the diagnostic criteria, headache attributed to lesion of the skull does not seem to be such a rare condition, even if specific studies are lacking in the literature. Particular attention, in children, should be paid to skull lesions with rapidly changing clinical features.

In spite of the fact that neurological examinations were normal, the rapidly changing temporal pattern of the headache attack and the appearance of painful swelling mass required a diagnostic analysis.

RESPONSE TO DULOXETINE IN PRIMARY STABBING HEADACHE

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Introduction We observed an improvement of primary stabbing headache (PSH) in five patients who had taken the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine, given to treat a comorbid depressive disorder.

Materials and methods Five female patients (mean age at the first observation: 49 yrs \pm 13.6), referred to our Headache Centres for recurrent episodes of primary headache attacks. The features of their headaches fulfilled the International Classification of Headache Disorders 2nd edition (ICHD-II) criteria for: migraine without aura ($n=3$); chronic migraine ($n=1$); migraine with aura; and migraine without aura ($n=1$). In addition, they all suffered with an irregular frequency of recurrent short-lasting pain, without any accompanying signs or symptoms, which met the ICHD-2 criteria for PSH. Because of the onset of a depressive disorder, diagnosed

according to DSM-IV-R criteria, they were treated with duloxetine, with the starting dose of 30 mg/die, increasing to the maintenance dose of 60 mg/day within 7–10 days.

Results Besides the beneficial effect of the duloxetine treatment for depression, patients reported a significant improvement of PSH. This was confirmed by comparing the diary cards they filled in six months before and after the beginning of duloxetine intake, respectively. Specifically, the improvement for patient 1 was from 1–2 episodes/week to disappearance, for patient 2 from 2 episodes/week to less than 1 episode/month, for patient 3 from several episodes on a daily basis to less than 1 episode/month, for patient 4 from 2 episodes every other day to 1 episode/week, and for patient 5 from 2–3 episodes/week to less than 1 episode/month.

Discussion Duloxetine is indicated for the treatment of depression, anxiety and diabetic painful neuropathy; its efficacy for the latter condition has been documented by both randomized clinical trials and clinical experience in the field. Its mechanism of action is likely to be secondary to serotonin and norepinephrine increase. The results obtained for PSH would be in favor of a peripheral involvement underlying this primary headache.

Conclusions The improvement of PSH during duloxetine intake for depression could indicate a potential role of this drug to treat this primary headache. To our knowledge, this is the first report of a beneficial action of duloxetine for PSH.

ROLE OF THE MYOFASCIAL PAIN TREATMENT “T.P.” AND CONTROL OF THE NEUROVEGETATIVE RESPONSE IN CASE OF CHRONIC, DRUG-FAST MIGRAINE

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Introduction In chronic headache, which shows at the objective examination the presence of myofascial T.P. in the pericranial muscles, the therapeutic approach is based on reflex-therapeutic techniques both directly (T.P. dry needling blockage of neural therapy) and indirectly, and on control over the neurovegetative response to nociception (B.G.S.). The updated therapeutic trend on pain in an holistic meaning also takes into consideration the control of the organic sensitiveness tied up with the biologic predisposition (MG – Ca – transmethylanthis – glutathione), as well as, the strengthening of the serotonergic system, and thus, with the reflex – therapy, of the endogenous antinociceptive systems, both ascending and descending. The preventive aspect is founded on the control of the main triggering factors, both endogenous and exogenous cardiovascular, metabolic, alimentary, endocrine and related to the psychic balance, as well as, on the correction of the patient’s structural inadequacies (visual, occlusive, podalic, ones).

Case report A 40-year-old woman, computer programmer with a history of migraine since the age of 14. At onset, disabling attacks were associated with menstruation with headache, together with nausea, phonophobia, and photophobia. Over the years the migraine crisis are spaced out by episodes of headache of different severity; slight constrictive – burdening, non-throbbing, forehead located. Therefore, she also showed a worsening in sleep conditions. Later, sleep problems were connected with depression symptoms: asthenia, increased fatigue, and reduced concentration ability with memory impairment.

She began taking 4 tables of paracetamol per day, alternating them with opioid – contained products. This medicine induced a partial improvement. After some years, notwithstanding of the increased self-administration, her headaches worsened. After consulting her doctor, who suggested she should interrupt whatever drugs she was taking, she stopped taking them for more than two months. Thus, going towards acute rebound symptoms. For this reason she

stopped following the doctor's suggestion and she started taking the medicine again.

When she reached our observation her headache diary showed chronic headache of light to disabling intensity. The medicine she used had not determined any improvement or only a slight improvement of the headache.

At anamnesis, we noted that the patient smoked 10 cigarettes per day and she often adopted incorrect postures for many hours a day because of her job. She suffered from insomnia disorders and she was depressed.

The objective examination showed a presence of T.P. in the cervical muscles with difficulty in movements of flex-extension, and neck inclination. Therefore, we diagnosed T.P. in the masticatory muscles because neurological examination was negative.

The myofascial pain represents an instigating factor for migraine because the pain pathways involved in migraine, also include that kind of reported pain, starting from the C1, C2, C3 vertebrae. In patients with migraine, 75% had neck pain.

By improving the tension in the neck and shoulders muscles, psychological-physical control and balance were also improved, making eventual pharmacological therapies more efficacious. The N.V.S. involvement is suggested by the presence of vegetative symptoms during the attack, as well as, the intercritical phase. Her dysfunction contributed to the nociceptor sensitivity, with peripheral and central consequences of pain resistance (allodynia), which represents the main cause of the insufficiency of therapeutic triptan response. This dysfunction plays an important role in the migraine mechanism and it can be used as a forecasting marker of the clinical triptan response.

The optimal relationship between doctor and patient, the teaching of behavioural techniques and educating the patient, together with changing posture habits and stretching exercises complete the therapeutic framework.

Conclusions In the case reported, we carried out an integrated therapeutic approach (B.P.T – B.G.S. – manipulation). Eight sessions with a consequent decrease of 70% of the existing headache in terms of: frequency, severity, duration, with a prompter response to the attack medicine and better humor tone.

At the end of the 8 sessions, we invited the patient to present every 30 days for a follow-up therapeutic session, to check the results of the initial treatments, the maintenance of the reached balance and any variation in the pain pattern; so as to control further trigger factors which could become evident by reading the clinic diary. We should remember that the co-existence of the tensile headache together with migraine determines an easier relapse, about 16% in the first year, 41% within 4 years. In the case presented, the results have remained stable for the first year.

TOLOSA-HUNT SYNDROME IN PAEDIATRIC EPISODIC CLUSTER HEADACHE. A CASE REPORT

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Introduction The Tolosa-Hunt Syndrome (THS) is a rare painful ophthalmoplegia frequently due to an involvement of the cranial nerves and of the sympathetic nerve-fibres going through the cavernous sinus and the superior orbit cavity, or, in rare cases, subsequent to other clinical conditions. THS is characterized by the paralysis of one or more of the third, fourth and/or sixth cranial nerves which usually resolves spontaneously, but tends to relapse and remit. Only a few patients described in the literature had cluster headache before the THS started, and none of them were in paediatric age [1].

Material and methods We describe a 15-year-old girl with a typi-

cal form of episodic cluster headache which had a third cranial nerve palsy during and after the cluster period.

Results The patient came to our observation after about 20 days of recurrent attacks which consisted of a very severe strictly unilateral pricking pain, localized in the right retro-orbital and temporal areas. The pain was not associated with nausea, photophobia or phonophobia. During the attacks she also had tearing, ipsilateral conjunctival injection and eyelid oedema; the right nostril was congested. During the cluster period, attacks occurred twice daily; each attack lasting 45–90 min, and most of them were nocturnal awakening the patient while asleep. Her physical and neurological examinations showed right palpebral ptosis with right inferior oblique muscle palsy. Angio-Magnetic Brain Resonance and Brain Magnetic Resonance imaging were normal. Prophylactic treatment was started with Prednisone up to 50 mg/day; symptomatic treatment was performed by high-flow-rate oxygen. After 1 week of treatment, the patient had a complete resolution of the attacks, but the neurological examination did not normalize. After one month, however, neurological examination was normal and the patient no longer referred diplopia.

Discussion and conclusions THS is a very rare cause of painful ophthalmoplegia characterized by unilateral orbital pain, ipsilateral oculomotor paralysis and prompt response to steroids. In this paper we report the first paediatric case of THS subsequent to episodic cluster headache. This rare cause of painful ophthalmoplegia generally is due to a lesion in the cavernous sinus or superior orbital fissure, which only in rare cases are definable as idiopathic. Careful evaluation and follow-up is essential for diagnosis.

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Management of primary headache and related disorders in childhood and adolescence

HEADACHE: WHAT DO CHILDREN AND MOTHERS EXPECT FROM PAEDIATRICIANS?

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Introduction Headache is a frequent occurrence among children and adolescents, and one of the most common causes for medical consultation. While serious conditions presenting with the chief complaint of headache are uncommon in the paediatric age, enormous sums are invested to perform very expensive and often unnecessary diagnostic investigations. Paediatricians should adopt a flexible and diversified diagnostic/therapeutic approach and, at the same time, should not forget to consider demands, expectations and worries of children and their parents. The aim of this study was to assess simultaneously children's and mothers' expectations and paediatricians' opinion about their expectations.

Methods *Patient population:* A sample of 100 patients (50 males, 50 females; aged 10 to 16 years), consecutively examined for the first time from February 2002 to May 2003 were enrolled in this study.

Questionnaires: On the occasion of the first consultation, before the clinical evaluation, two diversified questionnaires were self-administered to every patient and his/her mother: a) The mothers' and the children's questionnaires contained some multiple-choice questions to gather information, i.e., about the reasons for the consultation, the expectations regarding the paediatric and the headache specialist consultations, and the opinions about symptomatic and prophylactic treatments of headache; b) A third briefer

multiple-choice questionnaire was administered to a sample of 50 family paediatricians to assess their beliefs about the reasons why mothers ask for their consultation, the expectations of children and their mothers, and about symptomatic and prophylactic treatments of headache.

The 1988 International Headache Society (IHS) criteria were used for the diagnoses. We included a descriptive statistical analysis to compare them, item per item.

Results A total of 100 children (50 m, 50 f; mean age 12.3, SD \pm 3.2) and 100 mothers were interviewed for this study. The following are the most interesting results:

- Frequency and severity of pain were the two main reasons for paediatric consultation according to both mothers and paediatricians.
- Paediatricians thought mothers were looking for a doctor because they were worried about a tumour, but it is somewhat surprising that only a small percentage of mothers did it for this reason.
- Paediatricians' views were similar to both children's and mothers' expectations in reassurance about the severity and explanation of the cause.
- Children expected to obtain information about the progression of headache in the future more than mothers wanted and paediatricians believed.
- Paediatricians seemed to underestimate mothers' expectation to be referred to a headache specialist and to overestimate their pretension to profit from careful diagnostic investigations.
- A significant percentage of children, mothers and paediatricians believed that a symptomatic treatment was necessary in the presence of severe pain.
- Paediatricians assumed that a prophylactic treatment was recommended in the presence of a severe and long-lasting pain more than children and especially mothers actually did, reflecting mothers' disagreement with the opinion of children and paediatricians.
- Mothers were significantly more worried of side effects than children and especially more than paediatricians expected.
- One-fifth of the interviewed children believed that a prophylactic treatment could help to prevent the progression of the disease in the future, whereas only a small percentage of mothers agreed with them and also paediatricians underestimated the children's opinion.

Conclusions Our study showed that children and their mothers have different expectations regarding the consultation with the paediatrician and with the headache specialist. In the patient-parents-paediatrician triangle, paediatricians sometimes do not attach any importance to children's and mothers' wishes and, consequently, limit (if not invalidate) the outcome of their diagnostic-therapeutic approach. In fact, they run the risk both of overestimating (i.e., mothers' worry about a tumour; their expectation to get a symptomatic treatment) and underestimating (i.e., mothers' pretension to be referred to a headache specialist or children's claim to obtain information about the progression of headache in the future) children's and mothers' expectations.

EMOTIONAL AND BEHAVIOURAL PROBLEMS IN CHILDREN WITH IDIOPATHIC HEADACHE UNDER SIX YEARS OF AGE: A CASE-CONTROL STUDY

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Introduction Secondary headaches are rare in young children while environmental and psychological factors seem to play often a significant pathogenetic role. Nevertheless, few case-control studies, using standardized age-appropriate rating instruments for emotional/behavioural problems, have been conducted among preschool-age children.

Objectives 1) To evaluate the ICDH-II criteria sensitivity/specificity for headache in preschool-aged children; and 2) to compare the prevalence of life events and emotional/behavioural problems in preschool-aged children with idiopathic headache, with an age-, sex- and SES-matched control group.

Methods Thirty-two consecutive headache patients, referred before the age of six, and 64 age- and sex-matched controls were recruited. Headache diagnosis was based on the ICHD-II criteria and on "alternative" clinical criteria (e.g. duration less than 1 hour in migraine without aura, less than 30 minutes in tension-type headache). All recruited subjects underwent a structured interview to detect early developmental disorders (e.g. feeding difficulties or sleep disorders) and "life events" (accordingly on ICD-10 and Parenting Stress Index). All parents filled in the Child Behaviour Check List in order to assess the prevalence of emotional/behavioural problems; we considered pathological results over borderline score.

Results Thirty-two idiopathic headache children (16 M, 16 F; mean age 4.8 \pm 1.2 years; range: 2.3 – 6.6 years) and 64 controls (30 M, 34 F; mean age 4.7 \pm 0.9 years; range: 2.0 – 6.9 years) were recruited.

According to the ICHD-II, a "definite" diagnosis of migraine without aura (MO) or tension-type headache (TTH) was possible in 43.8% of children (14/32), respectively 9% (3/32) and 34% (11/32); 25% of children (8/32) were diagnosed as "probable" migraine and 28.1% (9/32) as "probable" tension-type headache; and one child (3.1%) showed a secondary headache. "Alternative" criteria allowed a definite diagnosis in 90.6% of patients (31.2% MO and 59.4% TTH).

No significant differences were found between patients and controls regarding the prevalence of "life events" (69% vs. 60%).

Headache patients (MO + TTH) showed significantly higher and more pathological CBCL scores compared with controls in the following scales/subscales: Total score (29% vs. 3%; p 0.001), Internalizing score (38% vs. 2%; p 0.000); Anxious-Depressed (19% vs. 0% $p=0.002$); Affective Problems (31% vs. 1%; p 0.000) and Anxious Problems (38% vs. 1%; p 0.000). The comparison of CBCL results between MO and TTH patients did not show significant differences. Finally, we found that TTH patients are younger than MO patients (4.5 years \pm 1.3 vs. 5.4 years \pm 0.9; $p=0.036$).

Discussion Our results suggest that the ICHD-II criteria are too restrictive to allow the classification of MO and TTH in preschool children. A duration of less than 1 hour for MO and less than 30 minutes for TTH, would seem to be useful and opportune.

Our results suggest that life events do not play a pathogenetic role, nevertheless the small sample size and the high frequency of life events in the general population elude any conclusion.

The CBCL results highlight that children suffering from headache show more psychological problems than controls.

In our sample, TTH patients are younger than MO patients. We can hypothesize that younger children are less accurate in describing symptoms (making TTH diagnosis more probable in this age group), on the contrary, taking into account the "continuum model" hypothesis, TTH and MO could be an heterochronic phenotypic expression.

HEADACHE AND PSYCHOPATHOLOGY IN CHILDREN AND THEIR MOTHERS: A CORRELATIONAL STUDY

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Introduction The genetic transmission of migraine in at least half of the cases (mainly in the maternal line) is no matter of debate, such as the comorbid association of headache and anxiety/mood disorders both in children and/or adolescents and adults. However, we do not know the way this association develops and the clinical implications it has in cross generations.

Objectives Main aim was to investigate the presence of psychiatric comorbidity in paediatric primary headaches and the contemporary presence of psychopathology in mothers. Secondary aim was to verify whether the differences were headache-specific and what were mothers' perceptions of children's problems.

Material and methods Clinical sample: 55 subjects, age range of 8–18 years (mean age 13.19) and 55 respective mothers. Thirty-one were migraineurs (19 M, 12 F; m.a. 13.14); 21 frequent episodic tension-type headache (3 M, 18 F; m.a. 13.1) and 3 had tension-type headache plus migraine (2 M, 1 F). Control group was composed of 76 subjects in an age range of 8–18 years (34 M, 42 F; m.a. 12.63) and 76 respective mothers. Diagnoses were obtained according to the ICHD-II and the DSM-IV criteria by standard diagnostic protocol. Psychometric tools: SAFA - Psychiatric Scale for children and adolescents 8–18 yrs (Anxiety and Depression scales); CBCL - Child Behaviour Checklist 4–18 yrs; MINI-Mini International Neuropsychiatric Interview (Current Major Depression (CMD), Past Major Depression (PMD), Recurrent Major Depression (RMD), non-Melancholic Major Depression (nMMD), and Generalized Anxiety Disorder (GAD)) (mothers). Comparisons between the two groups for frequency of MINI's scales and sub-scales was made by Chi-Squared Test. Correlation test by R of Pearson coefficient.

Results Most psychopathologies were related to Anxiety (SAFA A $p=.039$) and Depression (SAFA D $p=.0003$), internalizing (CBCL INT $p=.0001$) and externalizing problems (CBCL EST $p=.009$) in the clinical sample vs. controls. Results showed that the presence of disorders in patients (SAFA A; SAFA D) and the perception by their mothers (CBCL INT; CBCL EST; CBCL TOT) was associated to maternal psychopathology more in the clinical than in the control group: MINI CMD-CBCL TOT $p=.007$; MINI PMD-CBCL TOT $p=.006$; MINI RMD-CBCL TOT $p=.000$; MINI nMMD-CBCL TOT $p=.000$; and MINI GAD-CBCL TOT $p=.006$. The most significant comparisons between psychopathology in mothers and their children were: MINI CMD-SAFA A TOT $p=.011$; MINI CMD-SAFA D TOT $p=.000$; MINI RMD-SAFA A TOT $p=.043$; MINI GAD-SAFA A TOT $p=.003$; and MINI GAD-SAFA D TOT $p=.010$. Data showed that mothers belonging to the clinical group agreed more with what their children expressed about themselves compared to those of the children belonging to the control group (CBCL INT-SAFA A TOT $p=.01$; CBCL INT-SAFA D TOT $p=.008$). Headache children's mothers were more aware of their children's problems.

Discussion and conclusions The presence of psychopathology in mothers and children seems to be reciprocally related, in a way unrelated to headache diagnoses. The genetic or environmental link needs to be studied. The presence of psychiatric comorbidity with internalizing and externalizing disorders has been confirmed in headache patients and in the correlation of maternal and children's psychopathology. The relation is not headache specific.

PSYCHOLOGICAL FEATURES OF MIGRAINE CHILDREN WITH AND WITHOUT MIGRAINE EQUIVALENTS

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Introduction Recurrent abdominal pain (RAP), lower limb pain (LLP), cyclic vomiting (CV) are common disorders in children suffering from headache. They are currently named as migraine equivalents. In a recent study, we found a high prevalence of such symptoms (45.3%) in patients referred to our Headache Centre. The most common migraine equivalents were RAP (51.2%) and LLP (42.7%). Very few studies have compared the psychological features in migraine children with (ME) and without (MWE) equivalents.

Objectives To compare the psychological profile in these two groups (ME vs. MWE) of migraine patients.

Materials and methods A total of 57 migraine patients were included in the study. Twenty-nine patients (M:14, F:15) had migraine equivalent (RAP, LLP, vomiting) and 28 children did not (M:13, F:15). Patients' age ranged from 6 to 18 years. The psychological profile was assessed by means of: 1) the Child Behaviour Checklist 6–18 (CBCL), parent form questionnaire, 2) the "Scale Psichiatriche di Autosomministrazione per Fanciulli e Adolescenti" (SAFA-A and SAFA-S), and 3) the Stait Trait Anger Expression Inventory (STAXI). CBCL provides a general assessment of both internalisation and externalisation behaviours, while SAFA-A and SAFA-S investigate anxiety and somatization. Lastly, STAXI is a tool to measure the components of anger.

Results As for the CBCL results, ME children showed a higher score in the "Somatic complaint" subscale than MWE patients ($p=0.03$). No differences were observed between the two patient groups in Internalizing ($p=0.17$) and Externalizing scales ($p=0.91$). No difference between ME and MWE patients was found with SAFA-A, SAFA-S, and STAXI.

Conclusions Since SAFA-A, SAFA-S and STAXI failed to show any difference between ME and MWE children, our findings suggest that the psychological profile of migraine patients is not related to migraine equivalents. However, we found that the CBCL "Somatic complaint" subscale values were higher in ME than in MWE patients. Since CBCL is filled in by the parents, this result may be due to: 1) a higher emotional susceptibility to pain in ME than MWE children, or 2) greater attention and care by parents of ME patients toward their children's pain.

PSYCHIATRIC COMORBIDITY AND HEADACHES DURING THE DEVELOPMENTAL AGE: A STUDY IN 115 YOUNG PATIENTS

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Introduction The various aspects that characterize headaches during the developmental age, most of the times, need a deeper more organic and psychological study. Taking into consideration the general psychological factors associated to one another or linked amongst themselves, does not help to understand this kind of study. There is a strong difference between a generic psychological stress factor that provokes the headache crisis and a definite psychiatric disorder that is linked to it. Putting in evidence a psychiatric comorbidity allowed us to analyse both headache and psychiatric disorders in a proper way rather than analysing whether they were due to specific causes or by chance [1]. This study analysed 115 patients, between the ages of 4 to 17, who had been hospitalized in the Child Neuropsychiatric Division of the University of Palermo for headache syndrome, from 2001 to 2007.

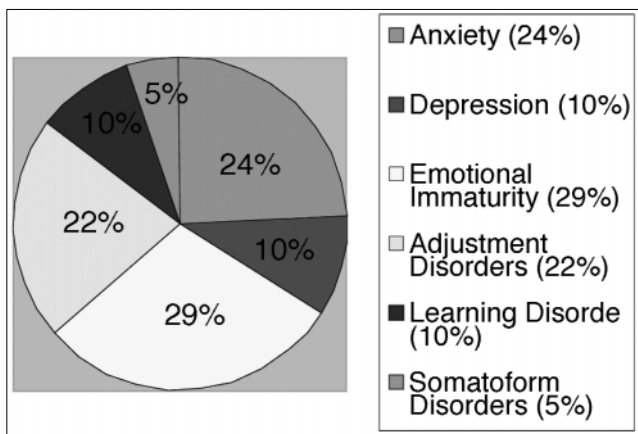
Objective Our aims were to find out how frequent the relationship with psychiatric disorders was in the various types of headaches

during the developmental age and to understand which kind of headache was more frequently connected to comorbidity.

Materials and methods The criteria used to classify and to diagnose are those reported by the International Headache Society (ICHD-II), moreover we referred to the Guidelines for the Diagnosis and Treatment of Headaches in young people published in 2003 by the Italian Society for the Study of Headaches. The methods used are individual interviews, interviews with parents, clinical interviews, psychiatric examinations and psychodiagnostic tests.

Results Eight different types of headaches were identified: 43 cases of migraine without aura (37%), 6 cases of migraine with aura (5%), 9 cases of periodic syndromes (8%), 30 cases of tension-type headache (26%), 2 cases of primary stabbing headache (2%), 8 cases of headache attributed to head and/or neck trauma (7%), and 17 cases of headache attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures (15%).

Even though we were aware of using the word “comorbidity” properly, most of all in the developmental age, we wanted to analyse in our sample group those cases where a psychiatric comorbidity was possible, referring to both “disorders” (that is to say behavioural or psychological problems different from “normal” lifestyle) and real illnesses. A psychiatric comorbidity was recognized in 36% of the sample group of 115 young patients and it has been associated with migraine without aura and tension-type headache. After a psychiatric and psychodiagnostic analysis of the sample group of patients, we obtained the following disorders:



Conclusions The highest percentage of psychiatric comorbidity was present in tension-type headache followed by migraine without aura and anxiety and depression are the most common psychopathological disorders for patients suffering from headaches [2]. Twenty-nine percent of the patients examined suffered from “emotional immaturity”, characterising the pathology where it is possible to see the characteristic elements of the “migrainous personality”, which Wolff first discovered and were later confirmed by other authors [3], which are: stiffness, meticulousness, excessive self-control, inadequacy, uncertainty, low self-esteem, sense of guilt, aggressiveness and repressed anger.

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OSMOPHOBIA IN JUVENILE TENSION-TYPE HEADACHE: A 3-YEAR FOLLOW-UP

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Background Osmophobia, proposed as an accompanying symptom of migraine (M) in the ICHD-II Appendix among the diagnostic criteria of migraine without aura (MO), showed a high specificity for this type of headache in juvenile patients [1] but, differently from the previous studies in adults [2], in childhood it was not exclusively present in migrainous patients but was reported, although less often, also in patients with tension-type headache (TTH) [1, 3]. This is a follow-up study aimed to evaluate the possible prognostic role of osmophobia; in particular we tried to understand if it could be considered as predictive of M in patients with a previous diagnosis of TTH.

Material and methods A longitudinal prospective evaluation was carried out on 37 patients from a multicentric survey conducted in 10 Italian Juvenile Headache Centres [3], selected by the presence of TTH and osmophobia during the attack (range: 9.3 – 20.3 years, mean \pm SD: 14.5 \pm 3.0 years; 18 males, 19 females). Patients were interviewed by using a semi-structured questionnaire covering the features of headache and of osmophobia at recruitment (T0) and at the end of the follow-up period (T1). Headache diagnosis was based on the ICHD-II criteria.

Results At baseline (T0) of the clinical follow-up (mean duration: 3 years; range: 1.6–4.2) all the patients presented as TTH: 28 episodic-TTH (ETTH) and 6 chronic-TTH (CTTH).

Evaluation of headache at T1 revealed persistence in 30 patients and remission in 2 patients, whereas 5 patients were lost at follow-up. In the 30 headache sufferers, diagnoses were: 20 M (66.7%, 10 males and 10 females) and 10 TTH (33.3%, 4 males and 6 females); in particular, 9 were MO, 1 migraine with aura (MA), 3 chronic migraine (CM), 7 “probable” M, 5 ETTH, 3 “probable” ETTH and 2 CTTH.

Family history of M was present in 40% of TTH patients at T1, but it was reported in 55% of patients diagnosed as M at the end of follow-up.

Headache history was longer in the “new” M patients than in those remaining in the TTH group: at T1, the duration of headache was 5.5 years in TTH group and 6.2 years in the M group.

Only 3 patients did not present osmophobia at T1 (diagnoses were 1 “probable” M, 1 ETTH and 1 CTTH). When osmophobia was present in association with at least one of the other accompanying symptoms at T0, 83.3% of these patients had their diagnosis changed to M at T1.

Conclusions In the juvenile population primary headache diagnosis is reported to shift at the follow-up from TTH to M in about 1/3 of cases. The diagnoses of our TTH patients with osmophobia

changed to M in 66.7%, therefore in a much higher percentage than in the literature. There was no significant correlation by gender and family history of M, even if the latter was more frequent in M patients; moreover, patients who changed their diagnosis to M had a headache history longer than patients who continued to suffer from TTH. Preliminary data from this short follow-up support the hypothesis that the presence of osmophobia in TTH juvenile patients could be considered predictive of M.

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MOTION SICKNESS IN CHILDHOOD MIGRAINE

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Introduction Periodic syndromes are a group of symptoms related to migraine, thought to be migraine equivalent. The IHS criteria of 2004 computed only three “periodic syndromes” as precursors of migraine: cyclical vomiting (CV) [G43.82], abdominal migraine (AM) [G43.820], benign paroxysmal vertigo of childhood (PV) [G43.821]. In clinical practice, it is well known that also growing pains (GP) and motion sickness (MS) are very frequent in paediatric migraine subjects [1]. Aim of this study was to assess the role of periodic syndromes as risk factors for childhood migraine

Materials and methods One hundred and sixty-nine subjects (83 F) aged 6–13 years (mean: 9.67; SD 2.79), consecutively referred, between January 2007 to February 2008, for migraine without aura (MO) to the Centre for Headache in Childhood of the Second University of Naples, were interviewed about periodic syndromes symptoms and compared with a matched control group. Chi-square test and logistic regression were performed in both groups to assess the difference in prevalence and the role of periodic syndromes as a risk factor for migraine.

Results The control group consisted of 365 subjects (175 F) aged 7–13 years (mean 10.01; SD 3.07); age and sex ratio were comparable. In MO children some periodic syndromes were more frequent than in the control group; in particular, the frequency of AM, GP and MS and OR was meaningfully higher than in the control group (Table 1).

Table 1

	MO%	Control%	Chi-Square	p	O.R.	I.C.
MS	39.05	15.61	34.481	0.000	3.46	2.28–5.26
CV	7.10	9.04	0.34	0.56	0.77	0.39–1.53
AM	21.30	13.15	5.191	0.023	1.79	1.11–2.88
GP	23.66	9.58	17.82	0.000	2.92	1.78–4.81

Discussion Periodic syndromes were considered the natural precursors of migraine, our study assessed the role of periodic syndromes as computed in the IHS criteria as risk factors for childhood migraine, but also MS, which is not included.

Conclusions We suggest that MS could be included among periodic syndromes and considered a strong risk factor for migraine headache in school-aged children.

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HOW TO DISTINGUISH THE MIGRAINE TWIN FROM THE HEALTHY ONE

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Introduction On the basis of a previous study where a difference was found in migraine twins (MT) only in coping and in the reciprocal relationship with the surrounding world, this time, we wanted to evaluate whether the projective instrument of “the family test” was discriminating in distinguishing the migraine twin from the other.

Methods We used a simple, easy to implement and understand projective test: the Family Drawing Test by Corman. The test was administered to 40 pairs of twins (12 homozygotes, 28 heterozygotes), 29 MO, 11 MA; f. 25, m. 15; age range: 7/16 years.

Results Twins who were not migraine sufferers (MS) were characterized by a graphic representation that was consistent with older harmonic age and richer in details. Representations of interactions showed that these were spontaneous, open and not controlled at all. The subjects represented, had a greater autonomy of vital space, thus, the hypothesis of a mental representation of independence in the affective relational field of reference seemed confirmed.

The trait of MS has conversely appeared to be more marked, more primitive, and more simplistic in the figurative articulation; the relations between the characters appeared to be static, if not statue like; in this sense the hypothesis of the difficulty of the migraine suffering twin to represent affective communications as a mirror of the alexithymic difficulty present at the clinical interview, was confirmed. Another datum is that all migraine suffering twins are second born.

The assumption that migraine suffering twins show variables relating to inhibitive hostility feelings was not confirmed; this is conversely broadly confirmed on the inhibition to open up in interpersonal relations, being dependent on the communicative field established exclusively with the other twin; in migraine suffering subjects there is a greater tendency to stereotype graphic variables. The drawings were analysed in a blind control procedure by a group of clinical psychologists to confirm the qualitative differences found in the test. The clinical psychologists were able to identify, without any difficulty, the migraine suffering subjects, finding non-specific pathological characteristics, indicators, above all, of uneasiness in the family group and dysfunction in the structuring of the self.

Conclusions On whole, the drawing test has shown the differences between migraine suffering and non-migraine suffering twins, with a depressive vision of a chronologic age less than one year, an inhibition towards freedom and autonomy of the self, related to the investment on the other twin. This was confirmed by graphic elements of external anchorage to the self.

The family drawing test has proved to be a tool able to differentiate the MT from the other, not with peculiar characteristics, but because of his inability to cope with experiences of the outside world.

GINKGOLIDE B/COENZYME Q10/RIBOFLAVIN/MAGNESIUM FOR BRIEF PROPHYLAXIS OF MIGRAINE IN SCHOOL-AGED CHILDREN

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Introduction Primary headache is very common in school-aged children. The most frequent forms include migraine and tension-

type headache. Presently, little is known about the pathophysiology, treatment, impact, and outcome of headache in children [1]. Undoubtedly, in childhood headache management, drugs with minimal side effects are preferred. According to this point of view, herbal and vitaminic complexes have been used as prophylaxis. Aim of our study was to verify the effectiveness and safety of the association of Ginkgolide B/Coenzyme Q10/Riboflavin/Magnesium for brief prophylaxis in childhood migraine.

Materials and methods Ginkgolide B 80 mg- Coenzyme Q10 20 mg- Riboflavin 1.6 mg and Magnesium 300 mg association was orally administered as a brief prophylaxis therapy, twice daily to 32 school-aged patients (17 M; mean age 10.2 ± 1.9 years) affected by migraine recruited at the Centre for Childhood Headache of the Department of Child and Adolescent Neuropsychiatry of the Second University of Naples between January and April 2009.

To verify the efficacy of the association, we tested frequency (T_0) of headache before and one month (T_1) after beginning the therapy. Diagnosis of migraine headache was made according to the IHS criteria (2004). Migraine frequency Delta percentage was calculated at T_0 and T_1 .

Results At T_0 migraine mean frequency per month was 9.56 attacks ($SD \pm 4.27$) and at T_1 it was decreased at 2.89 ($SD \pm 4.05$) ($p < 0.001$), with Delta frequency percentage of 77.82.

Side effects were the following: vomiting in 1 patient (3.125%) and unpleasant taste in 1 patient (3.125%). Only in four patients (1 male) (12.5%) was there no therapeutic effect, and all were affected by migraine with aura.

Discussion Presently a multitude of drugs are available for the treatment of migraine, but not for childhood headaches. Moreover, in paediatric age it is necessary to have drugs with minimal side effects. Many therapeutic herbs and nutrients have far fewer side effects and may provide an alternative treatment or can be used to enhance the effect of prescription medications.

Conclusions The association of Ginkgolide B/Coenzyme Q10/Riboflavin/Magnesium, could be effective and safe for a brief prophylaxis in childhood migraine without aura.

References

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INDICATIONS ON THE EFFECTIVENESS OF PET THERAPY IN THE TREATMENT OF CHILDHOOD HEADACHE

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Introduction Pet therapy (PT) is a behavioural intervention that has been implemented in the last few years in several pathologies. In international literature there are few studies on the effectiveness of PT, even though in clinical practice many cases have been recorded of patients who obtained a benefit from this therapy.

In our group we use this intervention as a first choice treatment for childhood headache, since in several studies we experienced both a reduction in the parameters of headache and an improvement of associated psychological characteristics.

Objective The purpose of this study was to evaluate the characteristics of headache suffering subjects on which the behavioral therapy had a durable effectiveness.

Materials and methods All the patients who had ended the PT for at least two years were called back (2006–2007). Of the 151 patients, 134 were tracked down by phone and of these 119 declared that they no longer suffered from headache. All the clinical data for these 119 patients was reevaluated (64 MO, 10 MA, 21 ETTH, 24 CTTH) (67 f, 43 m; mean age 10.7 ± 3.9 range 6/16 years).

Results There was no difference between the two groups concerning the birth, the neurobehavioural and development aspects in the early years of life.

Among the characteristics of headache other than the specificity of tension-type headache (TTH) and of migraine, a faster onset was found for migraine: 3 years compared to 1 year for TTH sufferers, as well as, the presence of an event having a strong affective value in the genesis of the pathology in 75% of migraine sufferers versus 30% in TTH sufferers.

Differences were found in the psychological characteristics: 95% of migraine sufferers had anxiety, which in 25% was associated to depression, whilst in TTH sufferers anxiety was present in 69%.

A significant difference was found in the duration of the pet therapy: 20 ± 3 sessions for TTH sufferers, compared to 33 ± 11 in migraine sufferers.

Conclusions Not considering the specific differences between the two pathologies, other than the higher number of sessions in migraine suffering subjects, no significant differences were found between the two groups of patients. Once again this strengthens the concept that in the developmental age no substantial difference exists between the two forms, but that a *continuum* exists that sometimes leads the young patient to show migraine forms and other tension headache forms. The results from using Pet Therapy support the hypothesis that the latter stimulates adjusting psychological structures that act on neuronal plasticity. This study confirms the effectiveness of Pet Therapy in stabilizing the results, paradoxically with no failure, even in the absence of an experimental model.

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