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PREFACE

The annual Congress of a Scientific Society is a relevant moment for the Society itself and for its members. In this occasion, it is in fact possible to acquire new scientific knowledge, to consolidate friendships and collaborations and receive new stimuli for one's clinical and scientific activity.

The XXI National Congress of the Italian Society for the Study of Headaches which will be held in Pavia from 26–29 September 2007, does not escape this rule. With great pleasure we chose Pavia as the congress venue, also in order to remember and recognise it's historic role which it has always had in clinical practice and research in headaches. As one can see from the abstracts submitted, the themes dealt with are of particular interest and range from difficulties concerning models of care of headache patients; from the proposal for a revision of the ICHD-II classification criteria; from the more recent acquisitions in genetics and in pathophysiology in migraine and cluster headache, to the discussion on new drugs for acute treatment and for prophylaxis.

Of importance, the ample space dedicated towards the integrated activities with other scientific Societies whom promote clinical and scientific research activity of common interest with our Society. We would like to mention, in this regard, the multidisciplinary sessions with AIMS (Italian Association of Sleep Medicine), and with SIMEU (Italian Society of Emergency Medicine). Lastly, teaching courses regarding headaches in children, adolescents, adults and in the elderly have been organised.

The reading of these congress abstracts will certainly be useful in improving the scientific knowledge of all of us and in stimulating new research strategies.

Giuseppe Nappi
Honorary President
XXI National SISC Congress

Lorenzo Pinessi
President
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ORAL PRESENTATIONS

GENETIC MARKERS IN HEADACHE

GENETICS OF PRIMARY HEADACHES

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Recently, the study of the genetic liability to migraine has led to the discovery of the genes responsible for familial hemiplegic migraine (FHM), a hereditary variety of migraine with aura (MA) transmitted in an autosomal dominant fashion. In FHM three genes have been implicated, the first being CACNA1A for FHM1 and the second one ATP1A2 for FHM2, while the recently discovered SCN1A accounts for FHM type 3. How dysfunction engendered by mutations in these genes triggers the attacks is still unclear. In many families with these mutations, FHM is comorbid with paroxysmal or progressive ataxia and with epileptic seizures and other paroxysmal phenomena. It has been hypothesized that mutations in CACNA1A act by alterations in calcium influx and calcium currents in neurons, and this may facilitate the onset of spreading depression. Another explanation is that abnormal regulation of intracellular calcium changes the release of neurotransmitters leading to nervous dysfunction. For the ATP1A2 mutations, haploinsufficiency of the gene may result in abnormalities in potassium levels because of a defective exchange in Na/K exchange, leading to neuronal depolarisation with increased liability to the phenomenon of spreading depression. In fact, the pathogenic mechanisms could be common to both FHM type 1 and 2. The third gene, SCN1A probably acts again through modifications in electrical excitability of the neuronal membrane. While more work is needed to completely clarify the pathophysiological mechanisms of FHM, genetic studies have led to the discovery of several sites of linkage or genetic association for the so-called typical migraines, i.e., MA and migraine without aura (MO), many of which however are still in need of replication. In particular, chronic daily headache (CDH) represents a relevant disability in the general population, often associated with drug or substance abuse. The relative risk for CDH in first-degree relatives is increased 2.1- to 3.9-fold when compared to the general population. Variation in the dopamine receptor 2 was found associated with co-morbidity of MA and depression and anxiety. We found that CDH associated with analgesic abuse showed genetic association with specific functional polymorphisms at the dopamine receptor DRD 4 and at the dopamine transporter (DAT) genes, therefore calling for a role for dopamine metabolism and dopamine-related genes in the chronic headaches and analgesic abuse.

MOLECULAR GENETICS OF MIGRAINE: CHALLENGES AND OPPORTUNITIES

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Migraine is a complex neurovascular disorder that imparts a significant burden on patient and society. There is evidence of an important role of genetic factors in the disease and elucidating the genetic basis of this disabling condition remains the focus of much research. Genetic studies clearly showed that migraine is a heterogeneous genetic condition. In most cases, genetic susceptibility has a polygenic pattern of inheritance with the exception of familial hemiplegic migraine (FHM) which is a mendelian, autosomal dominant, condition. Three genes have been identified so far in FHM, CACNA1A, ATP1A2, and SCN1A. The success of FHM regarding discovery of genetic defects remains elusive in common migraine, and causative genes have not yet been identified. Genetic study of the common forms of migraine is beset by several challenges including the absence of easily measurable biological markers, uncertainty about the aetiologic and clinical overlap among migraine types. The FHM genes do not seem to be critically involved in the common forms of migraine. Recently, genome-wide scans in families with migraine (with and without aura) have identified several susceptibility loci for these common syndromes. These include 1q31, 4q24, 6p12.2-p21.1, 11q24, 14q21, 15q11-q13, 19p13, and Xq24–28. However, identification of the respective causative genes is still pending. During the last decade, several case-control association studies have been performed in order to analyse the association of migraine candidate genes with the disease. The selection of genetic markers for these studies is based on the hypothesis that the investigated gene is functionally relevant for the disease or is located in linkage disequilibrium with a casual genomic variant. Vascular related genes (MTHFR, ETA-1, NOS), neurotransmitter related genes (DRD2, DRD4, COMT, 5-HTT), immunological and hormonal related genes (TNFα, ESR-1, PGR, AR) have been investigated. These studies are prone to several bias because of the relatively small number of patients examined and population stratification, making replication of results difficult. At present, only the association between migraine with aura and the MHTFR gene has been clearly established. The remaining results need confirmation. There are still more questions than answers regarding the genetics of migraine. Solving them will require imagination and the joint effort of researchers from many different fields. Genetic investigation of migraine provides hope that new targets for medication and individual specific therapy will be developed.

MITOCHONDRIAL ALTERATIONS IN PRIMARY HEADACHE DISORDERS

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Introduction Contribution of mitochondrial energy failure to migraine with and without aura as well as to other forms of primary headache disorders has long been considered but it usually refers to anecdoctical reports. As the field of mitochondrial medicine takes shape and physicians in all specialties become increasingly aware of oxidative phosphorylation (OXPHOS) related disorders, prevalence and spectrum of associated phenotype remain largely unknown. Due to the double genetic origin of respiratory chain complex subunits, both disorders in the nuclear DNA (nDNA) and the mitochondrial genome (mtDNA) are possible.
Materials and methods We analysed the relative frequency of common and less frequent variations in the mtDNA in 30 patients suffering from primary headache disorders. Patients were referred from specialized Headache Clinics. Total DNA was purified from peripheral blood and mtDNA sequence variants were analysed by reported PCR-RFLP assays for pathogenic mutations or by direct sequencing. Mutation load was assessed by a described SnapShot assay.
Results Although the presence of reportedly pathogenic mtDNA mutations in patients with primary headaches appeared limited in our cohort,

a number of new variants were observed in a subset of cases with migraine with aura.
Conclusions Our data propose to consider mitochondrial alterations in primary headache disorders.

MAIN COMORBIDITIES AND COMPLICATIONS

CEREBROVASCULAR COMORBIDITY IN MIGRAINEOUS PATIENTS

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Migraine is a chronic condition, affecting roughly 12% of adults in Western countries with a 17% prevalence in women and a 6% prevalence in men. Prevalence peaks in middle life and is lower in adolescents and in subjects older than 60 years of age. Stroke is an acute disease with an annual incidence rate of about 2.75/1 000 with rates slightly higher in men (2.76/1 000) than in women (2.74/1 000) and progressively increasing with age. Despite epidemiological characteristics suggest that these two conditions do not have much in common, a complex bidirectional relationship exists [1].
Migraine represents a risk factor for ischaemic stroke; however, the relative risk is low ranging from 2 to 8. The risk mainly refers to women and not to men and is higher in women suffering from migraine with rather than without aura. The risk increases in the presence of comorbid conditions such as cigarette smoking and oral contraceptive use [2]. Moreover, migraineurs have a worst cardiovascular profile with respect to non-migraineurs with higher arterial blood pressure values, worst blood lipids profile, higher prevalence of cigarette smoking and a more frequent familial history of cardiovascular diseases in younger age. More recently, migraine has been associated, both in men and in women, also to an increased risk of developing cardiovascular disease, that is not only stroke but also myocardial infarction, coronary revascularization, angina, and ischaemic cardiovascular death. This evidence, together with findings from some experimental studies lead to the hypothesis that migraine may be associated to an endothelial dysfunction which is responsible for the higher cardiovascular risk and the worst cardiovascular profile for migraineurs. Further supporting this hypothesis we can add that the asymptomatic brain lesions which may be encountered in migraineurs are sometimes not much dissimilar from those encountered in hypertensive subjects.
Migraine with aura has also been associated with an increased prevalence of right-to-left shunt, usually across a patent foramen ovale (PFO) [1]. However, it has not yet been established if patients with PFO and migraine have a further increase in the risk of stroke and a likely explanation is still lacking. Some studies reported an amelioration or a resolution of migraine after PFO closure but to date closure of PFO for migraine prevention is not indicated [1].
Some uncommon conditions associated to migraine and stroke as major clinical features include cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), mitochondrial encephalopathy, lacticacidosis and stroke-like episodes (MELAS), and autosomal dominant vascular retinopathy, migraine, and Raynaud's phenomenon [1]. Despite the fact that they are classified as secondary headaches and not as migraines according to the IHS classification, they may represent a genetic determined form of migraine [1].
A stroke may also represent a direct consequence of a migraine attack (migraineous infarction). To diagnose a migraine-induced stroke one or more symptoms and signs of migraineous aura have to persist for more than 60 minutes, brain neuroimaging must confirm an ischaemic infarction in a relevant area, the neurological deficit must exactly mimic the migraineous symptoms of previous attacks, the stroke must occur during the course of a typical migraine attack, and all other causes of stroke must be excluded although stroke risk factors may be present.
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MIGRAINE PROPHYLAXIS IN PATIENTS WITH COMORBIDITY

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Comorbidity "refers to the presence of any additional coexisting ailment in a patients with a particular index disease" [1]. Comorbidity can influence the clinical course of the disease by affecting the time of detection, prognostic anticipation, therapeutic selection and post therapeutic outcome. Comorbidity of migraine and several other disorders have been reported in clinical series, case control studies, and epidemiological surveys.
There is dramatic variability in the methodology of studies of comorbidity and migraine, and this limits the conclusiveness of the findings. However, the list of medical disorders most strongly associated with migraine includes: stroke, epilepsy, allergies, asthma, mood disorders, bipolar disorders, major depression, and anxiety disorders. The most important implications of this comorbidity include its consideration in the treatment and aetiology of both disorders.
Prophylactic therapy should be considered only under one or more of the following circumstances: i) incidence of attacks is more than two or three per month; ii) attacks are severe and impair normal activity; iii) patient is psychologically unable to cope with attacks; and iv) optimal abortive therapies have failed or produced serious side effects. Prophylactic anti-migraine treatment has to be individually tailored to each patient taking into account the form of migraine, the ensuing disability, the patient's history and demands and the associated disorders.
The choice of preventive treatment in migraine patients with comorbidity is influenced by relative contraindications and relative indications (e.g. β-blockers: relative contraindication: asthma, depression, congestive heart, Raynaud disease, diabetes; relative indications: hypertension, angina, essential tremor).
Future studies need to be designed to specifically investigate patterns and courses of comorbidity in migraine and other diseases using standardized diagnostic definitions and reliable methods of ascertainment of both migraine and the comorbid condition. Ultimately, identification of comorbidities should yield insights into the pathophysiology of migraine.
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MIGRAINE AND PSYCHIATRIC COMORBIDITY: FROM BASIC FINDINGS TO CLINICAL ASPECTS

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Migraine is a complex disease which has long been recognised as being non casually associated with several psychiatric disorders (comorbidity). Association mainly involves major depression, generalised anxiety disorder (GAD), phobias and panic disorders. Studies from community populations also suggest that the risk of developing affective and anxiety disorders, including suicide attempts, may be higher in patients suffering from definite clinical subtypes, i.e., migraine with aura. The association between migraine and depression/anxiety disorders appears to be particularly strong and bi-directional, having been observed either when looking at migraine occurrence in patients with depression/anxiety, or when looking at the occurrence of psychiatric disturbances in migraine subjects. Most authors would also rule out the possibility that mood disturbances are merely induced by repeated migraine attacks. The coexistence of anxiety and depression, in turn, negatively affects migraine-related disability and patient's quality of life. By contrast, there is inconsistente evidence to suggest a possible association between migraine and substance abuse or dependence, although the latter conditions are known to be comorbid with affective disorders (especially bipolar disorders); furthermore, medication overuse and psychiatric comorbidity are currently considered as main factors contributing to migraine transformation into a chronic daily headache pattern. Psychiatric comorbidity seen in daily or almost daily headache may be peculiar of those patients, and not merely due to recurrent or chronic pain. In general, common determinants are thought to underlie both migraine and psychiatric disorders: the intimate nature of these determinants remains elusive, but genetic, biochemical and environmental factors have beeen repeatedly claimed. Genes involved primarily in brain serotoninergic and dopaminergic pathways and their products (receptors, enzymes, mediators), for insance, have been so far investigated with conflicting or inconclusive results. However, the therapeutical implications of psychiatric comorbidity in migraine are of great importance, and although there are yet no recognised definite guidelines, the coexistence of depression and anxiety deeply influences pharmacological and non-pharmacological options of the clinician.

ASSOCIATION BETWEEN MIGRAINE AND HEADACHE ATTRIBUITED TO STROKE: A CASE-CONTROL STUDY

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Background Study Although a complex relationship between migraine, mostly migraine with aura, and ischaemic stroke has been extensively suggested, the association between an established history of migraine and headache attributed to acute brain infarction or cerebral haemorrhage has not been comprehensively investigated [1, 2].

Materials and methods Headache attributed to acute ischaemic or haemorrhagic stroke was analysed in a case-control series of 96 stroke patients with a previous history of migraine (M+) and 96 stroke patients without (M-), matched for demographic characteristics and stroke risk factors. Ischaemic and haemorrhagic stroke were diagnosed using clinical criteria and confirmed by neuroradiological testing. Lifetime history of migraine was defined using ICHD-II criteria.

Results (M+) patients had a greater probability of complaining of headache (p=0.00), often with migraine-like features (p=0.00), before (p=0.00) and during acute stroke than (M-) patients. In (M-) patients, headache occurred more frequently as a sudden symptom at stroke onset and more often had tension-type-like headache features (p=0.00, for both). Although haemorrhagic stroke is less frequent than ischaemic stroke (ratio 1:4), headache was more frequent in the former, mainly in the (M+) group (p=0.00). A preferential brainstem location of ischaemic stroke in (M+) patients emerged compared to (M-) (p=0.04). Conversely, the latter had a significantly higher percentage of infarction of the middle cerebral artery territory (p=0.02).

Conclusions Our findings support the hypothesis that vascular events preceding the clinical presentation can cause a dysfunction of the brainstem itself, which may be more predisposed in (M+) patients to be abnormally activated.

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PATENT FORAMEN OVALE AND TRANSCRANIAL ECHO-COLOR DOPPLER IN MIGRAINE

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Introduction Patent foramen ovale (PFO) prevalence in the general population is 16%–20%. In patients suffering from migraine with aura (MA), PFO prevalence is 41%–48%; in patients suffering from migraine without aura (MO) it is 23%–25%. Detection of PFO can be performed with transesophageal echocardiography (TEE), transcranial eco-color Doppler (TCCD), transthoracic echocardiography (TTE), tridimensional transthoracic echocardiography (Eco-3D) and cardiac magnetic resonance (MR).

Objective 1) To evaluate PFO prevalence in migraine with (MA+) or without (MA-) aura patients; 2) to compare TCCD findings with those detected by TEE, TTE, Eco-3D and cardiac MR; 3) to evaluate brain MR findings in PFO patients (pts); 4) to evaluate antiplatelet drugs and/or percutaneous closure effectiveness on migraine pattern.

Patients and methods Consecutive migraine outpatients of the Headache Clinic, Department of Neurology, Novara, who had undergone TCCD to detect PFO were included in the study. Diagnosis of migraine was according to International Classification of Headache Disorders criteria. Telephone interviews performed six months after TCCD, were carried out to evaluate other diagnostic tools and treatments.

Data were analysed with chi-square and Fisher test.

Results We enrolled 118 consecutive outpatients (16 males, 102 females; mean age 38.5 years, range 15–72 years): 94 patients (79.7%) with MA and 24 (20.3%) with MO. Of these, 57.6% (68 pts) were positive for PFO with TCCD: 55 MA (58.5% of MA pts), 13 MO (54.2% of MO pts), and 42.4% negative: 39 MA (41.5%); 11 MO (45.8%). Shunt was small in 20% of pts, moderate in 14.7% and large in 64.7%. Thirty-two of 35 pts resulted positive with TCCD and with TEE; 30 of 41 pts were positive with TCCD and with TTE. Eight pts positive with TCCD underwent Eco-3D, that was positive in all 8 pts. Cardiac MR confirmed PFO in 4 of 6 pts. Antiplatelet drugs improved headache in 35 of 44 PFO+ pts, transcutaneous closure in 12 of 17.

Conclusions The prevalence of PFO in our migraine patients was higher than the prevalence in the general population. We did not find a statistical correlation between PFO and migraine with or without aura. These results are in accordance with TEE, Eco-3D and TTE ones in PFO detection.

NEUROPHYSIOLOGY AND PSYCHOPHYSIOLOGY IN HEADACHE: THE ROLE OF THE BRAINSTEM

THE TRIGEMINOFACIAL REFLEXES

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Introduction The trigeminal nerve conveys sensory information from most parts of the head and partly from the neck, allowing perception of the intensity, quality, location and duration of noxious stimuli. The trigeminovascular system is directly involved in the pathophysiology of migraine.

Migraine Studies A neurophysiologic method able to test the trigeminal system, consists in the study of the trigeminofacial reflexes, which have been largely applied in migraine. In most of the studies, the blink reflex (BR) was employed, which consists of bilateral eyelid closure in response to a stimulus applied in the area innervated by the trigeminal nerve. Though the three components of the BR, named R1, R2 and R3, have essentially mechanical afferents, being an indirect test for trigeminal nociception, some abnormalities of R2 and R3 excitability have been attributed to central sensitisation phenomena at the trigeminal level [1]. More recently, a failure of DNIC control over the trigeminal afferents, has been shown by the use of the BR [2]. The trigeminal central sensitisation phenomena were studied applying a new method developed in order to obtain a selective activation of the A delta fibres (nBR). Habituation of the nBR is reduced interictally in migraine patients. This could be related to the habituation deficit of evoked cortical responses, a reproducible abnormality in migraine which has a familial character, or to central trigeminal sensitization due to repeated attacks. The corneal reflex (CR) is a purely trigeminofacial nociceptive reflex, with the afferents represented by the sensory projection from the cornea. Its application to unilateral migraine, has confirmed the persistence of trigeminal sensitisation during the non symptomatic phase [1].

Conclusions Through trigeminofacial reflexes it is possible to explore the excitability of the pathways, including the nucleus caudalis, involved in the transmission of nociceptive messages at trigeminal level. The modulatory influences on these nuclei, exerted by the antinociceptive system, can be explored by these methods, as can the pharmacological effects induced by centrally acting drugs. They are easy, non expensive and non invasive methods, enabling to increase our knowledge about the mechanisms of trigeminal sensitisation.

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ROLE OF ATTENTIONAL/COGNITIVE FACTORS ON TRIGEMINAL REFLEXES AND ON EVOKED POTENTIALS TO TRIGEMINAL STIMULATION

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Introduction The role of attentional/cognitive factors in cerebral processes related to trigeminal stimuli has been less investigated than that in the central nervous system processing of somatic inputs. Cognitive factors may interfere with trigeminal inputs mainly at two sites: the brainstem and the cerebral cortex.

Review of the literature The most important neurophysiological technique used in investigating the brainstem trigeminal circuits is represented by the blink reflex (BR) recording [1]. BR includes two main components: 1) an oligosynaptic response, named R1, which is very stable and resistant to supra-segmental influences, including cognitive factors, and 2) the BR R2 component, which is mediated by low-threshold Aβ-fibers and is strongly influenced by cognitive manipulation. It was seen that the BR R2 component is reduced in amplitude when subjects focus their attention on the stimulus, while it is increased when their attention is diverged from the stimulus. Abnormal R2 behaviour during cognitive manipulations was found in several diseases, such as Parkinson's disease and schizophrenia. In migraineurs, the R2 BR response was found to decrease less in amplitude following the increase in attention towards the stimulus, as compared to healthy subjects. The cerebral processing of trigeminal inputs can be assessed by recording scalp evoked potentials (EPs) to trigeminal stimulation. Scalp EPs to electrical stimuli are strongly contaminated by reflex responses originated in the pericranial muscles. On the contrary, the brain responses to painful laser stimuli (laser evoked potentials – LEPs) have proved to be very useful in investigating the processing of trigeminal nociceptive inputs at the cortical level. LEPs to painful laser stimuli delivered on the face are generated by Aδ-fiber inputs. Two main LEP components have been identified: 1) the N1 potential in the temporal region, contralaterally to the stimulation, and 2) the biphasic N2/P2 response at the vertex. While the N1 potential is originated in the somatosensory cortex, namely in the SII area, the N2/P2 LEP component is mainly generated by the anterior cingulated gyrus. Attention divergence from the laser pulse can markedly reduce the N2/P2 amplitude in healthy subjects, but not in migraine patients, thus suggesting a hypervigilance of migraineurs towards painful stimuli [2].

Conclusions Present findings suggest that trigeminal input processing can be strongly modified by changing the subject's attention level, and abnormalities in this modulation, which have been demonstrated in several diseases, may disclose a trigeminal circuit dysfunction both in the brainstem and in the cortex.

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CORTICO-SUBCORTICAL CONNECTIONS IN MIGRAINE PHYSIOPATHOLOGY

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Migraine is an ictal disorder where central nervous system dysfunctions are supposed to play a pivotal role. Electroneurophysiological methods, which seem particularly appropriate to study the migraine pathophysiology, showed an interictal dysfunction of sensory cortices, and possibly of subcortical structures, in migraine with and without aura. The predominant abnormality is a deficient habituation of evoked responses to repeated stimuli, probably due to cortical, and possibly widespread, neural "dysexcitability" [1].

The majority of evoked potential studies in migraine have shown one main abnormality: a lack of habituation in successive blocks of EP averagings, described for every modality of stimulation (visual, auditory, somatosensory and olfactory) and responsible both for the increased amplitudes of EP components and the increased intensity dependence of evoked potentials. Although habituation of cortical evoked responses is

a complex neurobiological phenomenon, it might crucially depend on the preactivation excitability level of the sensory cortices. The preactivation level of cortical excitability depends on the so-called "state-setting, chemically addressed connections" that originate in the brainstem and involve serotonin and noradrenaline as transmitters. Low interictal activity of these systems, especially of the raphe-cortical serotonergic pathway, could indeed be responsible in migraineurs for the observed electrophysiological abnormalities. Thalamo-cortical activation seems as well to be reduced in migraine patients interictally, which strongly support this hypothesis. A role for cholinergic subcortical structures in migraine has been also suggested on the basis of the findings of reduced sensory gating in migraineurs [2].
In conclusions, cortico-subcortical connections in migraine are certainly involved in migraine susceptibility. Further and more sophisticated electrophysiological studies may help in the future to recognize the pathways implicated.

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THE ROLE OF THE BRAINSTEM DESCENDING CONTROL SYSTEM

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Upon receipt in the brainstem and spinal cord, nociceptive information is subject to extensive processing by a diversity of mechanisms, certain of which enhance, and certain of which inhibit, its transfer to higher centres.
It is known that trigeminal and spinal nociception are subject to descending inhibitory modulation by supraspinal structures. Periaqueductal gray (PAG) and rostral ventral medulla (RVM) has been demonstrated to play a pivotal role in this sense. Activation of neurons within the PAG or RVM decreases responses to noxious stimuli of trigeminal and spinal neurons, inhibiting both the ascending projection neurons and the nociceptive reflexes.
It is also well known that the nociceptive reflex responses and pain sensation are strongly depressed by painful stimuli that activate diffuse inhibitory controls (DNICs). The pain modulation induced by activation of DNICs occurs through inhibition of the transmission of nociceptive signals by means of spinobulbo-spinal loops, and a final postsynaptic inhibitory mechanism that exerts its effects on the wide dynamic range (WDR) neurons at nucleus trigeminalis caudalis as well as on the dorsal horn at spinal level.
In episodic and chronic migraine, neuroimaging studies have emphasized the importance of cortical and subcortical structures, including PAG, raphe nuclei (RN), locus coeruleus (LC) and RVM, with modulatory nociceptive and antinociceptive. Such neuronal structures may contribute to the pathological changes in the physiological properties of trigeminal and spinal neurons and could explain the subsequent sensitization of the nociceptive pathways at several levels of the central nervous system observed during both the acute pain such as migraine attack and chronic pain condition such as chronic primary headache.
A permanent dysfunction of descending modulatory pathways, exerting their action on both trigeminal and spinal neurons, may account not only for the transformation of episodic to chronic pain condition but also for a widespread abnormal nociceptive processing along the extracephalic pain pathways, inducing a spread process of sensitization. It is unclear as to whether deficiencies in pain modulation mechanisms, such as DNIC, reflect a characteristic that predisposes the development of chronic form of pain or that it is a consequence of the syndrome itself.
In order to clarify the role of the descending control of pain structures in the development of acute and chronic form of pain, our group explored the functioning of DNICs in several acute and chronic form of primary headache, evaluating also the role of symptomatic medication overuse, by the neurophysiologic exploration of the trigeminal and spinal system.

THE HABITUATION PHENOMENON IN THE BRAINSTEM REFLEXES

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Lack of habituation of cortical evoked potentials is a well known phenomenon in migraine patients during the interictal phase. Regarding the subcortical structures, a similar deficit of habituation was also found in the nociceptive blink reflex (nBR), an electrophysiological tool investigating the brain stem activity.
As reported for cortical evoked responses, during a migraine attack, the nBR show a normal habituation pattern. Moreover, in migraineurs nBR habituation deficit decreases with the increase of attacks frequency. The finding showing that the habituation deficit of cortical visual evoked responses and that of the brainstem nBR are correlated in migraine patients, suggests that the same neurobiological background underlie the cortical as well as the subcortical dysfunction.
Interestingly, asymptomatic subjects with a 1st degree relative affected by migraine present the same nBR habituation deficit observed in full-blown migraineurs between attacks. This was proposed as an endophenotypic marker of migraine.
As suggested to explain the lack of habituation of cortical evoked responses, a low serotonin disposition may play an important role in determining this phenomenon also at the level of subcortical structures (brainstem).

PHARMACOECONOMICS IN HEADACHES

THE EVOLUTION OF PHARMACOECONOMICS

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The idea that economic theory might be relevant to the day-to-day use of pharmacists or clinicians would have raised a general scepticism only a few years ago. The distance between medicine and economics is not new and it is perfectly motivated by the different mission of the two disciplines. However, in public health decision-making, at different levels (national and local) some kind of integration and consistency should be found.
The role of pharmacoeconomics does not remain the same during the different phases of drug development, and also the consequences of its results may be different. During the early phases it helps to identify commercially viable options and find the market niche that could be commercially exploited, while at the later stages it performs the function of informing decision makers concerning appropriate use of the drugs that have been developed.
Pharmacoeconomics could be considered really as a management tool that should be applied to strategic and operational decisions about phar-

maceutical development, production or consumption and new product introduction. Emphasis in the earlier phase is on informing decision makers about product development (essentially go/no go decisions), while the emphasis at the later stage shifts to rational prescribing and utilisation.
The aim throughout is to ensure the most efficient use of limited resources.
The use of models in describing and analysing the problems of the real world should be encouraged but, in the meantime, a strong validation process should be guaranteed in the data input. An economic model is a simplified picture of reality and provides a useful framework for understanding the nature of the important parameters involved in achieving a certain outcome. The simple economic model used in describing the process of production is the production function, in which various inputs are combined to produce some outputs. The same analogy can be applied to any health-care programme whether at the local, national or international level, or indeed, at an individual level.
The ultimate objective of economic evaluation is to provide a menu of choice for decision-making regarding allocation of resources between different programmes. To do this the analysis has to include health costs and outcomes of at least two alternatives, or else evaluation will be only partial and incomplete.
As there are potential conflicts of interest between different segments of the population and/or the majority of the population and that of a minority, it is important to make the perspective of the analysis clear before opting for a certain type of analysis. The simple question to ask is: from whose perspective are the costs and outcomes being evaluated? Is this from a GP's point of view or that of hospital managers? One could get different answers to the same question for different interest groups, as the categories of costs to be included differ from one group to the other. From a patient's perspective it may not matter if the relative cost of a drug therapy is quite high compared with the alternative outcome. The hospital manager may have a quite different view. Ideally, the analysis should always include the perspective of society, thus comparing the social cost with the social consequences of alternative programmes.
An important issue related to pharmacoeconomics is related to the source of data for analysis and modelling that includes cost data; several analysis extracted data from RCTs, but also efficacy and safety data, because usually in RCTs no cost data are collected; observational studies (OS) are also good data sources, even though cost data are not always available. Administrative databases, such as disease and health technologies registries, AEs reporting and regular health-related surveys have an important role to play not only in assessing effectiveness (i.e., how well the drugs perform in everyday practice, different from efficacy usually reported in RCTs or OS) of treatments but also their costs. NICE classifies the Administrative Database important as proxy outcomes and to estimate costs.
A recent research (AIDA, Italian Administrative Database Atlas) tracked the administrative database at both the national and local level in the Italian scenario. The results of the project showed that in Italy there are several national (NHS, ISS, AIFA) and local (RHS, Regional Epidemiologic Observatories) trusts that collect administrative data at a good level in terms of quality and updating, but often the access to these data is restricted and available data are always published only in aggregate form.
The lack of data sharing in Italy actually limits the use of the information collected in administrative databases in HTA.

BASIC PRINCIPLES OF PHARMACOECONOMICS APPLIED TO CHRONIC HEADACHE CARE

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Against a background of increasing demands on limited resources, pharmacoeconomics is gaining an increasing impact on decision making. Cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) are considered the main techniques to support a fair choice among the available alternatives, on the perspective of both the National Health System (NHS) and the society. Migraine is a very common disorder, affecting from 8% to 14% of adult populations in developed countries. Prevalence is highest during the peak productive years - between the ages of 25 and 55. The results of health-related quality-of-life studies demonstrate that migraine has a considerable impact on functional capacity, resulting in disrupted work and social activities. The indirect costs of migraine greatly outweigh the cost of treatment, creating opportunities for cost-effective intervention. The direct costs of treatment for migraine are relatively small compared with the indirect costs. Many migraineurs do not seek medical attention, have not been accurately diagnosed by a physician or do not use prescription medication. A small minority of individuals with more severe headaches consume most of the healthcare resources devoted to migraine, while most individuals generate relatively low direct costs. Prevention, early intervention or effective treatment strategies for headache disorders may be highly cost effective, not only for the individual but also for society. The literature suggests that triptans are cost effective compared with older types of migraine treatment. The majority of pharmacoeconomic evaluations indicate that from the societal perspective triptans are dominant: health outcomes are improved while the overall cost of migraine is reduced. However, the results are more ambiguous from the perspective of the health care payer: reductions in non-drug medical costs are unlikely to offset fully the high drug cost. A stratified-care treatment strategy is a highly cost-effective method of managing migraine in the primary care setting compared with stepped care, delivering improved clinical outcomes at no additional cost. Migraine preventive medications considered effective reduce headache frequency by 50% in approximately 50% of treated patients. Economic savings associated with reduced migraine frequency offset approximately two thirds of the cost of preventive TPM therapy. There is wide variability in patients' strength of preference for different attributes of migraine therapy. Choice of therapy for migraine headache should be individualized based on patients' preferences. WTP measures appear to be a valid and feasible metric for quantifying treatment preferences for migraine therapies.

MIGRAINE AND DIFFERENCES OF GENDER

HORMONAL TREATMENTS AND MIGRAINE DURING THE REPRODUCTIVE LIFE CYCLE IN WOMEN

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The ICHD-II classification codified that migraine or headache may increase in frequency or newly develop during the regular use of exogenous hormones, typically for contraception or hormone replacement therapy. Conflicting results on the use of hormonal preparations and migraine are related to the clinical setting (headache centres or gyneco-

logical clinics) and to the multitude of pharmacological combinations, to their biochemical properties, dosages and routes of administration. In a gynecological setting, headache is the most common side effect of oral contraceptives but only studies from neurological and migraine clinics clearly documented an increased incidence and severity of migraine in women who use oral contraceptives and are established migraineurs. In particular, a trend toward an increased incidence of attacks during the drug-free interval of the cycle may be present and hormones may contribute to the occurrence of neurological symptoms. The mechanisms whereby manipulation of gonadal steroids influence migraine are still unknown, but the abrupt fall in plasma estrogen levels just before menstruation is a well-known critical factor which can explain why women suffer especially in the drug-free week. That being so, to minimize the entity of estrogen fluctuations, continuous combined hormonal contraceptive formulations can be used as well as estrogens in the drug-free week.

As far as hormonal therapies at the time of menopause (HRT) are concerned, they seem useful in ameliorating migraine during the perimenopausal period, when hormonal fluctuations are erratic and unpredictable, but they exert a negative impact on the natural history of migraine during postmenopause in which the disease tends to improve. Indeed, greater use of anti-migraine preparations by estrogen users than by nonusers were reported and a recent cross-sectional study found that current hormone therapy (HT) use was associated with higher rates of migraine headache than nonuse.

However, prospective studies documented significant differences according to the type, the regimen and the route of administration of HRT by using headache diaries. Transdermal route with estradiol and continuous combined regimens by using progestins with less androgenicity seem to be the best options for postmenopausal women with migraine because they do not negatively affect the frequency of attacks and significantly reduce the analgesic consumption.

ENDOCANNABINOIDS DEGRADATION SYSTEM AND MIGRAINE EFFECTS OF GENDER

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Introduction The endocannabinoid system plays a role in modulating pain including headache and is involved in the common neurobiological mechanism underlying drug addiction and the reward system [1]. Gender specific differences have been observed in both human and animal studies implying sex hormone and interactions of related factors with mechanisms regulating endocannabinoid production and pain [2]. Anandamide (AEA) and 2-arachidonoylglycerol are the most biologically active endocannabinoids, which bind to both central and peripheral cannabinoid receptors. The level of AEA in the extracellular space is controlled by cellular uptake via a specific AEA membrane transporter (AMT), followed by intracellular degradation by the enzyme AEA hydrolase (fatty acid amide hydrolase, FAAH). AMT and FAAH have also been characterized in human platelets.

The natural history of migraine is still poorly understood, and some migraineurs remit with age whereas others progress to chronic migraine (CM). CM is frequently associated with medication-overuse headache (MOH). Our purpose was to study the role of endocannabinoid metabolism in episodic migraine (EM), CM and MOH and to evaluate whether gender differences might account for our findings.

Subjects and methods We assayed the activity of AMT and of FAAH in platelets isolated from four groups of subjects: MOH (n=30), CM without MOH (n=21), episodic migraine (n=28) and controls (n=23). All subjects were studied outside of headache attacks and far from analgesic drug intake. Since there is growing evidence of an interplay between endocannabinoids and sex hormones, we collected blood samples from all menstruated females during the same menstrual phase i.e., the late follicular phase.

Results FAAH activity and AMT activity in all groups were significantly lower in males than in females. AMT and FAAH levels in platelets were found selectively increased in women with episodic migraine. Conversely, these markers were significantly reduced in CM and MOH in respect of either controls and episodic migraine group. This latter finding was observed in both males and females with CM and MOH.

Discussion Changes observed in the biochemical mechanisms degrading endogenous cannabinoids may reflect an adaptative behaviour induced by chronic headache and/or drug overuse. Since we cannot exclude that abnormalities in the endocannabinoid system are occurring at peripheral level rather than at central level, it is possible that peripheral inflammation may also play a role in the observed effects.

We observed that gender differences in all groups in AMT and FAAH levels are in line with recent observations concerning sex differences in pain perception.

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ASSOCIATION BETWEEN MIGRAINE HEADACHES AND HYPERTENSIVE DISORDERS IN PREGNANCY

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Migraine is a recurrent primary headache disorder representing one of the commonest neurological disorders in adult females. The one-year prevalence of migraine in women is about 17.1%; if adjusted by age this value rises to a peak of 24.4% in women during their childbearing years.

Gestational hypertension (GH) and preeclampsia (PE) are hypertensive disorders starting after the 20th week of pregnancy, in previously normotensive women. Both GH and PE are associated with worst outcomes. PE complicates 3% to 7% of all pregnancies and is still a leading cause of maternal and perinatal morbidity and mortality.

Interestingly, migraine and PE share some common patho-physiological features related to vascular function, platelet activation and enhanced clotting, and their possible relation has been investigated. Nine out of 11 studies published so far suggest a positive association between headaches and hypertensive disorders of pregnancy. However, all studies were retrospective and in most of them the diagnosis of migraine was not done according to the International Headache Society (IHS) criteria for primary headaches. Furthermore, also the criteria for the diagnosis of PE were not homogeneous among studies.

In a recent retrospective, case-control study we applied rigorous criteria for both migraine and PE diagnosis. A strong association was found between the two clinical conditions. Therefore, in order to confirm such an association we are conducting a prospective, multicentre, observational study.

EXPERIMENTAL MODELS

HUMAN MODELS OF MIGRAINE: NEW DATA AND FUTURE PERSPECTIVES

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The last two decades of migraine research has shown that animal and human models of headache may provide unique possibilities to study mechanisms underlying migraine. In particular, animal models of migraine had a substantial impact on development and early screening of novel anti-migraine drugs. However, an animal model that is identical or almost identical to human migraine has not yet been developed. In contrast to animal models human experimental headache models are much more similar to spontaneous migraine attacks in migraine patients. Moreover, human models of migraine allow more controlled conditions, i.e., to study the pathophysiological events during the course of an attack.

ANIMAL MODELS OF MIGRAINE AND THEIR CONTRIBUTION TO UNDERSTANDING PRIMARY HEADACHE MECHANISMS

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In the last two decades animal models of human disease have proved extremely helpful in advancing the understanding of brain disorders and in developing new therapeutic approaches. Models for studying headache mechanisms, particularly those relevant for migraine, have lead to an improved understanding of the potential mechanisms of the disorder and of the action for antimigraine treatments.
Model systems employed have focused on the pain-producing cranial structures, the large vessels and dura mater, in order to provide reproducible physiological measures that could be subject to pharmacological exploration. A wide range of methods, using both *in vivo* and *in vitro* approaches, have been devised and are now currently employed in several laboratories worldwide; available models range from electrophysiological studies, to manipulation of the mouse genome in order to produce animals with human disease-producing mutations.
No single existing model in experimental animals may explain all the features of migraine; however, the various systems available can offer valid ways to dissect migraine's components and to allow a more focused development of new treatment strategies.

NEUROINFLAMMATORY MEDIATORS OF BRAIN DAMAGE INDUCED BY MIDDLE CEREBRAL ARTERY OCCLUSION: MODEL OF TRANSIENT FOCAL BRAIN ISCHEMIA IN RAT

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The proinflammatoy cytokine interleukin-1β (IL-1β) has been implicated in the pathogenesis of brain damage induced by cerebral ischemia [1]. Matrix metalloproteinases (MMPs) are markedly upregulated in the central nervous system (CNS) in response to injury and appear to be involved in the propagation and regulation of neuroinflammatory processes that accompany most CNS pathologies. MMPs cleave protein components of the extracellular matrix, but also process a number of cell surface and soluble proteins including receptors, cytokines and chemokines [2]. Here we investigate the putative involvement of IL-1β processing in the detrimental effects exerted by the early upregulation of MMPs in ischaemic stroke.
Brain ischemia was induced in male Wistar rats by transient (2 h) middle cerebral artery occlusion (MCAo). GM6001, a broad-range MMPs inhibitor, and its negative control (GMneg) were administered through the external carotid artery, 15 min prior to MCAo. Cerebral infarct volume was evaluated 24 h after MCAo by staining coronal brain slices with 2,3,5-triphenyltetrazolium chloride. Pro-IL-1β immunoreactivity was detected by western blotting and mature IL-1β levels by a rat specific sandwich ELISA. Total gelatinolytic MMP activity was performed by *in situ* zymography; MMP-2 and MMP-9 gelatinolytic activities were detected by gelatin gel zymography. Caspase-1 activity was measured fluorimetrically.
In situ and gelatin zymography revealed a significant increase in MMP-2 and -9 activity in the ischaemic cortex and striatum after 2 h MCAo followed by 2 h reperfusion. Increased gelatinase activity in the ischaemic cortex was coincident with a significant elevation of mature IL-1β and this does not appear to implicate a canonical caspase-1-dependent processing of pro(31 kDa)-IL-1β to yield mature (17 kDa) IL-1β. Quite importantly, GM6001, but not its negative control, abolished the early IL-1β increase in the ischaemic cortex, reduced the cleavage of the cytokine pro-form and resulted in a significant reduction of ischaemic brain volume. These data suggest that MMPs may initiate IL-1β processing during the early stages of reperfusion, thus contributing to tissue damage following transient focal brain ischemia.
In conclusion, our results emphasize the crucial interplay between MMPs and mediators of neuroinflammation (e.g. IL-1β) during the early development of tissue damage observed following transient ischemia, further underscoring the potential of MMPs inhibitors in stroke therapy.

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ICHD-2R: REVISION AND PROPOSALS

CHRONIC HEADACHES

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The term "daily chronic headache" (DCH) is used to describe a broad, heterogeneous group of headaches that are not exhaustively dealt with in the new, revised edition of the International Classification of Headache Disorders (ICHD-II). In response to criticism raised about the previous edition of the 1988 International Headache Society (IHS) classification (ICHD-I), ICHD-II now lists chronic migraine and new daily persistent headache (NDPH). However, the diagnostic criteria established for chronic migraine provide a picture of this disorder that does not entirely correspond to real clinical situations. These ICHD-II diagnostic criteria – attacks of migraine without aura occurring on 15 or more days per month for at least 3 months with use of triptans, ergotamine, or opiates or combined analgesics for less than 20 days per month and with plain analgesics for less than 15 days per month – define a

high-frequency migraine that has nothing to do with DCH. On the other hand, NDPH is described by ICHD-II as a rare clinical entity, not unquestionably proven, and hardly distinguishable from tension-type headache. The insurmountable obstacles encountered when applying ICHD-II to DCH depend on the fact that the committee members who drew up this classification, like ICHD-I before it, purposely meant and explicitly stated it to be a classification of attacks, not of patients. This approach is basically incompatible with a type of headache, like DCH, that in the overwhelming majority of cases develops gradually and progressively over many years and is affected by multiple endogenous as well as environmental factors. These factors have an impact on what might be a genetically predisposed terrain that eventually evolves into the presenting clinical picture. Among the many issues still unsolved about DCH are the choice of the best treatment options and the actual role played by overuse of symptomatic medication, the baseline personality traits of sufferers, stressful events, and concurrent disorders.

SECONDARY HEADACHES IN THE ICHD-2: NECESSITY FOR A REVISION

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Introduction The chapter regarding secondary headaches has been substantially modified in the new International Classification of Headache Disorders (ICHD-2), being coded from the V to the XII paragraph. The aim to improve the efficacy of the classification has surely been reached, even if the authors themselves underline the importance of further studies to optimize the results. The general structure of the classification, with respect to secondary forms of headache, is divided into 4 main points with the aim to: a) describe the headache, b) describe presence of a possible causative disorder, c) describe causation, and d) request that headache improves or disappears with improvement or disappearance of the causative disorder. The authors, borrowing the style applied to the primary headaches, limit the use of general terms, such as "sometime", "often", "usual", with the aim to provide specific references, promptly assignable. The use of this model, which should have guaranteed a simple, reproducible and exhaustive diagnostic organization based on the cause-effect relationship between two conditions, is impaired by some problems: - in literature, primary studies specifically addressed to the definition of secondary headaches are insufficient; - the use of rigid and specific criteria sometimes does not reflect the real evidence based situation (restraints on the time of resolution of headache with respect to the resolution of the causative disease); - sometimes the relationship between some systemic diseases and headache appearance is not adequately demonstrated (i.e., HIV headaches); - some conditions are still not classifiable on the basis of the present criteria.
Objectives a) To highlight the principal problems related to the chapter of secondary headaches; b) to analyse them with respect to literature data currently available; c) to propose suggestions and hypotheses able to address problems of the current classification.
Methods a) The selection of chapters that have to be discussed, results from the analysis of a check list administered to a group of neurologists with specific expertise in different fields of secondary headaches; b) Electronic and manual bibliographic research.
Results and conclusions To date, definite results are available just for some topics. The cardinal problems concern: a) the definition of "secondary headache", not clearly stated. Some disorders, patently belonging to the "secondary headaches" (i.e., Tolosa Hunt syndrome and symptomatic cranial neuralgias), are currently coded in the chapter of "cranial neuralgias", b) the relationship between the hypothesized causative disorder and the headache is not supported by adequate studies (i.e., headache related to HIV infection). Results of primary studies with the specific aim to define a clear relationship between the two previous conditions will address the question; in the meantime, this condition should be reported in the "appendix" c) usually criterion "d", accurately indicating the time of improvement/resolution of headache with respect to the causative disorder, which is only supported by the "opinion leader" principle. Literature data, often insufficient and conflicting, sometimes clearly contradict the statements of this criterion, which, in our opinion, should be revised by a deep analysis of the present available studies.

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PROPOSAL OF CHANGING SUBTYPE 8.1 "HEADACHE INDUCED BY ACUTE SUBSTANCE USE OR EXPOSURE" AND SUBTYPE 8.3 "HEADACHE AS AN ADVERSE EVENT ATTRIBUTED TO CHRONIC MEDICATION" OF ICHD-II

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Headaches as adverse reactions and symptom of intoxication, are included in subtype 8.1 of ICHD-II, even if, for example, headache induced by phosphodiesterase inhibitors has a completely different pathogenesis from headache induced by carbon monoxide or by cocaine. We propose a revision of subtypes 8.1 and 8.3, so that the classification could be used in a clinical setting for diagnostic and therapeutic aims.
In literature, adverse reactions are divided into two types: pharmacological (type A) and non-pharmacological ones (types B). Adverse reactions of type A are an extension of the main pharmacological action of the drug and are induced by an increase in pharmacological activities (A=augmented). They are frequent, foreseeable, dose-dependent, with high morbidity, but practically non-existent mortality, and can be already detected in the pre-clinical phase of the study of the drug. Non-pharmacological adverse reactions are not related to the main pharmacological action, they are an unusual and/or unexpected effect of the medication (B=bizarre), rare and unforeseeable, they have very low morbidity, but they can be mortal, and they often only appear after prolonged treatments. However, headaches as adverse reactions which are not induced by an increase in the main pharmacological activity of the drug (i.e., which cannot be classified as type A) do not belong to type B, since they can be frequent, but never rare or mortal, and they often also appear after prolonged treatments. This is the case of headaches induced by antimicrobials, antiviral agents, interferons, corticosteroids, and H2 receptor antagonists. These headaches are probably caused by factors such as benign intracranial hypertension, flu-like syndrome, or aseptic meningitis. We only define these adverse reactions as non-A-non-B in order to easily indicate them. We propose to classify the headaches of subtypes 8.1 and 8.3 into 4 subforms: 1. headaches induced by drugs which can also worsen a pre-existent headache; they are divided into two subgroups, depending on the pathogenesis of the headache as an adverse

reaction (- type A; - type non-A-non-B); 2. food additive-induced headaches; 3. acute or chronic intoxication-induced headaches; 4. exogenous hormone-induced headache. We propose that food-induced headaches should be moved to the appendix, to indicate that further evidence is needed to prove their real existence. In particular, we need to increase the number of clinical case histories with objective instead of anecdotal data, in order to decide whether they are a clinical reality or rare to the point of being unique cases.

HEADACHE ATTRIBUTED TO AIRPLANE TRAVEL: THREE NEW CASES WITH FIRST REPORTS OF FEMALE OCCURRENCE AND CLASSIFYING CRITERIA

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Headache attributed to airplane travel (AH) is characterized by very severe, strictly unilateral pain attacks in the periorbital region, rarely accompained by ipsilateral vegetative signs, not exceeding 20 minutes in duration, and related to landing and/or, taking-off. Despite the lack of data in the literature - only 8 cases have been reported [1, 2] - the clinical features of AH are fairly stereotyped. All previous cases reported were male; we present three new cases, of whom two are female.

Case 1 A 60-year-old woman, suffering from migraine without aura since her twenties, in 2006 during the last two airplane travels, while landing complained of a very severe headache in the right periorbital region, without any accompanying symptom or vegetative sign, lasting 15 minutes. Her physical examination was normal as was cerebral MRI. The pain was so severe that she decided not to travel by plane anymore.

Case 2 In 2003 during landing, a 50-year-old woman reported the occurrence of a very severe pain located bilaterally in the orbital region, associated with tearing and lasting 5 minutes. She had travelled by plane since her twenties every year without any disturbance. The following five air travels were without problems. In 2006, during landing in both the airports of destination, she complained of an attack with the same features described above.

Case 3 In two occasions during landing, a 30-year-old man reported a sudden, very severe, sharp pain in the right periorbital region, associated with profuse tearing, congiuntival injection and ptosis; the pain disappeared in 20 minutes. He had not experienced any problems during the previous air travels. General and neurological investigations were normal as were cerebral MRI and AngioMRI.

This report brings to eleven the cases in literature, adding the first two female patients, and allowing further considerations on the diagnostic criteria of this clinical condition.

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BIOCHEMICAL MARKERS IN HEADACHE

INTERACTIVE ROLE OF ENDOVANILLOID AND GLUTAMATE IN NEURAL SENSITIZATION IN THE BRAINSTEM PAIN MODULATORY PATHWAYS

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The heat- and capsaicin-activated vanilloid TRPV1 receptor is one of the most widely recognized alternative molecular targets for the endocannabinoids anandamide and *N*-arachidonoyldopamine. There is evidence that TRPV1 is expressed in the brain including the periaqueductal gray (PAG), where it seems to be involved in the descending supraspinal pathways of nociception. Supraspinal antinociception is mediated in part by excitatory neurons originating in the PAG and impinging on OFF neurons of the rostral ventromedial medulla (RVM). We recently hypothesized, based on pharmacological and electrophysiological data, that activation of glutamate release by endogenous TRPV1 agonists in the ventrolateral (VL) PAG causes activation of OFF antinociceptive neurons of the RVM (1Here, we aimed at providing conclusive support to this hypothesis by examining in rats the effect of intra-VL-PAG injections of TRPV1 agonists and antagonists, alone or in combination, on: 1) the nocifensive response to heat in the plantar test; 2) neurotransmitter (glutamate and GABA) release in the RVM. Furthermore, we examined, by means of immunohistochemistry, the possible localization of TRPV1 in glutamatergic or GABAergic neurons using vesicular glutamate transporter 1 (VGLUT1) or vesicular GABA transporter (VGAT) as markers. Capsaicin injection into the VL-PAG increased the threshold of thermal pain sensitivity in healthy rats, whereas the selective TRPV1 antagonist 5'-iodo-resiniferatoxin (I-RTX) evoked hyperalgesia. A per se inactive dose of I-RTX abolished capsaicin-mediated analgesia. Intra-VL PAG injection of capsaicin also evoked robust glutamate release in RVM microdialysates, whereas I-RTX significantly decreased the release of this neurotransmitter, and at a dose inactive per se blocked the effect of capsaicin. As a secondary effect to capsaicin-induced glutamate discharge, a faint stimulation of GABA release was also observed. TRPV1-immunoreacivity (ir) in the VL-PAG and RVM localized mostly to the cell bodies. In the VL-PAG, high density of VGLUT1-ir and VGAT-ir on axons terminals surrounding TRPV1 positive cells indicated glutamatergic and GABergic input on TRPV1-ir neurons. Also in the RVM, VGAT and VGLUT1 staining was found around somas that were clearly TRPV1-expressing, but these latter somas were often also stained for VGLUT1. Double immunofluorescence staining conclusively identified several TRPV1/VGLUT1 positive cells in the RVM.

The present study study, together with our previous electrophysiological findings, indicates that glutamatergic neurons of the VL-PAG respond to TRPV1 stimulation by releasing glutamate into the RVM, thereby activating other TRPV1-expressing glutamatergic neurons (presumably OFF cells) in this area to produce analgesia. Importantly, in view of the results obtained with the TRPV1 antagonist alone, this pathway is tonically activated by endovanilloids, presumably anandamide, as suggested by our previous finding of TRPV1-mediated antinociception following intra-VL-PAG injection of a FAAH inhibitor [1].

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THE ROLE OF TRPV1 CHANNEL IN THE MECHANISM OF ALLODYNIA

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Recent acquisitions in molecular biology, distribution and role of the transient receptor potential vanilloid 1 (TRPV1) have greatly strengthened previous hypothesis that this channel may exert important functions in different pathophysiological circumstances, and specifically in pain and inflammatory diseases. Amelioration of various pain conditions has been obtained with prolonged exposure to capsaicin, a procedure resulting in desensitization of nociceptive sensory neurons. This observation in addition to suggesting that TRPV1 could be a potential target for the development of novel analgesics, underlined the possibility that TRPV1 may function as a polymodal signal detector, and more generally speaking TRP channels can integrate information from environmental and endogenous stimuli. The ability of TRPV1 to detect thermal and chemical stimuli enables the nociceptor to survey the local tissue environment for evidence of injury and inflammation, adjusting its heat sensitivity accordingly [1]. Chemical sensitization of TRPV1 is mediated by two main mechanisms. Whereas some factors, such as extracellular protons or bioactive lipids, interact with the channel directly, thereby serving as positive allosteric regulators, other components of the "inflammatory soup", including bradykinin or neurotrophins, mediate their effects indirectly by binding to their cognate receptors on primary afferent neurons and potentiating TRPV1 through one or more downstream signaling pathways. Additional factors that cause nociceptors sensitization may be environmental or alimentary. Some of these, including ethanol, are relevant for the migraine mechanism because it is a common notion that alcoholic beverages is a trigger of migraine attack. At room temperature, ethanol does not activate TRPV1, that however, is markedly stimulated at 37°C [2]. Ethanol lowers the threshold temperature for TRPV1 (42°C) activation by 8°C, thus making the nociceptor excitable at physiological temperatures. In addition, ethanol remarkably increases TRPV1 sensitivity to anandamide and low extracellular pH. Finally, the recent observation that certain TRPV1 antagonists show efficacy in reducing thermal and mechanical hyperalgesia in different paradigms of inflammatory or neuropathic pain emphasize the role of TRPV1 in peripheral sensitization of nociceptors. As TRPV1 expressing neurons have been implicated in the mechanisms of various inflammatory and pain diseases, the proposal of reducing their functioning by targeting TRPV1 is considered an important strategy in developing novel analgesic medicines.

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RECENT ACQUISITIONS ON BIOCHEMICAL CHANGES IN CHRONIC HEADACHES

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Chronic headaches represent a challenge for the clinicians because of the diagnostic and therapeutic difficulties. The pathogenetic basis of these complex headaches are only partially understood. The most recent findings support a failure of the endocannabinoid system, as emerged by reduction in anandamide and palmitoiletanolamide in platelets of chronic migraine (CM) patients. This is in line with experimental findings of mutual interaction between serotonin and endogenous cannabinoid 2-acil-glicerole in modulating different signalling pathways in pain control. These data concur with results of a study of our group which demonstrated the finding of a low level of anandamide (AEA) in the cerebral spinal fluid (CSF) of patients affected by CM. This derangement seems to be related to increased calcitonin gene-related peptide (CGRP) and nitric oxide (NO) production because of the failure of the inhibitory role of endogenous cannabinoids on the trigeminovascular system activation. The reduction in CSF of AEA does not seem specific for CM patients, but appears to be related to chronic head pain per se. Data obtained in experimental animal models point to the role of certain neurotrophins in the pathogenic mechanisms underlying chronic pain, including chronic head pain. Increased levels of nerve grow factor (NGF) in the CSF of patients with chronic daily headache (CDH) and a significant correlation between the liquoral levels of NGF and brain-derived neurotrophic factor (BDNF) and glutamate in CDH patients have been demonstrated, allowing to hypothesize the intervention of both neurotrophins in enhancing glutamatergic transmission underlying chronic sensitization in CDH. Further evidence supports an implication of growth factors in CM. A reduction in CFS levels of glial cell line-derived neurotrophic factor (GDNF) and somatostatin in CM patients. GDNF has a potent analgesic effect mediated by modification in the expression of P substance, capsaicin receptors and increased expression of somatostatin in nociceptive neurons. The correlation between GDNF and somatostatin suggests that central sensitization occurring in chronic head pain can be in part attributed to the decrease in somatostatin release due to the failure of GDNF mechanisms.

PLASMA OREXIN LEVELS ARE REDUCED IN CLUSTER HEADACHE PATIENTS

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Introduction Cluster headache (CH) is a primary headache with a close relationship to sleep. It presents a circa-annual rhythmicity; attacks occur preferably during the night, in rapid eye movement (REM) sleep, and they are associated with autonomic and neuroendocrine modifications.

Since there is evidence that orexins A and B, which are synthesised by the posterior hypothalamus and play a role in body homeostasis, regulation of feeding and sleep-wake cycle, can pass the blood-brain barrier and are expressed in peripheral tissues, we speculated that their circulating plasma levels could express variations in their hypothalamic secretion in CH patients [1].

Methods We measured orexin A and B levels using commercially available human orexin-A RIA kits in the plasma of 15 CH patients during the cluster period. Measurements were made during a CH attack and 3 hours afterward. Orexin A and B levels were also measured in the plasma of 15 age- and sex-matched, apparently healthy controls.

Results No significant changes were found in the levels of orexin B between cluster patients (at two time points) and controls. Orexin A levels were significantly lower in CH patients compared with controls with no significant variations between levels determined during the CH attack and 3 hours afterward (23.4±10.9 *vs* 56.2±13.6 pg/mL, $p<0.004$). The lowest levels were detected during nighttime attacks.

Discussion and conclusions In patients with CH an irregular sleep-wake pattern and abnormalities of REM sleep have been described in

relation to the cluster period. After the cluster phase these alterations abated. All these abnormalities are consistent with posterior hypothalamic dysfunction. Reduction in orexin A levels could express a hypothalamic disturbance in CH. This could be the expression of an alteration in the structure of REM sleep and a chemoreceptor dysfunction with sleep apnoea, which can favour CH attacks during sleep. Measurement of orexin levels could be related to sleep disturbances of patients suffering from this primary headache, with particular regard to comorbid sleep apnoea [2].

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ANANDAMIDE MODULATES NITROGLYCERIN-INDUCED HYPERALGESIA IN THE RAT

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Systemic nitroglycerin (NTG) provokes spontaneous-like migraine attacks in migraine sufferers and induces a condition of hyperalgesia in the rat with a delay of several hours. Recently, it has been reported that anandamide (AEA), a CB(1) receptor agonist, is tonically released to play a modulatory role in the trigeminovascular system, which seems to suggest a contribution of the endocannabinoid system to the pathogenesis of migraine. The aim of this study was to test the possible role for AEA in the mechanisms mediating nitroglycerin-induced hyperalgesia. The formalin test – a model of tonic pain – was performed in male Sprague-Dawley rats that were injected with AEA (20 mg/kg, i.p.) or saline 30 minutes before NTG or vehicle injection (10 mg/kg, i.p.).

AEA-induced a significant decrease in the nociceptive behaviour during both phases of the formalin test in the animals treated with vehicle and it abolished NTG-induced hyperalgesia during phase II of the formalin test.

These results point to a role of the cannabinoid system in NTG-induced hyperalgesia and support the possibility that this class of drugs may be effective in the treatment of migraine and other inflammatory pain states.

PHARMACOLOGY AND PHARMACOGENETICS IN SYMPTOMATIC AND PROPHYLAXIC TREATMENT

PARACETAMOL REVISITED

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Paracetamol is one of the most popular and widely used drugs for the treatment of pain and fever. It occupies a unique position among analgesic drugs. Unlike NSAIDs it is almost unanimously considered to have no antiinflammatory activity and does not produce gastrointestinal damage or untoward cardiorenal effects. Unlike opiates it is almost ineffective in intense pain and has no depressant effect on respiration. For more than a century the mechanism of action of paracetamol has been one of the mysteries of pharmacology. About one year ago, two independent groups (Zygmunt and colleagues and Bertolini and colleagues) produced experimental data unequivocally demonstrating that the analgesic effect of paracetamol is due to the indirect activation of cannabinoid CB1 receptors. In brain and spinal cord, paracetamol, following deacetylation to its primary amine (p-aminophenol), is conjugated with arachidonic acid to form *N*-arachidonoylphenolamine, a compound already known (AM 404) as an endogenous cannabinoid. The involved enzyme is fatty acid amide hydrolase. N-arachidonoylphenolamine is an agonist at TRPV1 receptors and an inhibitor of cellular anandamide uptake, which leads to increased levels of endogenous cannabinoids; moreover, it inhibits cyclooxygenases in the brain, albeit at concentrations that are probably not attainable with analgesic doses of paracetamol. CB1 receptor antagonists, at a dose level that completely prevents the analgesic activity of a selective CB1 receptor agonist, completely prevents the analgesic activity of paracetamol. Thus, paracetamol acts as a prodrug, the active one being a cannabinoid. These findings finally explain the mechanism of action of paracetamol and the peculiarity of its effects, including the behavioural ones. They also raise a series of questions, since cannabinoids, in addiction to nociception, are involved in short-and long-term forms of synaptic plasticity, including depolarization-induced suppression of both excitatory and inhibitory neurotrasmission, long-term potentiation and depression, and long-term depression of inhibition. The obvious implications are that cannabinoids and similarly acting drugs may regulate cognitive functions, modulate food intake, affect both female and male reproduction, provide neurprotection and be involved in neurodegenerative diseases; pathophysiology of shock; inhibition of fertilized oocyte implantation; inhibition of cancer growth, angiogenesis and metastasis. Curiously, just when the first CB1 agonists are being introduced for pain treatment, it comes out that an indirect cannabinomimetic had been extensively used (and sometimes overused) for more than a century.

PHARMACOGENETICS OF TRIPTANS

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Pharmacogenetics is the discipline that investigates the role played by genes on differences in drug responses. Triptans mediate vasoconstriction of meningeal vessels via stimulation of vascular 5-HT_{1B} receptors, while they inhibit neurogenic inflammation by stimulation of presynaptic 5-$HT_{1D/1F}$ receptors. Yet, approximately 25% of all migraine users and 40% of all attacks do not respond to triptan treatment. It is therefore possible that genetic variations of these receptors could be among the factors that influence the individual variability to triptans. In particular, single nucleotide polymorphisms (SNPs), DNA sequence variations that have not undergone natural selection, might participate in this behaviour. At least 14 SNPs have been described on

the 5-HT_{1B} gene, and four of these have a reported minor allele frequency of >20%, namely T-261G, A-161T, C129T and G861C. Therefore, among the hypothesis to explain the high percentage of non-responders, is the possibility that genetic single nucleotide polymorphisms that alter the receptor, for example changing the transcriptional rate and therefore the amount of target protein might change the clinical response to these drugs. We have evaluated two polymorphisms in the promoter region of the 5-HT_{1B} receptor (T-261G and A-161T) and the synonymous variation G861C in the coding region were genotyped by restriction fragment length polymorphism in 105 migraine patients. In our sample population, 71% of patients responded to triptans. Allelic and diplotype frequencies were not significantly different between responders and non-responders. On the other hand, extrapolation of *in vitro* data on promoter activity would suggest that patients with higher copy number of receptors respond slightly better. Our data therefore do not support the involvement of 5-HT_{1B} single nucleotide polymorphisms in mediating the inter-individual variability to triptans.

PHARMACOGENETIC AND MIGRAINE PROPHYLAXIS

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It is well understood that administering the same drug to a group of patients may produce a significant inter-individual variation in clinical response. Some patients fail to respond to a drug entirely, while others suffer unwanted adverse effects. Genetic factors, most notably polymorphisms in genes encoding drug metabolising enzymes, drug transporters or drug targets, are now known to play a key role in response to drug. In migraine, preventive therapy is usually undertaken in patients who have more than two headache episodes per month or those very much disabled by headaches. A variety of drugs from diverse pharmacological classes, discovered by serendipity, are in use for migraine prevention. However, these drugs have varying degrees of adverse effects and can halve the frequency of attacks in no more than 50% of patients. A pharmacogenetic approach to migraine prophylaxis is now needed in order to maximise the benefits of preventive therapy. We suggest studying the functional polymorphisms of drug metabolising enzymes and receptors in order to identify individual determinants of drug response. *Cytochrome P450* enzymes are a superfamily of proteins involved in the metabolism of a huge variety of exogenous and endogenous compounds. Although more than 50 P450 genes have been identified, three genes (CYP3A4, CYP2D6, and CYP2C19) seem to be responsible for the metabolism of most commonly used drugs in the prophylaxis of migrane. These three genes are all highly polymorphic, varying between individuals and different ethnic groups. In people who are "poor metabolisers", inactivating polymorphisms in one or more genes result in a complete lack of specific enzyme activity and a severely compromised ability to metabolise drugs. This means that the drug will remain in the body longer and thus lower doses of the drug may be effective. In "ultra-rapid metabolisers", multiple copies of a specific P450 gene lead to the production of excessive quantities of active enzyme. *Adrenergic receptors* (ARs) are directly or indirectly involved in the control of a large panel of physiological functions and are the targets of drugs for the treatment of several common diseases including migraine. The genotyping of human populations has revealed that the genes encoding α1A-, α1B-, α2A-, α2B-, α2C-, β1-, β2- and β3-AR are polymorphic in their coding region as well as in their regulatory domains and non-coding regions. The functional consequences of these genetic variations include changes in expression at transcriptional or translational level, modification of coupling to heterotrimeric G-proteins resulting in a gain or a loss in function, and alteration of GRK-mediated receptor phosphorylation/desensitization or of agonist-promoted down-regulation. Polymorphic variants of β1-AR (Arg389Gly-Ser49Gly), β2-AR and G-protein α_s subunit ($G_s\alpha$), are correlate with response to β2-agonist therapy (metoprolol). Another class of drugs used in profilaxis of migraine is *calcium channel blockers*. These drugs can present a nonspecific resistance, involving drug-efflux transporters such as ATP-binding cassette sub-family B member 1 (ABCB1, also known as MDR1 and P-glycoprotein 170). A polymorphism of the gene C3435T is associated with increased expression of the protein that influences the response to antidepressant-drug treatment. These data provide evidence of a drug target polymorphisms associated with the clinical use of different drugs and set the stage for a prospective evaluation of how pharmacogenetic diagnostics can be used to improve dosing decisions in the use of different drugs.

HPA AXIS DERANGEMENT IN CHRONIC MIGRAINE. EFFECT OF BOTULINUM TOXIN TYPE A

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Chronic migraine (CM) is the most disabling form of headache among those in the ICDH-2 classification. The failure of its treatment is often due to a superimposed medication-overuse headache (MOH) a new form of secondary headache, which has been defined as an interaction between a medication used excessively and a susceptible patient.
Subjects selected in the present study, all triptan abusers, attended the rehabilitation procedure (intravenous detoxification) in outpatient regimen for at least 5 days.
One week after the end of the MOH rehabilitation procedure, the hypothalamus-pituitary-adrenal (HPA) axis activity was specifically monitored by measuring hormones in saliva, thus allowing the stressful event of venipuncture to be avoided. The participants were instructed how to collect saliva samples at home, which was performed twice a day (08:00 h and 20:00 h). Salivary cortisol, testosterone, DHEA-S and their ratios were measured in 20 women with CM, previously affected by MOH, in comparison to 20 healthy women (C). Moreover, after withdrawal from MOH, 10 women with chronic migraine were treated subcutaneously with botulinum toxin type A with a dosage of 100 U (CM+BoNT-A Group).
Morning and evening levels of cortisol were significantly increased in CM with respect to C. With regard to the cortisol/DHEA-S ratio, an inverse marker of psycho-physical well-being, CM Group showed significantly higher values than controls. Moreover, testosterone/cortisol ratio (anabolic/catabolic index of physical performance) was significantly lower than controls in CM patients.
CM+BoNT-A showed, both in morning and evening measurements, intermediate hormone levels between controls and CM.
Further studies are required to elucidate the clinical relevance of HPA derangement in chronic migraine. However, it is clearly important that neuroendocrine factors be controlled in future investigations, since migraine is often associated with di-stress, which is highlighted as a trigger factor of migraine attacks but may also appear as a reaction to migraine attacks.

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CARE MODELS AND OTHER THERAPEUTIC STRATEGIES

ORGANISATION AND STANDARDS OF HEADACHE SERVICES IN EUROPE: GUIDELINES OF THE EUROPEAN HEADACHE FEDERATION

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In the last two-three decades the number of health structures named "Headache Centre" has grown vastly in European countries. However, in our opinion, the standard for setting up a headache centre and the numbers required has not been properly defined. A working group of the European Headache Federation (EHF) has evaluated the headache care needs. According to recent epidemiological data, for every 1,000,000 people there are 110,000 adults with migraine [1], 90,000 with significant disability [2], 600,000 with occasional other headaches (mostly episodic tension-type headache) less disabled, and 30,000 with headache every day [3], most of them significantly disabled. Published data from a large UK general practice [4] showed that 17% of registered patients aged 16-65 years consulted for headache at least once in 5 year while 9% of this group were referred to secondary care. A consensus has been reached in order to recommend that minimum consultation needs, at a "specialist" level, per adult patient per year is 30 min for the first visit and 30 min total for follow-up; average consultation needs per child patient per year is approximately 1.25 h in total. The headache services should be organised on three levels: **Level 1** (Headache primary care): accessible first contact for most people with headache, primary care physicians and/or nurses providing front-line headache services and acting as gatekeepers to: **Level 2** (Headache clinics): run by trained physicians in primary or secondary care, referring when necessary to: **Level 3** Academic headache centres: specialistic secondary care, hospital-based. The headache expert should have a training standard according to the operational level of the centre.

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MULTILEVEL APPROACH IN MEDICATION-OVERUSE HEADACHE

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Medication-overuse headache (MOH) is very frequent in specialty and tertiary care. Its management is a complex undertaking that demands pharmacological treatment but also a multilevel approach based on psychological support and education to prevent relapses.

In our Headache Centre we have developed a complete programme (CARE) for the management of MOH patients during hospitalisation and follow-up. All patients with a possible diagnosis of MOH (p-MOH) admitted for the first time to the Headache Unit are being recruited for this prospective, non randomised study. All are admitted as in-patients for 8-10 days for infusion-detoxification therapy. Upon entry to the study, each patient undergoes a standard battery of tests to evaluate the presence of drug abuse/dependence disorders (semi-structured interview, DSM-IV) and comorbid psychopathologies and to establish their personality profile (MMPI-2). Preventive therapy is initiated during the hospital stay. The course of care also includes rehabilitative counselling and the imparting of instructions for the post-discharge period. On discharge, patients receive rehabilitation counselling, a two-year schedule of follow-up visits and a headache diary for recording days with headache and use of symptomatic drugs. They are also given a letter for their GP detailing the protocol and giving the name of a neurologist contactable by phone or e-mail throughout the two-year period. According to international classification criteria (ICHD-II), the diagnosis of MOH is confirmed two months after interruption of overuse.

To date, 140 patients (28 males, 112 females; mean age: 44.5±11.4 years) out of a total of 251 with p-MOH have completed one year of follow-up. Ten patients were lost at follow-up at the first visit (2 months) and another 16 at one year. Two months after detoxification (first visit), the diagnosis of MOH was confirmed in 92 patients (71%) who, no longer overusing medications, had reverted to an episodic headache pattern. The MOH diagnosis was not confirmed in the other 38 patients (29%), who still reported chronic headache, 29 of them (22%) despite interrupting symptomatic medication overuse and the other 9 (7%) never having interrupted overuse.

At one year the overuse relapse rate was 24.6%, which is lower than indicated in the literature (about 41%). Chronic headache was reported by 38.8% of patients (44/114), but in spite of this, only 62.2% of them had reverted to overuse.

We suggest that a continuous and close patient-physician relationship, associated with a multilevel approach (psychological, educational, etc.) could reduce the risk of relapses into overuse.

ADVICE ALONE TO WITHDRAW THE OVERUSED DRUG IS AN EFFECTIVE DETOXIFICATION STRATEGY FOR MEDICATION-OVERUSE HEADACHE

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The simple imparting of advice to withdraw the overused substance is one of the most cost-effective intervention in medicine. There are at least two good reasons for considering the usefulness of physician's advice alone for medication-overuse headache (MOH). Firstly, MOH is a highly heterogeneous disorder including simple and complex cases presenting different needs for care. Secondly, there is a general consensus that patient's education is crucial for proper management of MOH. On these basis we have recently investigated in a series of studies the effectiveness of simple advice for the management of MOH. In the first paper [1] we enrolled 120 MOH patients having migraine as primary headache and low medical needs (no previous detoxification experience, no co-existent, significant and complicating medical illnesses, no current psychiatric comorbidity, no overuse of opioids, benzodiazepines, and barbiturates containing agents). Patients were randomly assigned to three different withdrawal strategies. Group A received only intensive advice to withdraw the overused medication. Group B underwent a standard outpatient detoxification programme (drug withdrawal + prednisone p.o. + preventive treatment). Group C underwent a standard in-patient with-

drawal programme (drug withdrawal + prednisone p.o. + antiemetics and fluid replacement i.v + preventive treatment). We were able to detoxify 75.4% of the whole cohort with no difference among treatment strategies. In a second study (currently under review) we prospectively evaluated for 1 year the patients detoxified in the previous study to evaluate the rates and predictors for relapse. At one-year follow-up, the relapse rate was 21.6%. On multivariate analysis three variables emerged as significant predictors of relapse: duration of disease with more than 8 headache days/month (OR=1.85, p=0.04), lower improvement after drug withdrawal (OR=1.48, p=0.04) and number of previous preventive treatments (OR= 1.51, p=0.01). In an ongoing research we have studied the effectiveness of advice alone in a cohort of 100 consecutive MOH/migraine patients with low and high medical needs. After 2 months 84 patients completed the study. Of these 85.7% were considered responders (95.2% in non complicated group and 76% in complicated group, p<0.03). In conclusion: a) in non-complicated MOH/migraine patients effective drug withdrawal may be obtained through the imparting of advice alone, b) in these patients relapse seems to depend on a greater severity of pre-existing migraine, and c) advice alone may be an effective strategy in 75% of complicated MOH patients.

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MIGRAINE CARE PROJECT OF THE CALABRIA REGION: NETWORK HUB & SPOKE CLINICAL MANAGEMENT

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Introduction When you hear of migraine you should not think of it simply as a headache. This system allows to obtain an univocal, comparable and testable diagnosis, among which migraine represents the most frequent case of primary headache. Consequently, the disability becomes chronic, affecting the quality life of patients. In Calabria [1], the economic and social issues of the illness are underestimated at the moment because of its episodic nature and limited request for specialistic treatments, which adds to a lack of headache research centres.

Operative proposal In Calabria, one of the most relevant problems in the health service is to control the demand for medical services. As far as medical services are concerned, the scarcity of resources and the limited funds available call for a course of action that regulates the supply/demand relationship. This issue is linked to the one concerning the problem of bringing medical services closer to the population by developing and conferring value and quality to health prevention in all its organizational forms. Applying this new operational model of headache management, means integrating individual clinical expertise with clinical evidence from systematic research. Its principle goal to reach a clinical decision should be based on the best available scientific evidence from previous experience and the conclusion based on such evidence should stimulate quality improvements in patient care.

Discussion This general goal [2] can be achieved by providing the technological platform of a suitable set functionalities that are able to: integrate biomedical data within electronic health record systems, for easy and ubiquitous access to heterogeneous patients' data; provide services for both healthcare professionals and patients: including education and learning, knowledge and support for specific actions, teleconsulting; and support clinical decisions in the medical domain, based on pattern recognition in historical data discovery analysis and inferences on patients'clinical data.

Conclusions On the other hand, optimisation of the therapeutic processes will assure control and reduction of the overall economic and social costs of medical care, by decreasing the frequency of hospital admissions and healthcare migration. The strategies will have to be based on a regional management model so as to provide the social and economic issues with a sound basis.

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POST-ACUTE HEADACHE CENTRE: RELEVANCE FOR THE MANAGEMENT OF HEADACHE IN THE EMERGENCY DEPARTMENT

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Background A previous six-month retrospective analysis of all patients visited for nontraumatic headache in the Emergency Department (ED) of the University Hospital of Trieste revealed high frequency of "not otherwise specified" (NOS) headache diagnoses (34.4%), and low use of prophylactic treatment (1.5%) including triptans.

Objective Aim of the present study was to evaluate clinical effectiveness of a new Post-Acute Headache Centre (PAHC) in order to improve the management of headache patients accessing the ED.

Methods A PAHC was created within the Headache Centre of the University of Trieste in October 2006. Patients accessing the ED because of nontraumatic headache were firstly evaluated in ED. Afterwards all patients with a ED diagnosis of primary- or NOS headache were sent by the ED physicians to the PAHC. A six-month prospective analysis of all consecutive patients attending the PAHC was performed. Demographic and clinical information, symptoms of presentation to the ED, diagnostic tests and consulting visits, ED diagnosis, therapies administered, presence of headache at discharge from ED, as well as the diagnosis and therapies administered in the PAHC were analysed using SPSS 12.0.

Results Sixty-one patients, 45 females (73.8%) and 16 males (26.2%), mean age 43±16 years were evaluated. The most frequent cause of presentation to the ED was unresponsiveness to treatment (54.1%) and severity of attacks (27.8%). ED diagnoses were NOS headache in 42 patients (68.9%), primary headache in 17 patients (27.9%), secondary headache in 2 patients (3.3%). Fourteen patients (23%) underwent a head CT scan. Consulting visits (92.3% neurological evaluation) were required in 39 patients (63.9%). Therapy within the ED comprised of NSAIDs in the large majority of patients (84.8%), whilst triptans were used only in 3.3% of cases. No prophylactic treatment was initiated. In 34 patients (55.7%) headache was still present at ED discharge. Time to access to PAHC was 6±4 days after discharge from ED. The diagnosis after PAHC evaluation was primary headache in 50 patients (82%), secondary headache in 9 patients (14.8%), not classified headache in 2 patients (3.3%). In the PAHC, the most administered attack therapy were triptans (50.8%). Twenty-one patients (34.4%) met criteria for prophylactic treatment.

Conclusions Our data demonstrate PAHC's effectiveness in classifying, in specifically treating NOS-ED headache, and in identifying secondary forms. A large number of patients needing prophylactic treatment started proper therapy soon after ED evaluation. Our study demonstrates high efficacy of this approach for management of post-acute ED headache.

NEUROPSYCHOLOGICAL AND PSYCHOPATHOLOGICAL ASPECTS

DIFFERENCES IN THE COURSE OF DEPRESSIVE SYMPTOMATOLOGY IN PATIENTS WITH OR WITHOUT MIGRAINE-COMORBIDITY DURING ANTIDEPRESSANT TREATMENT WITH FLUVOXAMINE AND VENLAFAXINE

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Introduction The headache subtype that has been most extensively investigated for psychiatric comorbidity is migraine [1]. In a previous study [2] on euthymic patients treated in the long-term with lithium or SSRIs, we supported the hypothesis of a bidirectional association between these two diseases considering the familial and pharmacological patterns. As regards to treatment of migraine that is comorbid with mood disorders there are no evidence-based indications to date.
Methods In the naturalistic study herein presented, we compared the course of depression during 6 weeks of antidepressant treatment with fluvoxamine (up to 300 mg/die) and venlafaxine (up to 300 mg/die) in a sample of 242 depressed in-patients with a primary mood disorder diagnosis, subdivided according to the presence of a migraine comorbidity. To assess migraine diagnosis a IHS questionnaire was administered at discharge by two medical investigators. At the end of the sixth week of treatment, clinical response was defined as a reduction of HAM-D to 8. Regression analysis and repeated measure ANOVA were used for statistical analyses of collected data.
Results At the end of the observation period, the antidepressant response rate in the whole sample was 66.5%. Using Regression Analysis a younger current age was the only clinical variable related to the antidepressant response. No significant (p<0.35) difference was observed from a statistical point of view among the drugs, even if in the migraine depressed sample venlafaxine showed greater improvement than fluvoxamine on HAM-D scores (ANOVA). On the other hand, bipolar in patients without migraine showed a significantly (p<0.0160- ANOVA) earlier reduction in Ham-D mean scores during antidepressant treatment than bipolars in comorbidity. In unipolars with and without migraine comorbidity the course of depressive symptomatology was similar.
Discussion Our data indicate that migraine comorbidity does not affect antidepressant response per se in primary mood disorder patients. Nevertheless comorbidity between bipolar forms and migraine could be considered a poor outcome index during antidepressant treatment. Moreover, our data confirm that venlafaxine, considering its serotonin reuptake inhibition as well as its effect on the noradrenergic pathway is an efficacious drug in headache syndromes.
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ANALGESIC INTAKE AND SEXUAL ADDICTION IN MIGRAINE: A DYSFUNCTION OF MOTIVATED ADAPTIVE BEHAVIOURS?

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Background Analgesic consumption in episodic migraine is associated to paradoxical increasing of headache frequency and to medication-overuse headache (MOH). Recently, MOH was associated with behaviours of substance dependence and with compulsive reward seeking because of the presence of symptoms such as tolerance and withdrawal [1]. According to this model, a disorder of motivated adaptive behaviours involving prefrontal cortex could be supposed. As recently observed in substance abusers, drug addiction and compulsive sexual behaviour are associated with high rates of psychiatric comorbidity [2]. The aim of this study was to evaluate the clinical relationship between sexual addiction and analgesic intake in patients with episodic migraine.
Subjects and methods One hundred and thirteen patients (65 women and 48 men) affected by episodic migraine with (MA) and without aura (MO) according to ICHD-II classification participated in the study. Exclusion criteria included: primary headaches associated with sexual activity, medication-overuse headache, chronic migraine and sexual or psychiatric comorbidity. Medication use was tested by means of daily drug intake (DDI). After three diagnostic interviews with an expert sexual therapist, Sexual Addiction Screening Test (SAST), Leeds Dependence Questionnaire (LDQ), Beck Depression Inventory (BDI) and Zung Self-rating Anxiety Scale (SAS) were administered to all patients.
Results Mean DDI was 1.70±0.2 with a slight difference between MO and MA (1.9 *vs.* 1.5). A significant positive correlation between DDI and LDQ scores was observed (r=0.89, p<0.0001), independent of age, sex and clinical features of headache. Values near to cut-off score of 12 in SAST were observed in 76% of patients. A significant direct correlation was observed between SDI and LDQ (r=0.87, p<0.0001) and between SAST and LDQ scores (r=0.91, p<0.0001), independent of anxiety assessment. High values of BDI (under cut-off threshold of 16 in all patients) significantly correlated with greater scores of both SDI/SAST and LDQ (r=0.89, p<0.0001).
Discussion Our results suggest that migraineurs are prone to both sexual addiction and analgesic overuse. Since recent findings from functional neuroimaging suggest a role of prefrontal systems in both sexual and drug addiction [1], depressive symptoms and both clinical features of sexual behaviour and medication dependency may share a common dysfunction of serotonergic and dopaminergic projections to frontal structures. Neurotransmitters dysregulation during reward seeking and drug addiction have been related to supraphysiological glutamatergic drive in prefrontal structure [2]. The evidence of an orbito-frontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine observed by Fumal et al seems to confirm our model [1].
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HEADACHE AS A POSSIBLE PREDISPOSING CONDITION TO ANXIETY AND DEPRESSION: RESULTS OF AN OBSERVATIONAL STUDY ON OUTPATIENTS FROM A TERTIARY HEADACHE CENTRE

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Introduction Anxiety and depression, either as symptoms or disorders are common both in migraine and tension-type headache patients. Merikangas et al. [1] suggested that anxiety might precede the headache onset and that headache in turn might be followed by depression. The results of a longitudinal study on the general population over a 2-year period, showed that subjects with baseline depression had an increased risk of incident migraine but not of other severe headaches; in addition, the risk of incident depression was higher in those with baseline migraine [2]. This study was carried out to verify the existence of a possible preferential onset sequence of psychiatric symptoms/disorders and headache in the case of their comorbidity and the possible correlation with headache type and attack frequency.

Methods A sample of headache sufferers consecutively referring to the Headache Disorders Centre of Bari and receiving the diagnosis of migraine or tension-type headache according to the diagnostic criteria of the International Classification of Headache Disorders (2004) were included. Personal and familial medical history with data concerning the natural history of headache, of possible psychopathologic symptoms/disorders and therapies was collected. A psychopathological evaluation by means of SCL-90R was performed on headache patients.

Results In about two-thirds of cases of headache with psychiatric comorbidity, headache onset was shown to precede the occurrence of psychopathological symptoms. In about 10% of cases, headache, anxiety and depression onset were concomitant. In most of the patients with both anxiety and depression, the two disorders were observed to begin together at the same time, after headache onset.

Conclusions The results of this study are not in agreement with the observations of Merikangas on the general population that anxiety might precede the headache onset and headache in turn might be followed by depression. Our results seem rather to indicate that headache is in most cases the first disorder to occur so suggesting that headache itself might represent a predisposing condition to psychopatologic symptoms/disorders.

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MEUROPSICOLOGICAL AND PSYCHOPATOLOGICAL FEATURES IN POST-TRAUMATIC HEADACHE

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One of the major problems concerning post-traumatic headaches (PTH), is that even after minor traumatic brain injury (MTBI), the brain is not like it was, no matter whether the injury is detectable or not with sophisticated diagnostic procedure. Therefore, changes in bio-behavioural components must be assumed and neuropsychological and psychopathological clues must be sought as well. It is common belief that MTBI is often followed by a post-traumatic syndrome including headache and that this syndrome is mostly in accordance with expectation of being entitled with damages. Most of patients who sustained MTBI seek medical advice because of their headaches, along with vertigo, dizziness, memory disturbances, and sleeping disorders. In most cases, this syndrome is the reason why those patients also go through several (and fairly normal) diagnostic procedures, and therefore, the final diagnosis is likely to be referred to a compensation reward expectation. Such seeking behaviour is therefore considered an indemnity syndrome. However, anxiety and depression due to the traumatic event usually happening in a sudden and unexpected and painful way are the biochemical background for seeking medical reassurance. The development of anxiety and depression may well be a consequence of the trauma rather than a "building up" phenomenon due to expectation. These patients should be thoroughly investigated for psychic disturbances and treated accordingly. Also, difficulties in coping with "a damaged head" should be taken as a symptom to be followed up and cared. An adequate pre-morbid assessment should also be obtained from family and community members.

More obviously, head pain is assumed to be one of the major complaints of patients who sustained moderate or severe traumatic brain injury (ModTBI, STBI). According to ICHD-II headache classification, acute headache occurs after 1 week from trauma and may cease within 3 month (acute headache) or later (chronic). This definition is evidently discrepant with the clinical feature of STBI patients, since lost of consciousness (GCS < 8) may persist for several weeks (or months) and post-traumatic amnesia is rather longer. Besides, these patients receive anticonvulsants therapy or beta-blockers, namely propranolol (the only effective drug in psychomotor agitation and disautonomic syndrome, according to Cochrane Analysis) that may affect pain perception. Analgesics compounds given to reduce central or peripheral pain or indomethacin given to prevent para-articular ossification (POA), may well be responsible for attenuation of head pain, if present. In our experience, acute post-traumatic headache is not a proper definition since, post-traumatic (post-coma) patients may complain of headache months later after STBI and this is true only for those subjects who regained adequate cognitive functioning and possibly an adequate pain perception along with high level integration that serve to discriminate a discomfort as head pain with its given characteristics. It is unrealistic to expect that the havoc those patients go through allow such a sophisticated discrimination and in fact, the number of STBI patients who experience a clear head pain are a minority. In patients with pre-traumatic headache, the fate is unsure, according to cognitive recovery, the better being the latter, the higher the possibility of regaining headache (and mostly migraine) thereafter. In women, recovery of hormonal fluctuations occur months (up to one year) following brain injury and the recovery of such physiological fluctuations may contribute to brain susceptibility to experience migraine pain again.

LECTURES

FROM PAIN PERCEPTION TO EMPATHY FOR PAIN

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Background Pain is an unpleasant, subjective, sensory and emotional experience associated to actual or potential tissue damage. Sensory-discriminative components (e.g. evaluation of locus, duration and intensity of a noxious stimulus) and affective-motivational components (e.g.

unpleasantness of the noxious stimulus) contribute to the experience of pain. Sensory and emotional components are represented in separate nodes of a complex neural network referred to as the pain matrix.
Empathy is the ability to feel what others feel. This definition implies that perceptual, motor or emotional states of a given individual activates correspondent neural representations in another individual who observes that state. This phenomenon plays a fundamental social role insofar as it allows the inter-individual sharing of experiences, beliefs, aims and inner states. Only recently has cognitive neuroscience dealt with the issue of empathy for pain in humans.
Methods Trancranial Magnetic Stimulation (TMS), Somatosensory Evoked Potentials (SEP), LEP (Laser Evoked Potentials) and Functional Magnetic Imaging (fMRI) were used to investigate the brain reactivity of an onlooker to the mere observation of potentially very hurtful stimuli delivered to specific body parts of a stranger model. This allowed us to explore a form of rudimentary empathy for pain, called sensorimotor contagion. In all studies, the participants observed needles penetrating different body parts. Observation of tactile stimuli delivered to the same body parts or of needles penetrating non corporeal objects were used as control conditions. Subjective ratings of self-oriented and other-oriented feelings induced by movies observation were also collected.
Results Data obtained with different techniques converge to indicate that viewing others' pain brings about changes of activity in neural structures largely overlapping with those modulated by the experience of pain on oneself. The brain reactivity to the pain of others correlated with subjective reports concerning the sensory more than the affective qualities of the pain attributed to the model.
Discussion and conclusions Although pain has long been considered as inherently private, our results hint at the social implications of this experience by highlighting that neural structures involved in both emotional and sensorimotor aspects of the personal experience of pain may be recruited also during empathy for pain. This may have a fundamental adaptive function. Indeed, on the one hand it allows to understand and indirectly experience others' pain and thus to minimize direct exposure to potentially fatal noxious stimuli; on the other hand, the consonance with others' pain may strengthen social bonds.

LINKS BETWEEN HEADACHES AND EPILEPSY IN ADULTS

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Epilepsy and many headache types (especially migraine) are neurological chronic disorders with episodic manifestations with a return to baseline between attacks. The links and affinities between the two conditions have been investigated for a long time (editorial in JAMA, April 9, 1898), but not fully understood.
Symptoms of migraine and epilepsy often overlap and differential diagnosis can be difficult in some patients; especially some migraine variants may be confused with epilepsy (basilar-type, confusional; and, in childhood: benign paroxysmal vertigo, and cyclical vomiting syndrome). In addition, migraine and epilepsy are highly comorbid: patients with both disorders are more than twice as likely to also have the other disorder. A shared pathophysiological mechanism (that is not necessarily the result of shared genetic factors), as an increased brain excitability, might account for comorbidity.
The two disorders can coexist in the same patient with a random and independent temporal course, but headache may trigger epileptic seizure (migralepsy) especially in basilar-type migraine and in catamenial epilepsy, and, on the contrary, post-seizure headache occurs even in the half of the patients (especially in generalized, and in idiopathic occipital seizures). Moreover, an ictal headache is the predominant clinical manifestation in about 1% of patients with epilepsy. In addition, several symptoms are common in both migraine and epilepsy: systemic (vomiting, nausea), visual (blurred vision, visual triggering factors), and other neurological disturbances (paresthesias, olfactory hallucinations, vertigo, post event letargy, confusion, impaired consciousness, loss of memory, depersonalization).
Clinical features that mainly contribute to the differential diagnosis are: the duration of the attack (briefer in epilepsy), consciousness (most frequently impaired in epilepsy), aura (usually visual in migraine, variable in epilepsy), onset (sudden, or in general faster, in epilepsy), and family history. The EEG is useful in the diagnosis of epilepsy and its subtypes, while it does not improve diagnostic accuracy for headache, even if, in particular, slow abnormalities can be detected during the aura.
The hypothesis of an increased neuronal excitability can explain some therapeutic similarities. Some antiepileptic drugs may be used also in preventive treatment of migraine: valproic acid and topiramate, in particular, and with an inferior level of clinical evidence gabapentin, zonisamide and levetiracetam.

BRAIN, PLATELETS, FATTY ACIDS: CORRELATIONS AND BIO METABOLIC ASPECTS

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Lipids play a key role in determining membrane fluidity, and changes in lipid and fatty acid composition have been reported to have significant effects and alter important cellular function [1].
Many studies have highlighted the important role played by lipids. It is possible that the different lipids are able to exert different effects on the fluidity of the membrane, which result in the enhancement or loss of important substances (membrane transporters) affecting the accessibility of the binding site to their respective substrates. Also, if it is difficult to draw a general conclusion regarding functional changes in response to such modifications, membrane fatty acids composition can be modulated through dietary sources, and provides the general framework that coordinates the fluidity of the membrane and consequently the efficiency of the membrane system. There is evidence that the platelet may be a useful model for the neuron, possibly better than the erythrocytes and that it is possible to use platelets for understanding the neurophysiology of various psychiatric disorders and some pathophysiologcal aspects of coronary artery disease. In some of the above mentioned conditions we have studied the platelet fatty acid composition. With the use of the Artificial Neural Network, other than the normal advanced statistic, we have highlighted the fatty acids which, in platelets, can be considered as strong markers of Major Depression and of Ischaemic Cardiovascular Disease. As a result we obtained the characterisation of the two pathologies through the identification of Palmitic Acid, Linoleic Acid and Arachidonic Acid (Major Depression) and Oleic Acid, Linoleic Acid, Arachidonic Acid (Ischaemic Cardiovascular Disease).
These compositions were strongly related to the degree of saturation and of unsaturation of the pathologic conditions with respect to the normal conditions.
The results obtained confirm the involvement of the fatty acids in the biochemical characterisation of the pathologies, probably linked to a different expression of the membrane behaviour [2].
The identification of peripheral markers of Major Depression and of Ischaemic Cardiovascular Disease could be very important to obtain an improvement in the diagnosis and treatment of the diseases.
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CLINICAL ALLODYNIA DURING MIGRAINE ATTACK AND DURING FREE PHASE IN MIGRAINE, PROBABLE MIGRAINE AND CHRONIC DAILY HEADACHE PATIENTS. PRELIMINARY RESULTS

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Introduction Cutaneous allodynia (CA) is a frequent symptom experienced by migraineurs during the attacks. Several studies have shown that the underlying mechanism of facial CA is the sensitisation of second order nociceptors and in the trigemino nucleous caudalis. Furthermore, migraineurs have also hyperalgesia, with a lower pain threshold to painful stimulation when compared to controls [1].

CA has been proposed as a risk factor for migraine chronification. In individuals with episodic migraine, the prevalence of CA is around 40% [2]. CA in those with chronic daily headaches is less studied. Accordingly, the aim of this study was to assess and contrast the prevalence of CA in migraine and chronic daily headache patients.

Methods We collected 219 outpatients (age 18 to 86 years old) consecutively evaluated in the Headache Centre of the "G. Rummo" Hospital in Benevento. Headache diagnosis was based on the International Classification of Headache Disorders criteria. Chronic daily headaches were classified according to the Silberstein and Lipton criteria [2]. Presence or absence of head allodynia during migraine attack and during free phase was assessed using a semistructured interview and the administration of a specific questionnaire.

Results Our sample consists of 122 individuals with migraine (M), 45 with probable migraine (PM) and 52 with chronic daily headaches (CDH). Overall, during severe headache attacks, 174 out of 219 patients (79.5%) complained of allodynia; of whom, 28 out of 45 PM patients (62.3%), 98 out of 122 M patients (80.7%), 48 of 52 CDH patients (92.3%). During the pain free phase, 71 out of 219 patients (32.4%), complained of one or more CA symptoms; 4 out of 45 PM patients (4.6%), 43 out of 122 M patients (35.3%), 24 out of 52 CDH patients (46.2%). In regard to patients with migraine with aura (MA) and migraine without aura (MO), we found no difference during migraine attacks. Interictally, 30 out of 100 MO patients (30%) and 13 out of 22 MA patients (59.1%) had CA.

Conclusions The prevalence of CA varies according to the headache diagnosis, both ictally and interictally. CA is more common in CDH than in migraine, and in migraine than PM.

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REALITY OF IMAGES AND IMAGES OF REALITY: MIGRAINE AURA, HALLUCINATIONS, ART

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Vision should no longer be considered a passive reception of "what" is out there [1]. Rather, vision implies an active search of what is important for the viewers, based on their capacity to assemble, store, retrieve or create images. Images are reconstructed (bottom-up analysis) from separate visual attributes, including shapes (contours and shadows), motion, spatial positions (dorsal visual stream), and colors (ventral visual stream). Compartments (also called nodes) of each brain area devoted to the processing of individual visual components are both sensation sites and perceptual sites (essential nodes) where signal becomes explicit and conscious (microconsciousness). Nevertheless, top-down mechanisms are constantly employed in visual processing and recognition. Orbitofrontal cortex is able to gate different visual modalities which attract independent, highly specific attention, and change the primacy (i.e., shape over colors and shadows) or the primary chronoarchitecture of the visual organization. Top-down mechanisms originating in the fronto-parietal cortex also contribute to the interpretation of ambiguity. Translation of the word into images (either derived from percepts or evoked from memory or knowledge) may vary along a perceptual to conceptual axis probably resulting from an interaction between parietal and frontal mirror neuron systems. Both perceptual and conceptual attributes are likely emphasized by "self". Symmetry and complexity are reductionistic components of the visual preference fixed during human evolutionary lineage, but aesthetic perception is driven by orbitofrontal cortex, an area involved in special decision making, evaluative judgement, distinct emotion dimension, and reward by abstract reinforce. In the history of art, the variety of styles characterizing different epochs and/or ages of artists clearly shows the importance of inner vision processes in expression and preference.

Recurrent visual hallucinations and dreams are examples of inner vision of proto-objects where top-down mechanisms are minimized [2] During wakefulness, combined impaired attention and poor sensory activation of correct proto-objects within a relatively intact scene representation impair (via a relative low cholinergic activity) the links connecting lateral frontal cortex to dorsal or ventral visual stream systems, thus sustaining visual hallucinations. Dreams are accompanied by low activity in striate and prefrontal cortex and high activity in extrastriate and rhinal-hippocampal connectivity. Combined attentional and visual perceptual impairments are found in migraine. Spatial contrast sensitivity, procession of contours, global form and motion, color vision are altered in interictal migraine without aura. During migraine aura, fortification spectra and other ziz-zag or curve or straight lines reflect the specific layout of visual cortical orientation maps; corona phenomenon, illusory splitting, mosaic fractured vision and Lilliputian hallucinations, stars, colored spots of light, and stained vision, may result from derangement of the connections nodes/essential nodes within extrastriate cortex V3A, V3, and V2, essential nodes in V4 and V5, and perceptual space parietal areas.

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JOINT SYMPOSIUM WITH THE ITALIAN SOCIETY OF NEUROPSYCHIATRY FOR CHILDREN AND ADOLESCENTS

HEADACHE IN CHILDHOOD AND ADOLESCENCE: THE THERAPEUTIC BALANCE MADE BY THE NEUROPSYCHIATRIST

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The diagnostic process for headache in childhood and adolescence foresees a critical evaluation of the neurobiological mechanisms and of the emotional dynamics which possibly induces the symptom complained by the specific patient in consultation.
At the end of the first visit with the patient and at the end of the first interview with his/her parents the clinician directs his therapeutic intervention by balancing the information received from these two interpretative categories.
In the following visits, the eventually induced modifications in the patient and in his/her family environment, may guide the clinician in redefining the therapeutic balance which may lead him to adopt different strategies of care.
The perspective of intervention when shared with the patient, can therefore embrace the search for a better pharmacological approach, an evaluation of the emotional environment and also the detection of the need and psychic suffering connected to the symptom.
Such care strategy, based on the repeated and shared redefinition of the therapeutic balance, is strictly connected to the possibility of modifying the emotional dynamics between the patient and his/her environment using the headache characteristics as a starting point and is strictly connected to the evolution over time of specific physician-patient therapeutic relationships.

SYMPTOMATIC TREATMENT OF PAEDIATRIC MIGRAINE: AN OPEN-LABEL STUDY WITH SUMATRIPTAN NASAL SPRAY

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Introduction The pharmacologic management of paediatric migraine attacks has been subjected to rigorous review, and acetaminophen, ibuprofen and sumatriptan nasal spray (SNS) have shown safety and efficacy in controlled trials [1]. Recently, encouraging data have emerged regarding the use of oral triptans also in paediatric controlled studies (i.e., zolmitriptan 2.5 mg, rizatriptan 5 mg). In this study we investigated a group of migrainous adolescents treated with 10 mg of SNS.
Materials and methods We included 30 patients, 15 males, age range 12-17 years, affected by 2 to 6 attacks monthly in the last 6 months.
We used the definition of migraine with (MA) or without aura (MO) according to ICHD-II 2004 criteria. We included only patients who failed at least one analgesic medication. Each migraine attack was treated within 30 minutes from the beginning of the headache of severe intensity, and a diary card was completed by each patient.
Headache severity was rated on a 4-point scale. Patients who did not experience "pain relief" (reduction of pain intensity by at least two points) at 2 hours postdose, were permitted to take escape medication (i.e., ibuprofen 10 mg/kg, orally).
Results Twenty-one patients were affected by MO and nine by MA. Pain relief was observed in 17 of 30 patients, 2 hours after SNS, and 9 of 30 patients after just 1 hour. Pain free after 2 hours was obtained in 7/30, and reduction of migraine associated symptoms was observed in 22 subjects. Rescue medication was used by 4 patients after 2 hours. An unpleasant taste was the only adverse event in 10 patients. Headache recurrence was not observed.
The patient's judgment was very good (n=7), good (n=19) or sufficient (n=4). There were no differences between male and female or between the two different subtypes of migraine.
Discussion and conclusions About 30%–50% of children and adolescents with migrainous attacks may be unresponsive to analgesics and NSAIDs. For many years studies have not shown efficacy of oral triptans in juvenile migraine patients, perhaps because of lower bioavailability with oral vs intranasal administration.
The results of this trial show a good efficacy and tolerability profile of SSN 10 mg in migrainous adolescents, similar to the data in the literature [1, 2]. Therefore, SNS 10 mg should be considered in acute paediatric migraine for subjects affected by severe attacks not responsive to other interventions.
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PROPHYLACTIC TREATMENT FOR HEADACHE IN CHILDREN AND ADOLESCENTS

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Headache is a common and disabling condition in children and adolescents. The complexity of headache on a pathogenetic and clinical level results from the interaction between biological, psychological and environmental factors. An appropriate management requires an individually tailored strategy giving due consideration to both nonpharmacologic and pharmacologic measures. With reference to prophylactic drug treatment for migraine, the available data suggest that flunarizine (5 mg/day) is probably effective while pizotifen and clonidine are probably ineffective. The efficacy data about propranolol, nimodipine and trazodone are conflicting. At the moment, insufficient evidence is available about cyproheptadine, amitriptyline, divalproex sodium, topiramate, levetiracetam, gabapentin or zonisamide. At present, there is a lack of evidence to support pharmacological, psychological, and cognitive behavioural treatments for tension-type headache and more studies into the treatment of this disorder in paediatric patients are needed. The management of headache in children needs an individualized therapeutic approach, directed to the whole person of the child, taking into account the developmental perspective and the high rate of psychiatric comorbidities. We think that for the prophylaxis of headache, interventions such as identification and avoidance of trigger factors, regulation of lifestyle, relaxation, biofeedback, cognitive behavioural treatment and psychological or psychotherapeutic interventions (e.g. psychodynamic), could be much more effective than pharmacotherapy. With reference to pharmacological treatment we think that there is a clear and urgent need for controlled, randomized, and masked trials. However, lack of evidence should not be confused with evidence of lack of efficacy of a treatment – a risk that is particularly high in the case of treatments not supported by rigorous studies.

THE TREATMENT OF CHRONIC DAILY HEADACHE IN CHILDREN AND ADOLESCENTS

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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%, but 15%–20% of patients referring to third level centres show CDH. The clinical features of CDH have not been definitively recognised, and different characteristics of the crises have been stressed over time. This issue needs to be focused and further studies are absolutely required.

We do not know the factors involved in the chronicization of headache. In adults, the role of analgesic overuse in the exacerbation and maintenance of headaches over time has been stressed, while in children and adolescents other factors seem to play an important role. CDH with developmental age onset represent a matchless opportunity to monitor the trend of the attacks over time, and to identify the factors likely involved in maintaining headache crises over time. The presence of psychiatric disorders has been identified as a negative prognostic factor for the persistence of headache (both migraine and tension-type) over time. CDH presents the highest association with comorbid psychiatric factors, both in adults and children or adolescents. Also, in a four-year follow-up the presence of psychiatric disorders is the strongest predictor of the persistence of headache over time, mainly when related to mood disorders. The treatment of CDH in children and adolescents is a challenge where new drug options need attention, but always taking into account the role of non-drug treatment.

INTERDISCIPLINARY SESSION WITH THE ITALIAN SOCIETY OF EMERGENCY MEDICINE

AIMS AND CONTROVERSIAL ASPECTS OF EPIDEMIOLOGICAL STUDIES REGARDING EMERGENCY HEADACHE

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Introduction Headache is one of the most frequently reported disorders in the adult population, migraine being the most debilitating and frequent primary headache (PH) affects 8% to 12% of the general population and is clearly underestimated. Headache also represents a frequent symptom for admission in the Emergency Department (ED), 1%-3% of the population presents in part with a secondary disease or a pure PH. Epidemiological data regarding the ED are mostly conflicting because of the nature of the data, prevalently retrospective, and also the imprecise diagnosis of "headache NOS" often made by the ED physician. Prospective data on headache in emergency, collected by our Headache Centre (HC), show that about half of the people presenting to the ED for headache have PH (about 0.8% of the population admitted in our ED). Of this group, 74% presented a migraine or its complications (mean age 36 years, female/male rate 3:1), 7% probable migraine, 7% other forms of PH (cluster, chronic tensive, etc.) and 13% secondary headache caused by a misdiagnosis in the ED. The most frequent cause of admission to the ED, in the PH group, (50%) was a prolonged attack, recurrence or migrainosus status. Treatment previously used was usually based on nonsteroidal inflammatory drugs, with a rate of triptan naïve of 87% of the migraine population, confirming that migraine is underestimated in the general population. Only 17% of ED migraineurs had a previous diagnosis of migraine from a general practitioner (GP) or a headache specialist. The disability of attacks of patients referring to the ED was obviously severe, but was also severe in the previous months before access to the ED. This has been demonstrated by the MIDAS scale administered to our population, with 79% of this group with III to IV grade, and a mean headache/day per month of 13.6 days. Repeaters, a well defined group of the population identified by Maizels as patients who referred three or more times for headache to the ED over a period of 6 months, represent 11.8% of our population [1].

Conclusions EDs are the best possibility to recruit naïve migraine patients with high disability. EDs are, in fact, like a funnel where a part of a city's population refers for different diseases. Data based on our experience on headache in emergency, confirm that migraine represents the most frequent PH observed in the ED. A strict collaboration between the HC and the ED, has the possibility to improve health care of migraineurs and reduce direct and indirect costs of migraine.

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THE DIAGNOSTIC APPROACH TO ACUTE HEADACHES IN THE EMERGENCY SETTING: THE NEUROLOGIST'S POINT OF VIEW

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Introduction Secondary headaches due to life-threatening disorders account for less than 5% of the cases admitted to EDs for acute non-traumatic headache symptoms. The crucial items for differential diagnosis are based on the clinical picture, the associated neurological and somatic symptoms/signs. The personal and family history of specific comorbidities and RFs. The systematic check for the so-called headache Diagnostic Alarms (DA) [1] may help increasing the alert for symptomatic headaches. A structured adequate approach should also include adherence to guidelines defining the emergent/urgent diagnostic procedures to be undertaken, while the validation of diagnostic criteria and guidelines should stem on the post-hoc final diagnosis according to ICHD-2004 criteria, to be defined at a short-term follow-up visit.

Patients and methods Over an 18-month period 290 cases of headache (mass lesions, pediatric and post-traumatic cases excluded) were observed at the local ED and re-evaluated for a final diagnostic definition between 3 and 8 weeks after discharge.

Results At discharge from the ED, secondary headaches show a slight prevalence (53%); migraine accounts for 35%, while over 30% of the cases are defined as "not otherwise specified" (NOS); 18% of the symptomatic group headaches (verified diagnosis) come from a former allocation to the group of primary ones. Diagnostic Alarms (DA) and warning signs confirm their relevance in the clinical practice but also their poor specificity. Other "possible-warning" features identified in the symptomatic were: strictly unilateral pain, specific precipitating mechanisms, and atypical presentation/course. Emergent and urgent non-contrast CT scans were performed following the ACEP-2002 recommendations [2]. Among acute and severe (*de-novo*) headaches, thunderclap headache confirms as being a high-risk diagnosis due to the number of possible aetiologies. The resolution power of the CT-LP strategy when SAH is strongly suspected was sub-optimal: delayed presentation, in fact, may decrease CT resolution, while false-positive LP (traumatic tap) may induce increase costs and risks for further and even invasive confirmatory imaging studies. Cerebral venous thrombosis, spontaneous intracranial hypotension and arterial dissection may as well present themselves with the clinical pictures of thunderclap, often with no or very poor neurological signs and, very frequently, false-negative CT scans.

Conclusions The revision of our case-series of acute/severe headaches reveals a sub-optimal approach to this condition in the daily emergency practice, stressing the need for more strict adherence to the available criteria, guidelines and statements and the requirement for imaging protocols adequate to the technical development of each local structure.

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HEADACHE: THE EMERGENCY PHYSICIAN'S POINT OF VIEW

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Headache is one of the commonest neurological symptom in adults and it is also one of the commonest neurological problems which the Emergency physician has to face. The prevalence of non-traumatic headache is between 1.7%–4.5% of all patients admitting to an Emergency Department (ED). Descriptive analyses show that there is a mild predominance of females in headache patients that referred to an ED; about one-third of headaches are of uncertain origin, reflecting the problem of making a specific diagnosis according to the International Classification of Headache Disorders in the ED [1].

The first problem of headache management in an emergency setting is to distinguish primary non-organic headaches from the secondary organic ones. The first, even causing great discomfort to patients, are usually benign; the latter are often malignant and, if unrecognized, can cause high morbility and mortality.

This problem of differential diagnosis leads to a question: which patients are likely to require urgent investigations?

CT scan is mandatory when patients describe a severe headache ("worst headache in their life"), with acute onset or with focal neurological signs or with syncope or important vomiting at the onset. Patients with headache of recent onset, progressively worsening headache or headache lasting for weeks or months are also candidates for a CT scan. Further investigation such as lumbar puncture (LP) is needed when there is a high suspicion of subarchnoid hemorrhage. If CT scan and LP are negative there are no indications to perform further urgent angiographic tests.

Another dilemma of the ED physician is whether CT scan must be performed before LP. Literature supports the safety of LP without screening cranial computed tomography in patients without altered mental status and papilledema and in presence of a normal neurological examination [2].

The most common type of headache clinical picture presenting in the ED is the patient with headache very similar to previous attacks in terms of intensity, duration and associated symptoms. In this setting, the emergency physician must identify primary headaches such as migraine. The contemporary presence of disability, nausea and photofobia represents a valid and reliable screening instrument for migraine diagnosis in the ED with a predictive positive value of 0.93. In such patients, CT scan may be avoided and good response to therapy (NSAID and/or metoclopramide iv) during an observation period of 3 hours seems to be a safe criterion for discharge.

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IMAGING OF HEADACHE

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The multidimensionality of imaging contribution in diagnosis is largely discussed in literature: the optimum application of conventional imaging and the contribution of non-conventional techniques for a deeper insight in this pathology is presently under debate.

Conventional Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT) with and without contrast agents are already a fundamental part of diagnosis and clinical follow-up in everyday practice, supplying major information about blood vessels and possible lesions in brain tissue. It is important to exclude a tumour mass, a vascular malformation or other pathologies causing headache.

Non-conventional MRI sequences, such as Functional MRI (fMRI), Diffusion Tensor Imaging (DTI), Spectroscopy and Spectroscopic Imaging (sMRI), add a great amount of highly specific information to the diagnosis and treatment of this pathology, allowing a more accurate stratification of patients' cohorts and validating differential diagnosis. fMRI and DTI investigate the functionality and connectivity structure of the major circuits, measuring altered responses to stimuli and anatomical alterations in fibers of interest on a consistent and validated statistical basis. sMRI measures possible alterations in metabolite concentrations, possibly in concomitance with the execution of specific tasks (functional sMRI), gaining information on the biochemical substrate, cellular metabolism and tissue integrity at cellular level. All of these techniques, developing strictly from research procedures to ordinary clinical practice, are highly sensible to alterations of normal appearing matter and allow a more accurate and earlier diagnosis and correlation with pharmacological treatment.

Imaging of headache is at present a significant tool that cannot be given up for clinical assessment through conventional techniques; it appears that the future evolution will involve a wider and routine application of non-conventional techniques as a source for more specific information.

HIGH RISK POPULATIONS AND COMORBIDITY

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Headache may be the sign of an illness, sometimes even severe, in many groups of patients. The list, though long, cannot be complete. We will review data about patients more often seen in Emergency Rooms and whose headache needs a very careful neurological examination, since it could be potentially dangerous.

This is true not only for already known headache patients (because having a diagnosis of primary headache does not mean that one is protected against the risk of developing an overlapping organic illness in the future), but most of all for patients who report a headache for the first time.

Headache is more likely to be a sign of disease in older than in younger people. Several diseases with increased prevalence in the elderly can cause headache, including giant cell arteritis, intracranial mass lesions, ischaemic cerebrovascular disease, and chronic obstructive lung disease with hypercapnia. Headache may also result from congestive heart failure (which produces venous congestion in the cranial cavity), increased intracranial pressure, and a variety of metabolic disturbances. Some disorders producing headache, such as stroke, cerebral venous thrombosis, eclampsia, and SAH, occur more frequently during pregnancy. Differential diagnosis of these kinds of headache is very important, because the pharmaceutical treatment is restricted. Women of childbearing age and suffering from migraine

with aura are at greater risk of migraine-related stroke. Additional risk of stroke in migraineurs occurs in oral contraceptive pills users and cigarettes smokers. Purported mechanisms for migraine-associated stroke include involvement of the vasculature (including vasospasm, arterial dissection and small vessel arteriopathy), hypercoagulability (elevated von Willebrand Factor, platelet activation) and elevated risk of cardioembolism (patent foramen ovale, atrial septal aneurysm). In the immunocompromised patient, the presence of headache should suggest beginning an evaluation for possible CNS infection. CNS infections remain a major cause of morbidity and mortality in immunosuppressed patients with malignancies. Due to immunosuppression, diagnosis is often more difficult in this group because of atypical presentations. Fever or headache are often the only symptoms. Clinical history and general examination should lead to appropriate tests such as neuroimaging, CSF analysis, cultures, and brain biopsy. Diagnostic evaluation should be pursued rapidly and aggressively, since specific treatments can often reduce morbidity and mortality. When a typical postdural puncture headache loses its postural component, investigations should be performed to rule out cerebral venous thrombosis or meningitis or intracranial (intracerebral, subdural) haematomas.

EMERGENCIES AND HEADACHES IN CHILDHOOD

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Headache is a frequent symptom in paediatric age and 10%–20% of children between 7 and 16 years of age are currently involved [1, 2]. The Paediatrician's role is to distinguish the primary from the secondary forms, which are more rare. Among the secondary forms, we would like to point out headache during a fever episode (very common, i.e., during viral respiratory infections), depending on otorhinolaryngoiatric (sinusitis), or oculistic (refraction defects), or dental causes (malocclusion), with an overestimated incidence. Serious neurological causes represent less than 0.5% of headaches.
In approaching headache it is essential that both a family history (familiarity is typical), and physiological history be carried out (age of the child, presence of failure to thrive) and subsequently a pathological history (duration of the attack, localization, characteristics and intensity, frequency, eventual presence of aura, association with nausea, vomiting, phono/photophobia, presence of nocturnal awakenings or previous cranial trauma) should be undertaken. Alarming factors are: under 5 years of age; unexpected onset; nuchal localization; duration longer than 24 hours; headache at awakening; projectile vomiting in the morning, not preceded by nausea; worsening course and cranial trauma.
The physical objective examination is indispensable in evaluating the presence of fever, of signs/symptoms of sinusitis or infection of the CNS, puberal development and statural and ponderal growth, and the presence of arterial hypertension.
The neurological examination (including vision of the fundus oculi and the evaluation of rigor nucalis), blood and instrumental examinations, integrated with neurological consult and eventually EEG are essential in order to resolve the differential diagnosis between primary and secondary forms.
The most common form presenting to the Emergency Department is tension-type headache. Its characteristics are usually of mild intensity, multiple weekly frequency, constrictive/serious pain, commonly present in the afternoon or evening, not associated with other symptoms. A detailed history identifies psychological or environmental factors (such as scholastic or familial stress) that could establish the symptomatology on which it is more opportune to act rather than on the single attack. During its acute phase, this headache responds poorly to pain-killers.
Treatment of the headache [1, 2] takes advantage of commonly used drugs, such as acetaminophen (first choice), and NSAIDs (second choice), of which ibuprofen is the most used. It is also important to consider an eventual association with an antiemetic, of which domperidone is the most commonly used.

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EMERGENCY MANAGEMENT AND HEADACHES IN THE ELDERLY

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Introduction Headache prevalence is age-dependent, decreasing progressively, especially over the age of 55–60 years. The aetiology of headache is also age-dependent. The incidence of primary headaches declines, whereas secondary headaches tend to occur more frequently with increasing age [1].
Materials and methods We reviewed the clinical charts of 9075 consecutive outpatients over the age of 18 years referred to our Headache Centres from 1995 to 2006. All data were collected prospectively and assembled in a database since 1995.
Results Of the 9075 patients evaluated, a total of 469 (5.2%) were over the age of 65 years at their first evaluation. In this group, primary headaches were diagnosed in 365 patients, secondary headaches in 64 cases, whereas cranial neuralgias and other headaches were identified in 40 subjects. Out of these 469 patients, 89 were seen urgently, due to the recent occurrence of the headache symptoms. Primary headaches were diagnosed in 33 cases, secondary headaches in 28 subjects, neuralgias in 13 cases, whereas in 15 patients the headaches could not be classified. Among primary headaches, the most common conditions seen at the emergency room were tension-type headache, cluster headache, migraine with aura and hypnic headache. The secondary headaches were represented above all by headache attributed to arterial hypertension, cervicogenic headache and giant cell arteritis. Among neuralgias and other headaches, trigeminal neuralgia was far the most common headache which required an urgent evaluation.
Discussion Different from younger patients, elderly patients commonly present with secondary headaches. It is thus mandatory in many cases to perform laboratory tests and neuroimaging, in particular when the symptoms have started recently and present atypical features. Notwithstanding, primary headaches and neuralgias were diagnosed more frequently than secondary headaches. Interestingly, the primary headaches that forced patients to seek emergency care were tension-type headache and above all cluster headache, that is usually considered as a disorder typical of young and middle-age individuals. Moreover, we could diagnose one case of migraine without aura, 2 cases of migraine with aura and 5 cases of hypnic headache, respectively. Intracranial neoplasm was found only in two cases.
Conclusions The prevalence of elderly patients in our population of headache sufferers seen at first aid was remarkable. The choice of headache treatment is challenging, since specific guidelines are lacking and also because geriatric patients commonly present comorbid-

ity with other diseases. In most cases laboratory tests and neuroimaging are mandatory, due to the relatively high prevalence of secondary headaches in the elderly.

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INTERDISCIPLINARY SESSION WITH THE ITALIAN ASSOCIATION OF SLEEP MEDICINE

NOCICEPTION AND CIRCADIAN RHYTHMS: THE ROLE OF THE NEUROPHYSIOLOGICAL APPROACH

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Noxious stimuli and painful disorders interfere with sleep, but sleep disturbances also contribute to the experience of pain. Thus, there is a reciprocal relationship between sleep quality and pain. A close relationship between sleep disturbances and chronic pain syndromes, including headache, fibromyalgia, and others, has been observed.

Animal studies have shown that the monosynaptic and polysynaptic spinal reflexes, including the nociceptive withdrawal reflex (NWR), are more stable during synchronized sleep than during wakefulness. Instead, during desynchronized sleep, both are either greatly depressed or abolished for long periods, and the threshold for evoking reflexes is increased. In humans, reflexes with a double component, such as the NWR, evoked during sleep, have been found to show an increased latency and duration of the second component, and absence of the first component.

We examined in detail the effects of the different sleep stages on the nociceptive component of the lower limb NWR. We found that either the NWR reflex threshold and latency were significantly increased during both non-REM and REM sleep. In addition, we found maximum amplitude and duration increases during REM sleep.

As the opiate receptor/endorphin system and descending supraspinal serotonergic pathways both play an important role in the modulation of sleep, both may be responsible for the NWR changes occurring during sleep. However, because plasma endorphin levels did not correlate with NWR circadian variations, the opioid system may only play a minimal role in the modulation of the NWR during sleep. On the contrary, the reduction of the brainstem serotonergic excitatory influences on the spinal cord may explain the increase in the nociceptive reflex threshold during sleep. This effect may occur directly at the level of the NWR circuitry or indirectly through a hyperpolarization of the spinal motoneurons. The prolonged latency and duration could be related to a reduction of the reflex excitability and/or to reflect temporal and spatial summation phenomena producing changes in the interneuron excitability, possibly secondary to the effects of different supraspinal influences during sleep. Sleep has been demonstrated to be also particularly important in spinal self-organization and maturation of the NWR.

HYPNIC HEADACHES AND OTHER FORMS OF NOCTURNAL HEADACHES: NOSOGRAPHIC PROFILES AND DIFFERENTIAL DIAGNOSIS

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The relationship between headache and sleep is complex.

A daytime headache may either remit or, more frequently, get worse during sleep, the relationship between headache and sleep varying during the patients' life. However, sleep-related headaches exist as a well recognized nosographic group and are meant to be headaches whose attacks regularly occur mainly during sleep or upon awakening. The prototype of the sleep-related headaches is the so called hypnic headache (HH), a primary, late-onset, form of headache, characterized by exclusive occurrence during sleep, chronic pattern of attacks (≥ 15 times per month), short duration, dull pain, absence of autonomic signs and symptoms. This particular form of headache raises several issues from a clinical and pathophysiological point of view.

HH must be differentiated from symptomatic headaches, including headache in obstructive sleep apnea, and from other primary headaches occurring, but not exclusively, in sleep: migraine, tension-type headache, trigeminal-autonomic cephalalgias (cluster headache, paroxysmal hemicrania, SUNCT), primary thunderclap headache, and hemicrania continua.

No exclusive relationship of HH with either REM or NREM sleep has been proven to exist whilst several lines of evidence indicate that HH is likely to be a chronobiological disorder ("alarm-clock headache").

Finally, an intriguing hypothesis has been recently advanced by the Pavia group about HH potentially being a phenotypical variation of migraine over time. This hypothesis is based on several factors: the partial overlapping of clinical features between HH and migraine, the tendency of migraine to disappear in elderly people, the typical onset of hypnic headache after the age of 50 and the observation that about 20% of patients suffering from HH have a past history of migraine. According to this line of reasoning, one may hypothesize that changes in external factors ranging from hormonal patterns and life style (in relation to menopause, retirement, etc.) may act upon a predisposed terrain and cause the appearance of different clinical characteristics over time ("phenotypical heterochronia").

CLUSTER HEADACHE AND SLEEP: IS THERE A ROLE FOR THE OREXIN/HYPOCRETIN SYSTEM?

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The association between cluster headache (CH) and sleep has long been recognized because of the predilection of attacks to occur during nocturnal sleep. Polysomnographic studies showed that, in episodic CH, the attacks are related to the REM stage of sleep. Furthermore, CH patients are at increased risk for sleep-related disorders, like obstructive sleep apnoea (OSA) and periodic limb movements during sleep (PLMS). At present, neurobiological mechanisms underlying this CH and sleep association are unknown. The orexins (or hypocretins) are neuropeptides made exclusively in the posterolateral hypothalamus. Two related peptides (orexin A and B, or hypocretin-1 and -2) are produced by cleavage of a single precursor protein (Hcrt). The orexin-1 receptor (Hcrtr1) binds orexin A only, whereas the orexin-2 receptor (Hcrtr2) binds both orexin A and orexin B. Hypocretinergic receptors are widely expressed in the central nervous system. Neurons containing hypocretin project to multiple neuronal systems, including the noradrenergic ascending nucleus, the brainstem serotonergic system, and the cholinergic system in the cerebral cortex. The binding of orexins/hypocretins to their receptors

promotes calcium influx within the neurons and exerts a post-synaptic excitatory effect. The discovery that orexin/hypocretin dysregulation causes the sleep disorder narcolepsy indicated a major role for this system in sleep regulation. In canine families with narcolepsy three mutations in the *HCRTR-2* gene were identified. In humans, most cases of narcolepsy are not linked to hypocretin ligand or receptor mutations but are associated with low cerebrospinal fluid Hcrt1 levels. Recent studies revealed a novel role for the orexin/hypocretin neuronal system in reward processing and addiction. In consideration of the central actions of orexins, we hypothesized an involvement of these peptides in CH. Using a genetic association strategy, we have shown that the 1246 G>A exonic polymorphism of the *HCRTR-2* gene is significantly associated with CH. This association was recently confirmed in a large study from Germay but was not replicated in a dataset of CH patients of Danish, Swedish, and British origin. To further investigate orexin/hypocretin involvement in CH, we have analysed several new polymorphisms and reconstructed genes haplotypes. Then, we have sequenced the *HCRT*, *HCRTR-1* and *HCRTR-2* genes in CH. Finally, we evaluated the effects of the 1246 G>A polymorphism on the binding activity and the dimerization process of the Hcrtr2 receptor. Our data confirms that the *HCRTR-2* gene modulates the risk for cluster headache and suggests a role for orexin/hypocretin peptides in the sleep disturbances of CH patients.

SLEEP-RELATED MIGRAINE: CLINICAL DETERMINANTS EVALUATION AND ROLE OF COMORBIDITY

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Introduction A preferential emergence of migraine episodes at nighttime or in the early morning was extensively ascertained and chronobiological studies indicated the greatest occurrence of attacks in the interval between 04:00–09:00 hours with no other time of the day approaching this likelihood. The preferential occurrence of migraine attack at nighttime and in the early morning hours might suggests both the existence of a relationship betwen migraine and sleep and possibly an impairment of the circadian rhythm control systems. The aim of this study was to verify the possible role of physiological variables (i.e., aging and gender) and/or of coexisting condition (i.e., blood pressure modification, sleep quality disturbances, psychiatric comorbidity) in favouring nocturnal presentation of migraine without aura (MO).

Methods Two hundred consecutive MO patients were evaluated by means of a clinical interview and headache diaries. Fifty-eight patients fit the sleep-related migraine without aura (SRMO) definition (at least 75% of the attacks occurring at nightime or at awakening); 60 MO patients with no preferential timing of occurrence attacks were also enrolled in the study.

All patients underwent clinical assessment, 24-hours ambulatory blood pressure monitoring (ABPM) and evaluation of hypocretin receptor T2 gene polymorfism. Pittsburg Sleep Quality Index, Beck Depression Inventory Scale and STAI-Y were also performed.

Results The percentage of SRMO patients increases with aging without significative gender differences. SRMO patients showed a worse clinical picture presentation with regard to intensity, disability and use of symptomatic drugs. No significative alterations of the main BP parameters obtained by means of ABPM were detected in SRMO patients in comparison with MO group. The percentage of patients with poor sleep quality according to PSQI was higher in both groups of migraine patients in comparison with normal control irrespective of the temporal distribution of their attacks. No significative differences were also detected between SRMO and MO groups in BDI and STAI values.

Conclusions The increasing percentage of SRMO patients with aging could suggest that migraine attack occurrence is related not only to the physiology of sleep; quantitative and qualitative modifications of sleep pattern and biological rhythms, occurring in aging might also play a putative role in modifying clinical presentation of this disorder. Similarly to hypnic headache it might be hypothised that an age-related impairment of the suprachiasmatic nucleus could cyclically activate a disnociceptive mechanism leading to both a sudden awakening and headache. The mechanism may be favoured both by normal physiological events such as the marked reduction of firing occurring in the dorsal raphe nucleus and locus coeruleus during the REM sleep phase and by age-related changes affecting REM sleep itself and awakening mechanisms.

HEADACHE AND SLEEP DISORDERS IN CHILDHOOD

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Clinical observations supported by experimental data suggest that sleep and headache share common anatomical, physiological and biochemical substrates, as shown by the possibility of coexisting also in the same patient of headache and sleep disorders and by their relative frequency in the general population and in children. Sleep represents the only well-documented behavioural state related to the occurrence of some headache syndromes while headache may cause various degrees of sleep disruption and seems to be associated with several sleep disturbances either in adults or in children. Children with migraine headaches appear to have a range of sleep disturbances: insufficient sleep, bruxism, and maternal co-sleeping are significantly more frequent compared to children from a normative community sample. Children with migraine experienced greater sleep disturbances in all domains including longer sleep onset delay, more bedtime resistance, shorter sleep duration, more daytime sleepiness, more night wakings, greater sleep anxiety, more parasomnias, and more sleep-disordered breathing. Even though several studies demonstrated a high prevalence of sleep disorders in headache subjects, sleep disorders are not seen as a comorbid or causative factor for headache. While patients complain about their sleep disorders, these manifestations are usually considered as "common insomnia" of psychological origin and tend to be considered not relevant by physicians. Early sleep disorders have been also related to psychiatric co-morbidity and involved in the endurance of headache in children and adolescence; in an 8-year follow-up study it has been found that the most frequent comorbid disorders at the onset of the headache were sleep disorders (12%) followed by anxiety (11%); of the 9 patients with sleep disorders as comorbid factor at the onset of headache, at follow-up 6 had enduring headache and 3 were headache-free.

DISORDERS OF AROUSAL IN HEADACHES

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Both the hypothalamus and the brainstem including the periacqueductal grey, the locus coeruleus and the median raphe nuclei are at the same time involved in the control of autonomic and sleep processes as well as pain perception.

Primary headaches such as migraines and cluster headache (CH) conform indeed to peculiar ultradian and circadian patterns and maintain well established relations with sleep stages, fatigue and time of day.

Adaptative homeostatic mechanisms appear to be perturbed in migrainers who, according to some authors, show reduced cyclic alternating pattern (CAP) rate indicative of reduced fluctuations in arousal level in NREM sleep. Migraineurs however report an increased rate of disorders of arousal (DOA), especially sleep walking, during developmental age in association to other less specific sleep abnormalities ranging from insomnia to excessive daytime sleepiness (EDS) and other parasomnias [1]. Recently, an interesting theory [2] was proposed regarding the serotoninergic role in cupling motor control with respiration in migraineurs, to explain the contribution of factors such as sleep apnea and snoring in promoting instability in sleep of these patients. In particular, a massive 5-HT release in the brain responsible for migraine attacks would also set, especially if accompanied by even mild sleep disordered breathing (SDB), time locked excitability of motor neurons with release of complex gross body movements usually unseen during sleep.

As indirect proof of this theory, 5-HT enhancers from lithium to paroxetine, often used in the treatment of different type of headaches may in fact trigger migraine episodes.

Genetic, dismaturative factors may be at stake challenging physicians to always find the best compromising treatment for daytime as well as sleep in migraine developmental subjects.

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ORAL COMMUNICATIONS

CLINICAL ASPECTS OF HEADACHES I

EVALUATION OF CUTANEOUS ALLODYNIA IN MIGRAINE AND TENSION-TYPE HEADACHE

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Cutaneous allodynia is a pain resulting from non-noxious stimuli to normal skin. Several previous studies suggested the association between cutaneous allodynia and episodic migraine (EM). These findings confirmed that the pathophysiology of migraine involves not only irritation of meningeal perivascular pain fibres but also a transient increase in the responsiveness of central pain neurons that process information arising from intracranial structures and skin; in fact, both second-order nucleus caudalis neurons that receive convergent input from cerebral blood vessels and meninges, and from the ophthalmic skin, both third-order trigeminovascular neurons that receive input from second-order dorsal horn neurons located in nucleus caudalis (i.e., process sensory information from the head) and in the cervical enlargement (i.e., process sensory information from upper limbs) are involved [1].
We investigated cutaneous allodynia in episodic and chronic migraine and, also, in infrequent episodic tension-type headache (ETTH) and chronic tension-type headache (CTTH).
The study was carried out in the Headache Study Centre of Modena University: each patient gave informed consent before participating (Helsinki declaration, revised in 1983). From March to July 2006, 56 patients (45 females, 11 males; mean age 45 years) were examined; a control group, selected from the general population, included 22 subjects (16 females, 11 males; age range 12-83 years).
For the evaluation of changes in skin sensitivity we used Von Frey's calibred monofilaments (0.02-300 gr) [2]: pain threshold was obtained in the absence of migraine (baseline) and during migraine attacks. A specific questionnaire administered to patients gave us information about personal sensitive perception of pain.
The data showed that in all types of headache cutaneous allodynia was present (ANOVA $p<0.005$): 83% in episodic migraine and 91% in chronic headache; 38% in episodic tension-type headache and 90% in chronic tension-type headache. In migraine, cutaneous allodynia is more frequently monolateral. Less than 10% of control subjects showed cutaneous allodinya.
Pain threshold was significantly lowered in tension-type headache (Bonferroni's t-test; $p<0.05$), especially in tension-type headache with major frequency (>15 days for month) (65%). In migraine, pain threshold was not modified by frequency of headache. These preliminary data confirmed that the development of central sensitization is more evident in tension-type headache, in particular if not adequately treated from onset.

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

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Introduction In the second edition of the International Classification of Headache Disorders (ICHD-II), published in 2004, osmophobia has been proposed in the appendix within the associated symptoms category of the criteria for the diagnosis of migraine without aura (MO). Following our recent retrospective investigations in primary and secondary headaches [1, 2], we planned a clinical prospective study about the presence and the role of osmophobia in patients affected by migraine (M), divided into those without (MO) and with aura (MA), or those with episodic tension-type headache (ETTH).
Materials and methods We analysed a consecutive series of patients referred to our Headache Centre from November 2006 to March 2007, with a diagnosis of M (MO and MA), or ETTH in accordance to ICHD-II criteria; patients with two or more forms of primary headaches were excluded. At the end of the visit, the patients received a semi-structured questionnaire to evaluate the possible presence of osmophobia in four consecutive attacks, with further specifications about its clinical features.
Results At present, we recruited from our Headache Centre 68 patients (51 females, 17 males; age 35± 10.7 years) who recorded four consecutive attacks (therefore, the total number of reported attacks was 272); of whom, 50 had MO, 2 MA, 16 ETTH.
In our study 53.8% (28/52) of migraine patients reported osmophobia during at least one attack. In particular, 64.2% (18/28) of them reported this symptom in four attacks, 14.2% (4/28) in three attacks, 17.9% (5/28) in two attacks and one patient in only one attack. Among the 16 patients diagnosed with ETTH, none reported the presence of osmophobia during an attack (p=0.0001).
In 60.7% (17/28) of osmophobic patients this symptom was present at the beginning of the pain, and in 64.3% (18/28) of patients it ceased when the pain ended. Most frequently offending odours were scents (78.6%), cigarette smoke (78.6%) and food (71.4%). The olfactory stimulus triggered attacks in 17.8% (5/28) of osmophobic patients.
Discussion and conclusions These preliminary data of the first prospective study on the subject, that should help to correct the memory-related bias which may influence retrospective studies, confirm that osmophobia is a very specific marker in the differential diagnosis between M (MO and MA) and ETTH.

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AGE AT ONSET AND GENDER RATIO IN CLUSTER HEADACHE: CLINICAL OBSERVATIONS OVER 12 YEARS

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Introduction Cluster headache (CH) is considered a disorder of young men, which predominantly begins at ages 20 to 40 years. The mean age at onset derived from several studies is 31.5 years. It is well known that CH affects more frequently men than women, the gender ratio ranging from 4.4:1 to 2.5:1. The reports on CH in elderly patients are sporadic and anecdotal.
Materials and methods We reviewed the clinical charts of 9075 consecutive outpatients referred to our Headache Centres from 1995 to 2006. All data were collected prospectively and assembled in a database since 1995.

Results A total of 188 patients (140 males and 48 females), constituting 2.1% of the entire population of headache sufferers, fulfilled the ICHD-II diagnostic criteria for CH. The overall gender ratio was 2.9:1, and interestingly, was 6.4:1 until the age of 55, whereas over this cut-off age it completely reversed, resulting in 0.8:1. The mean age was 43.5±16.1 years (range 16 to 85) at first observation and 37.0±15.3 (range 14 to 84) at onset, respectively. We diagnosed 26 cases with CH (3.1 according to ICHD-II), 131 episodic CH (3.1.1), 25 chronic CH (3.1.2), and 6 probable CH (3.4.1). The mean age of the females was significantly higher than that of males, 53.2±19.3 years at first observation and 46.0±18.2 at onset, compared with 40.1±13.4 and 33.9±12.9, respectively. Of the 36 patients aged over 65 years, 20 were females, and in this elderly subpopulation the prevalence of chronic CH was remarkably higher than in previous ages, accounting for 30.6%. In patients under 65, chronic CH was found in 9.2% of cases.

Discussion This study, confirming previous results, demonstrates that CH can begin in geriatric age [1]. Moreover, with regard to onset of CH, we found a significantly higher number of female patients aged over 55 years. To our knowledge we report the largest case series of CH elderly patients published in the literature to date.

Conclusions The onset of CH seems to be independent of the life period of the patients, even if the average age of onset peaks towards the third decade. Apparently peculiar to the female distribution, an increased frequency appears to occur in middle age and elderly patients. In the elderly group, females represented the majority of cases, in contrast with the evident male preponderance in the previous decades.

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MIGRAINE AND TENSION-TYPE HEADACHE DISAPPEAR DURING ACTIVE PERIOD OF EPISODIC CLUSTER HEADACHE: REPORT ON 5 PATIENTS

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Cluster headache (CH) and other primary headaches may coexist together in the same patient, however the possible relationship between the different types of primary headache is obscure.

In this report we describe the temporal relationship of occurrence of cluster headache bouts in 5 patients (4 males and 1 female, mean age: 41.8±1.63 years) suffering also from migraine without aura (MO) and/or tension-type headache (TTH), according to ICHD-II criteria, and selected from CH patients attending our Centre in Pavia.

In the woman the associated primary headache was MO with a weekly frequency; one patient suffered from both MO (with a frequency that varies from a minimum of 1 crisis every two months to a maximum of 4 crisis/month) and frequent episodic TTH. The other three subjects suffered from sporadic TTH.

The mean age at onset of cluster headache was 28.2±11.4 years. In three patients CH began after the development of the other primary headache. CH pain was always unilateral and recurred on the same side, except in one patient who has presented a side-shift in the last cluster bout.

In the female patient, migraine and cluster attacks occurred on the same side, while migraine attacks were bilateral in the male migraineur and tension-type headache was always bilaterally located. Patients used triptans for migraine attacks and analgesics and non-steroidal anti-inflammatory drugs for TTH episodes. Subcutaneous sumatriptan, at the dose of 6 mg, was effective for CH attacks in four patients, while the remaining one used 40 mg of eletriptan. In all patients the coexisting primary headache completely disappeared during the CH bouts, to re-appear shortly after CH remission.

Though based on a very small group of subjects, our observation that CH occurrence is consistently associated with a prompt spontaneous remission of coexisting migraine and/or tension-type headache appears intriguing in terms of possible interactions between central nociceptive pathways and control circuits. Based on available data, we can hypothesize that activation of the hypothalamic grey matter – the anatomo-functional trait of CH – may prevail over the activation of nociceptive structures involved in the pathogenesis of both migraine and TTH, thus preventing temporarily their manifestation.

BODY WEIGHT AND PRIMARY HEADACHES

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Background An increasing percentage of the population worldwide is overweight or obese as defined by the World Health Organization. Obesity has long been recognized as an important risk factor for type II diabetes mellitus, hypertension, and dyslipidemia. The adverse metabolic effects of excess body fat are known to accelerate atherogenesis and to increase the risk of coronary heart disease, stroke, and early death. Impaired insulin sensitivity (insulin resistance) has recently emerged as a risk factor for hypertension and stroke. Epidemiological studies have shown the presence of a strong association between migraine and vascular disease, such as hypertension and stroke. Recently, a high incidence of migraine with aura was observed among morbidly obese women [1] and obesity was identified as a risk factor for transformed migraine [2]. Insulin sensitivity was found altered in migraine patients. These observations indicate a possible link between obesity and headache.

Objective In order to further explore this association the incidence of weight variations and the clinical aspects of the headache were evaluated in a group of headache sufferers.

Methods A group of 419 subjects (303 females and 116 males; age range 18-65 years, mean age 39.31±11.37 years) attending for the first time the Headache Centre of the University of Turin in the period from 01.01.2006 to 31.12.2006, suffering from primary headaches, according to ICHD-II criteria, was examined.

Subjects were divided into four groups based on BMI, underweight (<18.5), normal weight (18.5 to 24.9), overweight (25 to 29.9), and obese (> 30).

The prevalence and clinical aspects of the different primary headaches were assessed.

Results Thirty-two (7.6%) patients resulted underweight, 255 (60.8%) had normal weight, 89 (21.3%) were overweight and 43 (10.3%) obese.

Migraine without aura appears to be almost equal in the four groups, while migraine with aura and chronic migraine are much more frequent in overweight and obese patients than in normal weight ones ($p<0.05$). On the contrary, patients suffering from migraine without aura and episodic tension-type headache were more frequently underweight ($p<0.05$). In migraine patients the clinical aspects of migraine attacks did not show any difference.

Conclusions On the basis of these data migraine with aura and chronic migraine appear to be more frequent in overweight and obese patients than in normal weight ones, according to other Authors' findings. The mechanisms of it are not clear yet and many different hypothesis try to explain this link. Larger studies, designed to examine the association between migraine and body weight are needed.

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MEDICATION-OVERUSE HEADACHE: PREDICTORS FOR RELAPSE IN TRANSFORMED MIGRAINE PATIENTS WITH LOW MEDICAL NEEDS: A ONE-YEAR PROSPECTIVE STUDY

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Background and objectives Predictors of long-term success of drug withdrawal have been investigated only in studies including non-selected populations of complicated headache patients. The aim of this study was to evaluate the predictors for relapse after successful drug withdrawal in MOH patients having migraine as the primary headache and reduced medical needs.
Methods Detail about populations under study, study design, inclusion criteria and short-term effectiveness of drug withdrawal strategies have been already published [1]. Relapse was defined as frequent use of any acute medication on more than 10 days/ month for at least 3 months.
Results Complete datasets were available for 83 patients. At one-year follow-up, the relapse rate was 21.3%. Univariate analysis showed that patients who relapsed had a longer duration of disease with more than 8 headache days/month, a longer duration of drug overuse, tried a higher number of preventive treatments, had a lower improvement in headache frequency after withdrawal and consulted a higher number of specialists. A binary logistic regression analysis was performed and two variables remained as significant predictors of relapse use: duration of disease with more than 8 headache days/month (OR= 1.85, p=0.04), and number of previous preventive treatments (OR= 1.51, p=0.01).
Conclusions In patients with migraine plus MOH and reduced medical needs, relapse seems to depend on a greater severity of pre-existing migraine.
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CLINICAL CHARACTERISTICS OF MEDICATION-OVERUSE HEADACHE ARE NOT DEPENDING ON DRUGS MISUSED

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Introduction The International Classification of Headache Disorders 2nd edition remarkably modified the diagnostic criteria of medication-overuse headache (MOH), and also introduced clinical criteria to differentiate headache between different overused symptomatic medications (SM). Subsequently, these clinical criteria were abolished, due to lack of reliable data from literature. Aim of the present study was to analyse, for the first time systematically, the clinical characteristics of headache in a sample of patients suffering from MOH.
Patients and methods We enrolled 73 patients with chronic daily headache who took SM ≥once per day for ≥3 months, and were treated with an in-patient withdrawal detoxification. The patients were divided according to the SM overused. The quality, the site, the severity, the accompanying phenomena, the pre-existing headache and the response to the medication used were evaluated. The data were analysed using the SPSS 12.0.
Results Sixty-four women (87.7%) and 9 men (12.3%), with a mean age of 54 [SD 13] years, participated in the study. The overused SM were: combination analgesics in 30 patients (41.1%), simple analgesics in 23 patients (31.5%), triptans in 12 patients (16.4%), ergotamine in 6 patients (8.2%), and opioids in 2 patients (2.7%). Migraine without aura was the commonest pre-existing headache (55 patients, 75.3%). Pain was more frequently pulsating (38 patients, 52.1%), bilateral (40 patients, 54.8%), and severe (48 patients, 65.8%). Accompanying phenomena were present in 55 patients (75.3%), the more frequent being nausea associated with phono-photophobia. The quality, site and intensity of pain, and the accompanying phenomena did not differ significantly among overusers of different SM (p=NS). Patients with pre-existing tension-type headache had more frequently pressing/tightening headache (p=0.003). Time to SM resolution of pain was superimposable for the different SM classes and it did not influence clinical characteristics of MOH.
Conclusions Clinical characteristics of MOH are more frequently migraine headache, regardless of overused SM. Our findings, therefore, indicate that different forms of MOH cannot be separated with regard to different types of overused SM. The response to overused SM did not influence the characteristics of MOH.

MEDICATION-OVERUSE HEADACHE CHARACTERISTICS AND PERSONALITY PROFILE: A CORRELATIONAL STUDY BY MMPI-2

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Introduction According to the ICHD-II classification, medication-overuse headache (MOH) refers to headache attributed to abuse of abortive medications, that may only remit when symptomatic drugs are withdrawn. On the psychological factors side, we know that psychiatric disorders are important factors for the chronification of headache. MOH patients show high levels of psychiatric disorders (just like chronic daily headache), but the likely role of personality factors needs further study to explain the shift from drug use to drug overuse. Very few studies have addressed the role of personality characteristics in MOH patients. The main aim of this study was to identify if a specific personality pattern exists in MOH patients according to MMPI-2, and if MMPI-2 sub-scales correlate with MOH characteristics.
Materials and methods The MMPI-2 was administrated to a sample of 80 in-patients (37 males, 43 females) enrolled at the Headache Unit of C. Mondino Foundation. The patients with MOH were randomly selected from a main sample of in-patients. In the first step, MMPI-2 scores >65 were considered as pathological, according to the normative sample. In the second step correlational analyses were carried out (SPSS, p<.05), to analyse likely correlations between MOH characteristics (age of headache onset, type and number/month of overused drugs, months from chronification, psychiatric comorbidity) and MMPI sub-scales.
Results Only one of the basic scales showed a mean score >65 (Hypocondrias:70.58), followed by Hysteria (60.28) and Depression (58.71) with scores in the moderate range of severity. Only Health Anxiety sub-scale showed a mean score close to the pathological range (64.48). From the correlational analyses, positive correlations were found only between Hysteria and Health Anxiety and number of drugs/month (r=0.20, r=0.26, respectively). The Admission Dependence sub-scale correlated positively with number of doses/month (r=0.26) and negatively with months of drug overuse (r=-0.23). The Potential Drug Dependence sub-scale showed a positive correlation with the months of overuse (r=0.22). Negative correlations were found between months of MOH and Antisocial Problems (r=-0.24) and Ipomania (r=-0.25).
Discussion The analysis of MMPI-2 scales showed a similar trend in other headache sub-types (literature data) with elevation in Hypocondrias, Hysteria and Depression ("neurotic triad"). Noteworthy, the sub-scales linked to the area of "dependence" related to MOH characteristics, highlighting areas which should be addressed in research and treatment planning.
Conclusions The role of behavioural factors linked to MOH needs to be studied in order to implement a complete treatment strategy for such patients.

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HEADACHE AND DEMENTIA

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Objective Data in the literature concerning the comorbidity of headaches with dementia are lacking in consistency, although the prevalence of headache in the elderly is relevant. We report the prevalence of headache in a population of elderly subjects with dementia seen at our Dementia Centre.
Materials and methods We retrospectively analysed data of 1 494 consecutive patients referred to our Centre from 2001 to 2006, focusing on headaches. This information was obtained by review of their medical records and interview of the patients' caregivers. All patients were affected by mild to moderate dementia (Alzheimer's disease, vascular dementia, mixed AD-cerebrovascular, Parkinson-dementia).
Results We identified 272 (18.20%) patients: 168 (61.76%) female, 104 (38.23%) male. Mean age was 76.35 years (range 66-83 years). Primary headaches were diagnosed in 84.55% of the cases, secondary headaches in 12.86%, and non-classifiable headaches in 2.57%. Among primary headaches, chronic tension-type headache had a prevalence of 43.04%, transformed migraine 23.47%, migraine without aura+tension type 18.69%, migraine without aura 13.47%, and migraine with aura 1.30%. Among secondary headaches, intracranial neoplasms had a prevalence of 22.85%, trigeminal neuralgia 20%, cervical spine disorders 20%, chronic post-traumatic headache 17.14%, headache ChE-I related 11.42%, and cervicogenic headache 8.57%. Age of onset occurred in the decade 51-60 for 138 (50.73%) patients; 61-70, for 92 (33.82%) patients; 71-80, for 32 (11.76%) patients; and 81-90, for 10 (3.67%) patients. The characteristics of pain and its manner of occurrence were similar to those reported in the younger population.
Discussion This study showed that headache is a common condition among elderly patients with dementia, with a higher prevalence (18.20%) with respect to epidemiological data of the population older than 65 years. The present findings underscore the importance of including questions concerning headache when taking the history of patients with dementia. Primary headaches were more frequent than secondary headaches. We found a significantly higher frequency in female patients. Regarding age of onset, headache frequency was higher in the younger decades of life. The frequency of ChE-I related headache was very low and required medication withdrawal.
Conclusions The prevalence of headache in elderly patients with dementia seems to be remarkable and noteworthy. Further clinical studies including a large number of patients are needed to examine the possible relationship between headache and dementia, to define health care planning and to implement correct preventive and treatment measures.

CLINICAL ASPECTS OF HEADACHES II

AN OBSERVATIONAL STUDY OF PATIENTS PRESENTING WITH HEADACHE TO THE EMERGENCY ROOM

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Introduction Patients presenting to the Emergency Room (ER) with a chief complaint of headache represent 2% or more of all ER visits [1]. Most commonly the headache is without serious underlying cause, but occasionally no can be related to diseases requiring prompt diagnosis and immediate treatment [2]. The objective of our study was to assess history, examination, final diagnosis and treatment of acute headaches presenting to the ER during a one-year period.
Materials and methods A retrospective study was performed in the ER of the Misericordia Hospital of Grosseto, including patients with headache who had attended the ER between 1 January and 31 December 2004. For each patient data collection was performed, recording demographic and clinical information, as well as final diagnosis at discharge.
Results Patients with headache (410) accounted for 1.25% of all patients (32 869) attending the ER of Misericordia Hospital in 2004. The median age was 45 years and the gender ratio (m/f) was 1.5/1. Computed tomography of the head was performed in 178 patients (43%). Twenty patients underwent radiography of the skull, 13 electroencephalographic examination and one patient lumbar puncture. In 95 patients, headache was treated by administering injected NSAIDs, of which the most used were ketorolac and indomethacin. At discharge 152 patients were diagnosed as having a headache, 31 as having headache associated with other symptoms and 38 as post-traumatic headache. Thirty-five (8.5%) patients were found to have a serious underlying cause of their headache, the most common being cerebral haemorrhage (4.6%). Cerebral ischaemia represented 3.4% of all cases and only 2 cases of cerebral neoplasm (0.5%) were identified. Fifty-one patients (12.5%) remained without a diagnosis. Seventy-six (18.5%) patients were admitted to Hospital, mainly in Internal Medicine and Neurology Units.
Discussion and conclusions Our study confirms the small proportion of patients with acute headache attending the ER. In fact, although a common symptom, headache rarely requires urgent attention. It must be assumed that something out of the ordinary has happened for patients to present to Hospital and so, until proven otherwise, headache must be considered a reflection of an underlying severe pathological process. In our study 8.5% of patients presenting with headache suffered from an intracranial potentially fatal condition. Therefore, the ER physician must recognize symptoms and characteristics of headache that signal a potential significant organic problem in order to improve the management of this patient group.
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MIGRAINE AND ALCOHOL: HOW MANY CONSUMERS?

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Introduction Alcohol as a factor which provokes migraine has been the subject of various studies. Nevertheless, we know very little about the consumption of alcohol in migraine sufferers. The aim of the present study is to evaluate the effects of the consumption of alcohol in an homogeneous group of migraine sufferers.
Materials and methods We included in the study 100 women, 18-54 years of age who were tested in specialist visits from 1998 to 1999, who suffered from migraine without aura (IHS classification), and resident in Tuscany. Just like in national studies conducted on the population carried out by the DOXA institute in 1997, migraine patients were sent a questionnaire requesting data on the consumption of alcohol in the three months prior to the study. The same criteria were utilized: non consumers (no alcohol consumed within the period), occasional consumers (alcohol consumed at least once in the period but less than once a week), and regular consumers (at least once a week).
Results Of the 100 migraine sufferers (mean age 34.3 years), 58 were non consumers, 38 regular consumers and 4 occasional consumers, significantly different from the female population of the DOXA 1997 study, where 30.2% were non consumers ($p<0.01$ with respect to

migraine patients), 50.8% regular consumers and 19% occasional consumers. In the age range of our study (15-54 years of age), the percentage of non consumers was even less (17%–23%). The comparison was also carried out with Tuscan women of the DOXA 2000 study which showed a prevalence of non consumers 32.3% ($p<0.01$ compared to migraine sufferers).

When asked if they noted that a specific type of alcohol (red wine, white wine, beer, spirits, etc.) which provoked migraine, the results showed that of the 100 sufferers, 6 identified white wine, 2 red wine, and 2 both red and white wine. Curiously, 8 of the women tested cited chocolate as a migraine trigger factor, 5 of whom also believed that wine was a factor.

Discussion and conclusions This study confirms my personal clinical impression that female migraine sufferers consume alcohol less frequently compared to the general population. About 10% of the sufferers believe that wine is a factor which provokes migraine. White wine seems more frequently considered a trigger in respect to red wine, as found also in a previous study in Friuli Venezia-Giulia [1].

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NEW ONSET HEADACHE IN THE ELDERLY: A DIAGNOSTIC CAVEAT

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A 68-year-old woman complained of the onset of a mild, pressing headache in the bilateral fronto-orbital region, with diffuse irradiation, lasting a few hours, without any accompanying signs or symptoms, and not aggravated by routine physical activity. She reported that her headache had a daily frequency since its onset four months before, and that it spontaneously disappeared in the last 2 weeks before our clinical evaluation. Her general and neurological examinations were unremarkable. She also reported recurrent episodes of head pain occurring as a series of stabbings in the parietal region with alternating side, lasting up to 2 seconds and without any other clinical manifestations; stabbing recurred several times in the same day, with an average frequency of 1 monthly episode. The stabbing headache began 10 years before and was unchanged.

As a consequence of the new onset headache, despite its spontaneous remission and the negative physical examination, we recommended a cerebral MRI, which revealed the presence of an extensive frontal meningioma of the falx cerebri. The spontaneous remission of the pain does not allow to establish a sure relationship between the headache and the meningioma. However, its dimension and clinical evolution (a few months later anosmia was observed), makes reasonable a causal association.

Although at initial observation the clinical presentation of this case could apparently fit the criteria for a primary tension-type headache and the temporal pattern would recall a new daily persistent headache, the onset in the elderly of a new headache has to be considered as a diagnostic caveat that should be adequately investigated.

ICHD-2R CRITERIA TESTING FOR THE DIAGNOSIS OF CHRONIC MIGRAINE AND MEDICATION-OVERUSE HEADACHE IN A HEADACHE CENTRE

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Introduction ICHD-II criteria for chronic migraine (CM) do not account for the modifications of headache characteristics due to chronicity, whereas the diagnosis of medication-overuse headache (MOH), only after discontinuation of overuse, has proven to be highly unpractical. The International Headache Classification Committee has, therefore, worked out the more inclusive criteria for CM and MOH, and these revised criteria are now presented in the Appendix to ICHD-2.

They need to be proven to be useful for testing headache patients in the clinical setting.

Patients and methods We tested 275 patients attending our headache Centre, who were affected by chronic headache evolving from a previous history of migraine without aura, which fulfilled criteria of transformed migraine with and without medication overuse (TM- and TM+), according to Lipton and Silberstein.

Two-months of patient diaries were analysed by ICHD-2 and ICHD-2R criteria using our computerized system based on the new classification criteria, with some modifications incorporating the ICHD-2 proposal [1].

Results Of the 105 patients with TM-, just 5.6% met ICHD-2 criteria for CM. According to ICHD-2R, 67.6% of TM- met criteria for CM ($p<0.005$ *vs.* ICHD-2). Using ICHD-2, only 16.4% of 170 patients with TM+ could be classified as affected by probable medication overuse + probable chronic migraine, but all received the diagnosis of MOH of ICHD-2R. Analysing the headache characteristics recorded in the two-month headache diaries with the new classification proposal, 71.1% had ≥8 days of migraine per month and could be classified as MOH and probable CM in ICHD-2R ($p<0.001$ vs ICHD-2).

Discussion As Bigal et al. suggested in a recent study [2], ICHD-2R addresses most of the criticism towards ICHD-2 and should be applied in clinical practice and research. The proportion of patients who could be classified according to ICHD-2R in our study is slightly lower than that reported by the above authors. Careful analysis of each day of patient diaries using our computerized system and differences in acute and prophylactic treatment could account for this discrepancy.

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HYPNIC HEADACHE: PROPOSED REVISION OF ICHD-II CRITERIA

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Introduction Hypnic headache (HH) is a primary headache that occurs exclusively during sleep. The natural history of HH is not well known, due to the paucity of case reports, and in particular, to the lack of adequate follow-up in several cases. Based on the observation of 23 patients, we propose a revision of the current ICHD-II criteria.

Materials and methods For the last 8 years we have evaluated 23 cases fulfilling ICHD-II criteria for HH.

Results We diagnosed 19 females and 4 males with HH. The patients' mean age at first observation was 65.1±8.5 years (range 51 to 83), whereas the mean age at onset was 62.1±9.7 years (range 45 to 82). Eleven patients (9 females and 2 males) had a chronic headache unremitting from the onset. Another patient showed an episodic pattern for 7 years, thereafter, the headache became chronic. Eight patients (6 females and 2 males) showed an episodic pattern, with active periods followed by complete remissions. In 5 cases a single bout has occurred until now, with a duration ranging from 1 to 8 months. The headaches ceased spontaneously in 2 patients, whereas in the other 3 cases they remitted after a treatment with caffeine. Another patient had two active

periods, lasting 8 and 10 months, respectively. The remaining two patients had several active periods, lasting on average 3 to 4 months, followed by remissions lasting 3 to 6 months. In both cases the headaches remitted after a prolonged treatment, with indomethacin and caffeine, respectively. Interestingly, 3 patients showed only sporadic headaches, with a frequency ranging from 1 attack per month to 1 attack every 6 months.

Discussion This case series of HH patients is the largest ever reported in the literature. Eleven of the 23 patients showed an episodic pattern, with active periods followed by complete remissions; among them, five cases had only a single bout until now, and three had sporadic infrequent attacks. Twelve patients had chronic headache.

Conclusions In view of these supportive findings, we propose that HH be divided into two subtypes, chronic and episodic [1]. We suggest that episodes of this disorder with remission periods of at least 1 month should be denoted by the term "episodic HH" and for those patients with at least a one-year history of HH and remissions lasting less than 1 month, the disorder should be called "chronic HH".

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DIAGNOSTIC DELAYS AND MISMANAGEMENT OF HEMICRANIA CONTINUA

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Aim of the study To investigate a clinical population of patients suffering from Hemicrania Continua (HC) with regard to diagnostic problems encountered, pattern of health care resources used, and problems pertaining to effectiveness of treatments.

Materials and methods We directly interviewed 19 patients fulfilling ICHD-2 diagnostic criteria for HC selected among 2105 subjects attending the Headache Clinic INI Grottaferrata over a 2-year period.

Results No patient had received the correct diagnosis before the visit to the Headache Clinic. Eighty-five percent of the patients consulted a physician within 5 months of symptom onset, but mean time to diagnosis was 5±4.7 years. The average number of physicians seen before the proper diagnosis was made was 4.4±2.2. GPs (100%), neurologists (81.2%), ENT surgeons (47.3%), ophthalmologists (42%) and dentists (31.5%) were the physicians most commonly consulted. All patients had received an incorrect diagnosis. Migraine (57.8%), CH (26.3%), sinus headache (21%) and atypical facial pain (15.7%) were the most common wrong diagnoses reported. A total of 31.5% of patients received ineffective invasive treatments. Patients tried on average 3.84±2.19 classes of drugs, of which NSAIDs (94.1%), triptans (26.3%), antidepressants (31.5%) and anitepileptics (21%) were the most commonly used. Patients rated 66.5% of medications as ineffective, 28% as partially effective (all NSAIDs), and 4.5% as effective (rofecoxib and nimesulide).

Conclusions HC is largely misdiagnosed and mistreated even by neurologists. There is need for increased awareness and education about CH.

SUNCT SYNDROME WITH PAROXYSMAL MIDRIASIS: PUPILLOMETRIC FINDINGS

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Objective SUNCT is a rare primary headache disorder characterized by short-lasting unilateral neuralgiform headache with conjunctival injection and tearing. Miosis has been described during pain but pupillometry failed to show major asymmetries. There are reports with unusual clinical features described. We report a juvenil case with unusual autonomic features: juvenile onset, mydriasis during attacks as part of autonomic phenomena. Previous reports failed to show significant anisocoria after sympathicomimetic drugs.

Methods A case of a 22-year-old female with a one-year history of SUNCT was first seen in our centre at the end of 2006. In the present work, vertical and horizontal pupillary diameters have been estimated by a 5.0 megapixel Sony digital camera. Measurements have been carried out both during the basal state and after topical, pharmacologic stimulation (by sympathicomimetic i.e., phenylephrine (1%, an agent acting directly on the postsynaptic receptors) and parasympathicomimetic agents i.e., pilocarpine (2%, parasympathetic agonist). Pupillary dilatation was measured at set time intervals, comparing the responses of the symptomatic (S) and non-symptomatic sides (NS). The anisocoria index (100*S/(S+NS)) was used for calculations.

Results In the basal state, there was no clear tendency to anisocoria. After phenyleprine, there was an overreaction on the symptomatic side with a prominent mydriasis. After pilocarpine, there was a reduction of pupil size with no significant difference between symptomatic and non-symptomatic side.

Conclusions This case emphasizes the possibility of involvement of autonomic symptoms and pain at different level and of ocular sympathetic supply in SUNCT. The supersensitivity to the directly acting sympathicomimetic agent, phenylephrine, in this case is more similar to Horner's syndrome than cluster headache.

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ACADEMIC EDUCATION IN HEADACHE MEDICINE

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The widespread perception of headache's social importance as public health problem with additional health-economic valence, has brought in the last ten years to the creation of outstanding assistance structures with a "fly wheel" function towards patients in terms of care and information.

A correct illustration on when to consult a physician or alternatively refer to an adequate diagnostic-rehabilitative structure, about the correct life-style to be held, or the exact administration of acute drugs for headache constitute part of the daily activity on health information given by such structures.

On the other hand, the exigency of a larger diffusion of field education is perceived among operators working daily outside of these "citadels". The majority of headaches can and must be identified and treated adequately in the first instance, in order not to preclude the access to these centres to chronic patients in drug overuse.

Furthermore, the binomial level of information/field education and assistance product inclines not to improve for several reasons. The fruition of a series of formidable informative/formative tools such as update through scientific journals and the Continuous Education in Medicine are facilitating the homogeneous diffusion of assistance in the headache area. However, the necessity is clear: over 60% of population is affected by primary headache. The creation of area garrisons for headache, as well as the largely diffused diabetes centres could permit the control of this widely felt social problem with acceptable standards of assistance.

Besides, the existing gap between adequate clinical management of headache and education of area experts should be considered also at a national level as a Public Health priority. The planning of *Lifting The Burden: Global Campaign against Headache* has been considered under this light and is currently in its phase of realization at international level, under the auspices of the World Health Organization (WHO).

From these considerations originates the necessity of an excellent aca-

demic education, able to convey innovations from basic research to daily clinic; "Headache Medicine" as the only multidisciplinary way to be accomplished towards the control of this invalidating pathology. *Post-lauream* education is lacking if compared with the demand of specific clinical expertise required nowadays by medical profession. It is necessary that academic structures producing headache research transfer their know-how into training activities, able to diffuse headache education through academic tools, independent and of high scientific profile with constantly updated programmes.
Post-lauream academic courses dedicated to headache, Masters of II level, are already active for the past several years and constitute an integrating part of the Global Campaign against Headache. The propagation of such academic activities is desirable in order to fill the existing gap between high qualification of clinic research and both the correct and wide management of headache.

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CLINICAL ASPECTS OF HEADACHES III

HEADACHES IN PROFESSIONAL SOCCER PLAYERS OF ITALIAN "SERIES A"

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The prevalence of primary headaches in Italian professional athletes was never previously assessed.
We performed a study which allowed to identify retrospectively the most common form of primary headaches (migraine with and without aura, tension-type headache, cluster headache) according to the International Classification of Headache disorders – II edition (ICHD-II). An anonymous questionnaire was submitted during the summer athletic preparation (time 0, baseline) and then during the championship season at day 1, 8, 16, 24, 32 (respectively, time 1, 2, 3, 4, 5) in a sample of professional soccer players of Italian "Series A"; whenever appropriate, the team physician completed the information with a direct interview and a general and neurologic examination. Four Societies of Italian "Series A" were involved (n=83); four players changed soccer team during the season and so did not complete the study, but they denied headache. In the total sample, we found three cases with a headache history (3.6%), all of them with features fulfilling ICHD-II criteria for episodic tension-type headache (ETTH). No new cases of headache were recorded during the study period. In conclusion, our study demonstrates a very low prevalence rate of primary headache, represented by ETTH, in a population of professional soccer players in comparison to the general population. A possible explanation could be that migraineurs or persons suffering from other forms of recurrent headaches are not able to follow this professional career.

HEADACHE AND SLEEP

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Background The clinically and nosologically complex relationship between sleep and headache have long been recognized, yet the exact nature of the association remains elusive. Since the 19th century it has been known that sleep disturbances might be associated with headache in general and with migraine in particular.
To date, no epidemiological studies have examined the comorbidity of headache (by specific IHS diagnoses) and the complete spectrum of sleep disorders in the general population, but several studies have examined one or more aspects of the headache-sleep comorbidity.
Sleep disorders are disproportionately observed in specific and non specific headache patterns. The sleep disorders associated with headache are of varied types.
Objective In order to further explore this association, sleep disturbances were evaluated in a group of headache sufferers
Methods A group of 333 patients (245 women and 88 men; age range 18-65 years, mean age 38.95 years, ±SD 11.88), referring for the first time to the Turin University Headache Centre in the period 01.01.06-31.12.06, suffering from primary headaches, according to ICHD-II criteria, were studied. The presence of anxiety and/or depression was also evaluated by means of STAI X1-X2 and BDI in patients suffering from migraine.
Results One hundred and twelve patients (78 women and 34 men) said they had some sleep disturbances, while 221 (168 women and 54 men, mean age 38.86 years (±SD 11.85)) said they had none.
In the group of 71 female patients suffering from sleep disturbances, 21 (30%) presented anxiety, 1 (1%) depression, and 25 (35%) both.
In the group of 28 male patients suffering from sleep disturbances, 1 (4%) presented anxiety, no one (0%) depression, and 3 (10%) both.
In the group of 142 females without sleep disturbances 29 (20.5%) presented anxiety, 4 (3%) only depression, 29 (20.5%) both.
In the group of 42 men, 4 (9%) presented anxiety, 3 (7%)depression, and 6 (14%) both.
Conclusions In accordance with earlier research and anecdotal observations, this data support a substantial migraine/sleep relationship and implicate sleep disturbance in headache patterns and severity.
The association between sleep and headache may be different in nature, but the disregulation of sleep processes apparently impacting headache threshold is common to all.
Moreover, our data suggest that, in migraine patients with sleep disturbances, anxiety is more frequent, while in those without sleep disturbances there is more often an association with depression. More studies will provide a better understanding of these results.

ROLE OF ULTRASOUND TOOLS FOR CLINICAL CHARACTERIZATION OF PATIENTS WITH RIGHT-TO-LEFT SHUNT AND CEREBRAL ISCHAEMIC EVENTS AND/OR MIGRAINE

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The role of patent foramen ovale (PFO) and right-to-left shunt (RLS), in the genesis of stroke, particularly in the young, has been established. Conversely, there is uncertainty on the opportunity to adopt active therapeutic interventions, such as PFO closure, surgical or endovascular, depending on the pathology: TIA, stroke or migraine with aura.
Concerning migraine, a recent meta-analysis showed that average risk of stroke for migraineurs was 2.16% higher than in people without migraine, and 2.27% when considering merely migraine with aura. Oral contraceptives increased eight-fold the risk of stroke. The average stroke prevalence in women in the general population is 9 per 100 000, 20 per 100 000 considering women with migraine, and 75 per 100 000 with regard to women taking oral contraceptives [1].
Therapeutic conduct still relies on good clinical practice judgement because of the lack of evidence-based guide lines and since uncertainties on the precise pathophysiological mechanisms leading to stroke exist, it is conceivable that an accurate definition of the clinical profile is a prerequisite for subsequent therapeutic choices. It is also relevant,

that for patients to make a decision, that both informed consent and decisions concerning non negotiable limitations to changes in one's life style be clearly explained.
The current gold standard for the diagnosis of PFO is contrast-enhanced transesophageal echocardiography (c-TEE) which is an invasive examination, rarely accepted by patients. c-TEE cannot be considered a screening test. Literature evidence indicate contrast-enhanced transcranial Doppler (c-TCD) and contrast-enhanced transcranial color-coded duplex sonography (c-TCCD or c-TCCS) as clinically useful alternative examinations [2]. Ultrasound tools showed sensibility and specificity levels similar to c-TEE, but possess at least 3 advantages: 1) not invasive; 2) possibility of qualitative estimate of RLS provocative manoeuvres; 3) flexibility and adaptability to different equipments. Such instruments are therefore the ideal ones for extensive clinical use and may provide useful functional information. It is conceivable that c-TCD or c-TCCD/c-TCCS might have a significant role as the initial screening test to give information that more accurately correlates with the risk of ischaemic events.

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WHITE MATTER LESIONS AND CEREBROVASCULAR REACTIVITY IN MIGRAINE PATIENTS WITH PATENT FORAMEN OVALE: A TRANSCRANIAL DOPPLER STUDY

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Objective Patent foramen ovale (PFO) with right-to-left shunt is a well established risk factor for ischaemic stroke in young patients, while its role as an independent factor in migraine is still debated [1]. Since the prevalence of PFO in migraine with aura (MA) is higher than in migraine without aura (MO), such an association seems to be unrelated to both migraine clinical phenotype and paradoxical embolism. The aim of this study was to evaluate the impact of cerebrovascular reactivity (CVR) in the presence of white matter lesions (WMLs) in migraine patients with patent foramen ovale (PFO).
Methods Basal mean flow velocity (MFV) and breath-holding index (BHI) were measured in both middle cerebral arteries (MCAs) and basilar artery (BA) of 20 outpatients with migraine and PFO association (Group A), 20 outpatients with migraine and no evidence of PFO (Group B) and 20 healthy controls (Group C). Subtypes of migraine were classified according to ICHD-II. PFO was assessed by TCD as previously reported. WMLs were evaluated with DWI/FLAIR sequences with MRI.
Results MA (80%; $p<0.0001$) and WMLs (60%; $p<0.001$) were more prevalent in Group A than in Group B and C. In Group A, the association between MA and WMLs in both circulations was statistically significant (χ_2 test=32, df. 12, $p<0.001$), independent of clinical features of headache. In Group B, the presence of WMLs was significantly associated to duration of disease and number of attacks (χ_2 test=30, df. 14, $p<0.001$), independent of migraine subtype. BHI was significantly lower in both MCAs and in BAS of Group A (0.78±0.12 and 0.72±0.2) than in Group B (1.16±0.1; 1.14±0.18) and controls (1.68±0.18; 1.53±0.2), (A *vs.* B: F = 4.91; $p<0.001$. A *vs.* C: F = 5.29, $p<0.0001$). Post-hoc analysis showed that BHI in both BA and MCAs of patients with MA, PFO and WMLs were significantly lower ($p<0.0001$) with respect to all vessels in the other subgroups.
Discussion These findings suggest a relationship between an impairment of CVR in both anterior and posterior circulation and the association of migraine and PFO, particularly in patients with MWA and WMLs. The reduced adaptation of intracranial microvessels in MWA could influence the susceptibility to ischaemic stroke and may be directly related to PFO, independent of repeated and/or prolonged microvascular events during attacks [2].

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3D KINEMATIC ANALYSIS OF NECK MOVEMENTS IN HEALTHY SUBJECTS: RELIABILITY OF THE PROCEDURE

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The purpose of this study was to assess the reliability of a 3D kinematic method of evaluating movements of the cervical spine. A multifactorial analysis of neck ROM using six passive markers, 6 CCD cameras, which allow the real time recognition of passive markers, 3D co-ordinates reconstruction with velocity and acceleration computing, has been used (Elite system- BTS – Milan). A previous device with two 2 CCD cameras was used but the software for the reconstuction required a rather time consuming procedure. The kinematic model designed required the reconstruction of 6 anatomical points, 3 of them describing the head and the other 3 describing the trunk. The selected points were as follows: for the head, nasion and right and left tragus bilaterally; for the trunk, the seventh cervical vertebra (C7) and the right (RS) and left shoulders (LS). The evaluation was carried out after 5 active consecutive movements at usual velocity as follow: flexion-extension, axial rotation and lateral bending. The highest and lowest score were discarded and the mean value of three movements was considered as real value. Range of motion (ROM) of the cervical spine was evaluated in 10 control subjects during flexion-extension, rotation and lateral bending movements. The test was repeated on two separate occasions.
Results The ROM test-retest difference expressed in degree was low for each of the movements evaluated. The test showed good reliability, with an intra-class correlation coefficient which was higher than 0.75 in extension movement and excellent in flexion, axial rotation and lateral bending.
Conclusions The method proposed for the 3D kinematic analysis of neck movement proved to be useful and non-invasive and showed good-excellent reproducibility. Furthermore, the method is easily applicable in clinical practice to evaluate neck function in cervical spine disorders.
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WORK ENVIRONMENT-RELATED DISORDERS IN HEADACHE SUFFERERS

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Primary headaches are a public health problem with their socio-economic burden depending on the reduced effectiveness at work or on the repeated absences of patients during the headache attacks. However, even the work environment may represent in headache sufferers a risk factor for the onset of attacks.
Sick building syndrome (SBS) is a work-related condition characterised by irritation of eyes and nose, drowsiness, fatigue, inability to concentrate, dizziness, widespread musculoskeletal complaints and recurrent headaches. The prevalence of SBS is commonly used as an indicator evaluating and/or

reflecting air quality, noise, luminosity, and the ergonomic design of a workplace. Air pollution due to inadequate mechanical ventilation, including air conditioning and humidification systems, promotes the development of frequent head pain in workers who are headache sufferers. Also, a non-ergonomic workstation may cause general malaise, neck postural pain and tension-type headache. Besides, a long-term visual display use without proper breaks or appropriate computer screen may commonly induce headache. The changing in sleep pattern depending on the recurrent succession of day and night shifts frequently causes headache in migraineurs. Therefore, headache may depend on the use or on the exposure to toxic substances utilized in work procedures. Contact with or inhalation of some inorganic and organic compounds employed in several heavy industries determines a mild headache associated with neurological and gastroenteric symptoms, more frequent with carbon monoxide intoxication.
Burnout syndrome is the consequence of a psychological work distress such as mobbing, difficult labor-management relations and work dissatisfaction, causing recurrent headaches. Mobbing, also defined as psychological harassment at the workplace, is defined as a situation in which a single person or a group of people engage in extreme psychological violence against another person. Headache is a frequent symptom in victims of mobbing associated with depression, anxiety, insomnia, gastritis, hypertension, colitis, and tachycardia. The association between work stress and headache frequency may be proportionally related. Building renovation and indoor environment recovery may reduce headache-related work loss due to absenteeism and to decreased productivity of the employees. Therefore, improved working conditions promoting job satisfaction and installation of well-designed workstations may reduce headache attacks and thus their indirect costs.

PATHOGENIC AND GENETIC ASPECTS IN HEADACHES

THE ROLE OF BRAIN CYCLOOXYGENASE-2 AND PROSTAGLANDIN-E2 IN MIGRAINE: FINDINGS IN AN ANIMAL MODEL OF MIGRAINE

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The animal model of migraine based on the systemic administration of nitroglycerin (NTG), a NO donor, has provided interesting insights into the pathogenetic mechanisms of migraine. Cyclooxygenase-2 (COX-2) increases prostaglandin-E_2 (PGE_2) production in the central nervous system and contributes to the severity of pain responses in inflammatory pain. PGE_2 synthesized in the brain is probably involved in modulating trigeminal nociception. In this study we evaluated the expression of COX-2 and PGE_2 levels within neuronal areas relevant for migraine genesis after administration of NTG. Male Sprague-Dawley rats were injected with NTG (10 mg/kg, i.p.) or vehicle and sacrificed 2 and 4 hours later. The hypothalamus and the lower brainstem were dissected out and utilized for the evaluation of COX-2 expression (western blotting) and for the determination of PGE_2 levels (ELISA immunoassay). COX-2 expression increased in the hypothalamus at 2 hours and in the lower brainstem at 4 hours. PGE_2 levels showed a differentiated pattern of change with a decrease at 2 hours in the hypothalamus and an increase at 4 hours in the lower brainstem. These results show for the first time that NTG is capable of interfering with the COX-2 pathway *in vivo* within specific cerebral areas.

MIGRAINE WITHOUT AURA AND CYTOKINES: AN ASSOCIATION STUDY WITH CANDIDATE GENES IN A SARDINIAN SAMPLE

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Introduction Migraine is a complex genetic disease, in which susceptibility genes and environmental factors contribute to development of this illness.
The pathophysiology of migraine is still unknown but the "sterile inflammation" or "neurogenic inflammation" seems to play a key role.
Tumour Necrosis Factors (TNF) (TNF-α and TNF-β) are cytokines implicated in inflammatory reactions and endothelial function. Several studies suggest that TNF may be involved in migraine. TNF-α and TNF-β genes are located on chromosome 6p21.3 in the human leukocyte antigen (HLA) region. TNF polymorphisms are located in a region characterised by wide polymorphic variation and are in linkage disequilibrium both with the HLA genes and with each other. The Sardinian population is a genetic isolate. Genetic studies suggest that genetic isolates play an important role in identifying candidate genes predisposing to complex disorders. To assess the possibility of an association between TNF gene polymorphisms and migraine disease, a case-control study was performed in a Sardinian sample.
Methods We evaluated 299 patients affected by migraine without aura (ICHD criteria, 2004) and 278 migraine-free controls. The controls were blood donors with no clinical history of headache disorders.
The polymorphisms G308A in the promoter region of the TNF-α gene, and G252A in the first intron of the TNF-β polymorphisms were determined by NcoI restriction fragment length polymorphism analysis.
Results At the polymorphic loci considered, the genotypic counts were in Hardy-Weinberg equilibrium in both controls and patients.
We found a statistically significant difference in allele (p=0.018; OR = 1.46, 95% CI: 1.066 to 2.023) and genotype (Trend χ^2 = 5.46, df = 1 p=0.019) frequencies of TNF-β, between cases and controls. Allele and genotype frequencies of TNF-α G308A polymorphism did not differ significantly between the two groups.
Discussion Our study demonstrates that the G252A TNF-β gene polymorphism is associated with migraine without aura. Our data are in discordance with the findings of an association study showing an increased risk of migraine without aura associated with homozygosity for the TNF-308G allele of the TNF-α gene [1]. The results of our study are similar to data reported in the first published work on Tumour Necrosis Factor gene polymorphism in migraine [2].
Conclusions These data suggest that subjects with the TNF-β2 allele have a low risk of developing migraine without aura and that the polymorphism of the TNF-β gene is in linkage disequilibrium with other genes responsible for migraine in the HLA region.
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RELATION BETWEEN NOCICEPTIN AND NOCISTATIN IN THE CEREBROSPINAL FLUID OF CHRONIC MIGRAINE AND MEDICATION-OVERUSE HEADACHE PATIENTS

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Introduction Nociceptin/orphanin FQ (NCP) and nocistatin (NST) are two important bio-peptides derived from the precursor protein prepronociceptin (ppNCP), involved in several central nervous system

functions including pain transmission.
Nociceptin is the endogenous ligand of the G-coupled Nociceptin/Orphanin FQ peptide (NOP) receptor. An increased expression of both nociceptin and the ORL-1 receptors has been demonstrated in experimental pain models, indicating their involvement in the mechanisms of pathological pain [1]. Nocistatin does not bind to the NOP receptor but it antagonizes the allodynic and hyperalgesic effect of intrathecal levels of NCP. Due to the relationship of the two neuropeptides to mechanisms involved in pain transmission and modulation, a modification of their levels in the cerebrospinal fluid (CSF) can be hypothesized in patients with chronic migraine (CM) and medication-overuse headache (MOH).
Methods NCP and NST levels were determined in the CSF of 20 CM patients and 20 patients with MOH. Control values for NCP and NST were obtained from the CSF of 20 subjects, for whom laboratory and instrumental investigations excluded diseases of the central and peripheral nervous systems.
NST and NCP were isolated from CSF samples by affinity chromatography combined with HPLC. Mass spectrometry was used for the identification and characterization of the peptides [2], and RIA was also used for determination of the two peptides.
Results NCP and NST levels were detected in all patients and in 80% of control subjects. NCP levels were significantly higher in the CSF of patients with CM and MOH (59.82±11.22 and 63.4±13.16 fmol/mL, respectively) compared with controls (12.06±3.19) ($p<0.003$, $p<0.001$) without significant differences between patient groups.
NST levels were also significantly higher in the CSF of both CM and MOH patient groups than in control subjects (88±14.23 and 74.4±12.34, respectively vs 23.±13.58 fmol/mL) ($p<0.01$). In addition, a weak correlation was found between CSF levels of NST in both patient groups (CM: R=0.32, $p<0.05$ and MOH: R=0.39, $p<0.04$).
Discussion A pronociceptive action of NCP can be hypothesized in both CM and MOH, which does not seem influenced by analgesic abuse, but may be related to chronic pain per se [1].
The increase of NST relative to that of nociceptin could be interpreted as a compensatory mechanism aimed at antagonizing the hyperalgesic and allodynic effects of nociceptin in both disorders [2]. Its antinociceptive effect, however, is not enough to reverse the biochemical events underlying central sensitization and pain maintenance in these two chronic, head pain conditions.
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FOLATE, VITAMIN B12 AND SERUM HOMOCYSTEINE LEVELS IN PATIENTS WITH CHRONIC MIGRAINE AND MEDICATION-OVERUSE HEADACHE

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Folate and vitamin B_{12} deficiency have been associated with neurological and neuropsyhiatric disorders. Moreover, the coenzymes formed from folic acid are instrumental in the conversion of homocysteine to methionine and this reaction requires vitamin B_{12} as a cofactor. Hyperhomocysteinemia is an independent risk factor for vascular diseases, such as heart disease and stroke.
Objective To examine folate, vitamin B_{12} and serum homocysteine levels in patients with chronic migraine and medication-overuse headache, compared to migraine patients.
Methods We analysed serum vitamins levels in 170 patients with chronic migraine and medication-overuse headache (MOH) (mean age 54 years) and in 50 patients suffering from migraine without aura (mean age 43 years). Homocysteine serum levels were available only for 118 MOH patients (mean age 52 years). Diagnosis were made according to ICHD-II criteria. All patients have been referred to the Headache Centre of Modena University Hospital. Venous blood samples were drawn in the morning, after an overnight fast. Serum vitamins and homocysteine levels were measured by immunometric techniques (folate: ion capture immuno assay, ICIA; vitamin B_{12}: microparticles enzyme immuno assay, MEIA; homocysteine: fluorescence polarized immuno assay) at our laboratory.
Results Folate levels below the reference range (4-20 ng/mL) were found significantly more frequently in MOH patients (27%) than in migraine patients (12%) ($p<0.05$, Chi-square test). A similar proportion of patients of the two groups had vitamin B_{12} lower than the references values (200-900 pg/mL). Homocysteinemia higher than the reference range (<20 umol/L for subjects over 60 years of age; <13 umol/L for subjects below 60 years of age) was found significantly more frequently in MOH patients (15%) than in migraine patients (2%) ($p<0.05$, Chi-square test).
Conclusions The low folate and high homocysteine levels that we detected in many MOH patients could contribute to the numerous medical and psychiatric comorbidities which have been reported in patients suffering from this disorder. Our results suggest that the assessment of folate, and homocysteine levels should be considered in MOH patients since folate supplement could help to improve their complex condition.

MIGRAINE MEDIATES THE INFLUENCE OF C677T MTHFR GENOTYPES ON ISCHAEMIC STROKE RISK WITH A STROKE-SUBTYPE EFFECT

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Objective To investigate the role of C677T MTHFR polymorphism in migraine pathogenesis and in the migraine-ischaemic stroke pathway.
Methods and results A first genotype-migraine association study was conducted on 100 patients with migraine with aura (MA), 106 with migraine without aura (MO), and 105 subjects without migraine, which provided evidence in favour of association of the TT677 MTHFR genotype with increased risk of MA compared to both control subjects (odds ratio [OR], 2.48; 95% CI, 1.11 to 5.58) and patients with MO (OR, 2.21; 95% CI, 1.01 to 4.82). Based on these findings, mediational models of the genotype-migraine-stroke pathway were fitted on a group of 106 patients with spontaneous cervical artery dissection (sCAD), 227 young patients whose ischaemic stroke was unrelated to a sCAD (non-CAD), and 187 control subjects, and a genotype-migraine partial mediation model was selected. Both migraine and the TT-genotype were more strongly associated with the subgroup of patients with sCAD (OR, 4.06; 95% CI, 1.63 to 10.02 for MA; OR, 5.45; 95% CI, 3.03 to 9.79 for MO; OR, 2.87; 95% CI, 1.45 to 5.68 for TT genotype) than to the subgroup of patients with non-CAD ischaemic stroke (OR, 2.22; 95% CI, 1.00 to 4.96 for MA; OR, 1.81; 95% CI, 1.02 to 3.22 for TT genotype) as compared to controls.
Conclusions Migraine may act as mediator in the MTHFR-ischaemic stroke pathway with a more prominent effect in the subgroup of patients with sCAD.

CORRELATION BETWEEN MIGRAINE, HOMOCYSTEINE AND POLYMORPHISMS OF THE MTHFR GENE: PRELIMINARY RESULTS

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Introduction Recently, some studies have suggested that some polymorphisms (C677T and A1298C) of the gene that codifies for MTHFR enzyme, are prevalent in migraine with or without aura. In literature there are few and contradictory studies relative to the determination of plasmatic levels of homocysteine in migraneurs [1, 2].
Since studies continue to demonstrate the pathogenetic hypothesis, i.e., that there is a point of contact between the pathophysiology of vascular cerebral disease and migraine attack, we deemed it useful to inquire into the possible correlation between these factors.
Materials and methods The intent of our study was to determine the plasmatic levels of homocysteine, before and after methionine loading, plasma levels of folic acid, vitamin B_{12} and the polymorphisms (C677T and A1298C) of the MTHFR gene, in subjects suffering from migraine with or without aura.
For this study, 54 patients referring to the Headache Centre of the Policlinic in Catania, affected by migraine without or with aura, diagnosed according to ICHD-II criteria, between the age of 20 and 52 years (mean age: 36 years), both males and females, prevailingly females were divided into two groups: Group A and Group B.
They underwent blood tests for basal dosages of homocysteine, vitamin B_{12}, folic acid, and also genetic determination of the polymorphisms C677T and A1298C of the MTHFR gene. They were then given methionine dissolved in orange juice (0.1 g/kg body weight) and underwent blood tests at two, four and six hours. Oversmokers, cardiopatic patients, patients with chronic renal insufficiency, hypothyroidism, neoplastic disease, and women in treatment with CO were excluded from the study.
Results The study showed that in the migraine group, the plasmatic levels of basal homocysteine were not sufficiently increased. Examining the plasmatic values of homocysteine (deltathcy) after methionine loading at 2, 4 and 6 hours, we observed that 33% of the subjects were intolerant to methionine, of these subjects, 30.43% of the patients were affected by migraine without aura and 50% with migraine with aura. With reference to genetic type, the study highlighted C677T and A1298C mutation (homozygous or heterozygous) in 96.2% of the total of subjects. In particular, we found a greater presentation of C677T mutation consisting in 71.72% in total.
The results presented are preliminary because the study is still in progress and it intends to compare the results obtained to a third group of subjects, our control group.

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HEADACHES IN CHILDHOOD AND ADOLESCENCE I

FAMILIAL RECURRENCE AND CHARACTERISTICS OF HEADACHE: A STUDY ON 200 CHILDREN AND ADOLESCENTS

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Background The interplay of genetic and environmental factors has been evidenced in migraine where nature and nurture may establish different phenotypic manifestations.
Objective Analysing if headache clinical characteristics change according to headache familial loading (absence or double if at least one parent and one of the grandparents had headache).
Materials and methods Two-hundred children (92 males, 108 females; mean age 10.99 years; range 4.6–17.9 years) and their parents were enrolled in our Headache Centre. A semi-structured interview was administrated to record headache history according to ICHD-II criteria (2004). Data were also collected on the occurrence of headache in first and second-degree relatives.
Results Two subgroups of children were selected: "double familiarity group" (n=97) (74 migraineurs and 23 other headaches (oHs) children), with headache both in first and second-degree relatives, and a "no familiarity group" (n=19) with absence of headache in relatives (11 migraineurs and 8 oHs children). Three different Loglinear analyses were performed, containing the two variables "familiarity" (double/absent) and "headache subtypes" in children (migraine/oHs), in order to verify associations with the following factors in children: intensity and drug efficacy; photophobia; vomiting, and presence/absence pre/perinatal complications. The model selected in the first analysis [LR Chi-square=16.87; d.f.=16; p=0.39] included the following significant effects: main effect of intensity: "headache subtypes for familiarity" interaction, given by 87.06% of double familiarity prevalence in migraine group vs 74.19% in the oHs one; "headache subtypes for drug efficacy" interaction, showing drug efficacy for 55.29% of migraineurs and 35.48% of oHs children. The model selected in the second analysis [LR Chi-square=8.81; d.f.=8; p=0.36] included the "headache subtypes for familiarity for photophobia" interaction, showing the highest incidence of photophobia in migraineurs children with double familiarity (74.32%) and the lowest one in oHs children with no familiarity (12.50%). The model selected in third analysis [LR Chi-square=12.07; d.f.=8; p=0.15] included the following interactions: "familiarity for vomiting", given by a higher incidence of vomiting in the double familiarity group (38.14%) compared to the non familiarity one (26.32%); "familiarity for pre/perinatal complications" showing a high incidence of complications in double familiarity group (54.64%) than in non familiarity children (42.11%). An ANOVA performed on familiarity, headache subtypes and age of headache onset produced no significant results.
Conclusions In the migraine group, double familiarity was more frequent and was associated to a higher prevalence of photophobia. Double familiarity also increased the probability of vomiting and was associated more often to pre/perinatal complications for both migraine and oHs children. However, further studies need to verify our findings because of the small number of sub-samples.

EPIDEMIOLOGY OF HEADACHE IN A PRE-ADOLESCENT POPULATION IN ALBA

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Information on the epidemiology of headache in children in the pre-adolescent age are scanty and prevalence varies from 4% to 45% depending on different studies [1, 2].
Objective We studied a representative population of children aged 3 to 11 years, attending one of three scholar circles in Alba, to evaluate the prevalence of headache in pre-adolescent age.
Methods A questionnaire was delivered to all the children's families attending the 3rd Scholar Circle in Alba.
The questionnaire was anonymous, and required the following information: sex, age, if the child suffered from some illness, headache, non

motivated abdominal pain, or cyclical vomiting or paroxysmal vertigo; information on therapeutic habits, both referring to drugs and non pharmacological practices; and finally, information on the history of familial diseases, known to be co-morbid with headache, that is headache, hypertension, diabetes, thyroid disorders, vascular diseases of heart and brain and venous thrombosis.

Results The questionnaire was given to 960 children, 663 children in elementary school, 489 in pre-school. They are 498 males (335 elementary school, 163 pre-school) and 491 females (328 elementary school, 326 pre-school). Six hundred and forty-seven families returned the questionnaire, 499 (74%) from elementary school and 141 (29%) from pre-school. Considering the difference between the two percentages, we analysed our data for each type of school. Sex is missing in 8 questionnaires and age in 7.

Elementary school Among 499 children (254 males, 240 females) who returned the questionaire, 150 (72 M, 78 F) suffered from headache (72 M, 78 F), 112 (42 M, 70 F) from abdominal pain, 16 (10 M, 6 F) from cyclical vomiting and, 9 (5 M, 4 F) from paroxysmal vertigo. Familiarity for headache was higher in children with headache (81%) compared to non-headache (50%), the percentage of the other illnesses questioned did not differ between the two groups, headache (H) and non-headache (NH) children (diabetes: H 46%, NH 35%; thyroid disorders: H 33%, NH 30%; hypertension: H 69%, NH 56%; myocardial infarction: H 37%, NH 26%; stroke: H 27%, NH 19%; venous thrombosis: H 11%, NH 7%).

Pre-school Percentage of questionnaires returned by pre-school children was lower (29%). In 141 (68 M, 71 F) children, 14 (7 M, 7 F) referred headache, 22 (10 M, 12 F) abdominal pain, 2 (M) vomiting, and 2 (M) vertigo. Distribution of familial diseases is similar to that of scholar children, i.e., headache: H 86%, NH 52%; diabetes: H 57%, NH 37%; thyroid disorders: H 64%, NH 29%; hypertension: H 86 %, NH 61%; myocardial infarction: H 36%, NH 27%; stroke: H 29%, NH 16%.

Conclusions We can estimate that overall headache prevalence among children in pre-adolescent age is 17%. Our data is reliable for scholar children in pre-adolescent age considering the high percentage of questionnaires we could examine, and showed a prevalence of 23%. Referring to pre-scholar children, our prevalence is 3%, but data must be confirmed since only 29% of families returned the questionnaire. We can however hypothesis that families who did not reply had healthy children and that the real data does not differ very much from ours.

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OSMOPHOBIA IN JUVENILE PRIMARY HEADACHES: A MULTICENTRIC STUDY

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Introduction The differential diagnosis between migraine and tension-type headache (TTH) is based on ICHD-II (2004) criteria that lists nausea, vomiting, photophobia and phonophobia as significantly associated symptoms. Osmophobia (OSM), which is altered odour perception, is reported in point D of the Appendix of this classification as possible accompanying symptom of migraine without aura (MO). Recently, this symptom has been found to be very specific but not very sensitive for the diagnosis of adult migraine [1].

Materials and methods We examined 753 patients presenting at 7 Italian Juvenile Headache Centres from 2005 to 2007 by means of a semi-structured questionnaire. The age range was 4-17 years, (mean 11.4±2.7 SD), with 345 males and 408 females affected by migraine (503) or TTH (250).

Results The prevalence of OSM during attacks in patients with primary headache was 26.7%, mainly in migraine patients (34.2%) compared with TTH patients (11.6%), without correlation to age or gender. However, in patients with TTH, the subgroup with OSM presented a greater family history for migraine *vs.* those without OSM (69.0% *vs.* 58.4%). OSM showed more specificity (88.4%) than phonophobia (55.6%) or photophobia (66.4%) in the differential diagnosis of migraine and TTH.

Discussion and conclusions In this group of primary headache sufferers, the prevalence of OSM during migraine attacks was similar to the adult data reported in the literature (24.7%–47.7%) [2, 3]. OSM was observed less frequently in TTH juvenile patients, while the prevalence of OSM for adults with TTH is still controversial. However, it is possible that the report of OSM in a subgroup of our patients with TTH represents a prognostic factor for an increased tendency to develop migrainous headache.

This study demonstrates that OSM represents a poorly sensitive (34.2%) yet specific symptom (88.4%) for the diagnosis of migraine. We emphasize that OSM could become a supportive diagnostic criterion for the differential diagnosis between MO and ETTH, even in children.

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ACUTE CONFUSIONAL MIGRAINE AND CONTRIBUTION OF SPECT TO DIAGNOSIS IN PAEDIATRIC AGE

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Introduction Acute confusional migraine (ACM) is a migraine variant that is characterized by confusion, with a variable degree of retrograde amnesia and mild agitation [1]. The confusional attacks may be accompanied by intermittent somnolence, irritability, visual and auditory disturbances, word-finding difficulties and focal neurologic deficits. The confusional period lasts for a few hours and is preceded or followed by a migraine attack. ACM could be caused by transient hypoperfusion affecting the dominant–sided posterior cerebral artery territory [2].

Materials and methods We report six children with ACM, who were brought to our attention between 2000-2007. Relevant anamnestic and clinical data were abstracted. Patients were investigated by laboratory screening, EEG, NMR and perfusional SPECT with Tc99m-ECD. EEG and, in three cases, SPECT were reperformed within two weeks of attack onset.

Results Four males and two females between 11 to 13 years of age were recruited. Four of six patients had a family history of migraine, all on the maternal side. Four patients manifested aura in association with headache and confusion. All these patients manifested visual disturbances; in three cases it was associated with motor or sensory deficits.

All patients presented autonomic symptoms. Headache was reported and dysphasia was recognized in all patients. Headache started before confusion in five cases. Confusion resolved within 24 hours; headache within three days. Amnesia of the event was present in all cases.
NMR was performed in four patients and was normal. SPECT was performed in three patients, during the attack. It showed hypoperfusion of the left temporal and occipital regions in one case, and diffuse hypoperfusion of the left hemisphere in two cases. EEG during the attack was performed in six patients showing slow electrical activity in the same regions hypoperfused by SPECT. The slowing interested the left hemisphere in all cases, but in one case it was bilateral. Within two weeks SPECT and EEG were reperformed, respectively, in three and in all cases. While reperformed SPECT was normal in all cases, EEG improved, but occipital slow waves continued in three cases.
Conclusions ACM is a migraine variant involving medial temporal structures and other cortical regions. Attack onset is often like migraine with aura followed by confusion and other cortical function impairment; confusion is seldom observed at onset. While laboratory screening, EEG and NMR can exclude, respectively, substance intoxication, metabolic disorders, epileptic seizures, structural lesions and encephalitis, SPECT is the appropriate examination to diagnose ACM, crucial for the individuation of vascular phenomena as the cause of the acute disorder. In all cases involvement of the left hemisphere was demonstrated. In three cases it was demonstrated by SPECT and EEG, in three other cases only by EEG.
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NEW DAILY PERSISTENT HEADACHE AND VIRAL INFECTIONS IN CHILDREN

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Introduction New daily persistent headache (NDPH) is a primary headache recently described and identified by ICHD-II 2004 as a separate entity from chronic tension-type headache. This headache was called De novo chronic headache or chronic headache with acute onset. This is a daily and unremitting headache soon after onset.
Incidence of chronic headaches ranges from 1.7% to 35% (Bigal, 2002). NDPH is a type of headache more frequent in children than adults. Various comorbidities were found as precipitating factors: psychiatric comorbidities (stress, ADHD, cognitive and behavioural problems), somatic comorbidities (allergies, thyroid diseases). Viral infections are among the various organic causes of this headache.
The aim of this study was to verify the role of viral infections on the history of NPDH in children. The viruses more frequently implicated are: Herpes virus (HV), Epstein Barr virus (EBV), Cytomegalovirus (CMV), Varicella-Zoster virus (VZV) (Vanast, 1987).
Materials and methods Among 150 patients admitted to the Paediatric Clinic of the University of L'Aquila, 25 children, 16 females and 9 males (range 5.05 to 14.09 years), suffering from chronic daily headache (CDH) (ICHD-II, 2004) were selected.
We determined: Ab anti CMV, EBV, HV1 (immunoenzymatic method), Neurophysiopathological tests (VEP- pattern reversal-, SEP of trigeminal nerve, Blink reflex).
Results Children suffering from CDH were 13% of the patients observed during one year. Forty percent of children suffered from NDPH. In 42% of children viral infections were the precipitating cause of headache (persistent fever and laboratory tests: IgM CMV, EBV and varicella). VEP showed the latency of the P100 wave higher and the amplitude reduced with respect to the average of controls. (Headache, 2001). The SEP values showed P19 wave amplitude reduced on the same side of pain in 66% of children. The latency of the Blink reflex R2c on the opposite side of pain was raised. Follow-up after 1 year confirmed that headache disappeared in 40% of children. Headache remained persistently chronic and daily in only 15% of patients.
Conclusions Viral illness is a precipitating cause of NDPH in 30% of children. Headache remission is greater than its persistence (40% *vs.* 20%). The behaviour of VEP, SEP and the Blink reflex underscore the fact that headache in this study sample was more secondary than primary-type headache. The hypothetical pathogenesis could be one of the following: failure of cellular function of neurons and lymphocytes, lymphokine release and autoimmune mechanisms.

BEHAVIOURAL AND EMOTIONAL SYMPTOMS IN CHILDREN WITH IDIOPATHIC HEADACHE

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Introduction Psychiatric symptoms are frequent in children with primary headache. We investigated the presence of emotional and behavioural symptoms in patients diagnosed with primary headache with the Screen for Child Anxiety Related Emotional Disorders (SCARED) [1], and the Strengths and Difficulties Questionnaire (SDQ) [2].
Materials and methods Parents of 150 children and adolescents who consecutively referred to the Headache Clinic of the Paediatric Department at the University of Padua, Italy, from September 2006 to March 2007, were asked to participate in the study and to fill out two questionnaires: the SCARED, a 3-point scale instrument to screen children with anxiety disorders, and the SDQ, an instrument for screening emotional and behavioural disorders with 25 items, 3-point Likert scale and 5 subscales (hyperactivity/inattention, emotional symptoms, conduct problems, peer problems, and prosocial behaviour).
Results Parents of 89 children (42 males and 47 females; mean age 11.2±SD 2.8, range 4.3-17.5 years) completed the SCARED and the SDQ. Headache diagnoses (ICHD-II, 2004) were: MwoA (55.1%), MwA (10.1%), ETTH (29.2%), and CTTH (4.5%). Unclassifiable headache was diagnosed in one case.
A total of 24.7% of the subjects were positive on the SCARED Any Anxiety Disorder subscale (11.2% males, 13.5% females), and 31.4% scored above the cut-off value for Separation Anxiety Disorder subscale (15.7% both males and females).
On the SDQ, 17 subjects (19.1%) resulted positive on the Total Difficulties subscale; 30.3% scored above the cut-off value for Emotional Symptoms subscale (16.8% males, 13.5% females) and 16.8% for Conduct Problems subscale (7.9% males and 8.9% females).
Eleven of 89 patients obtained high scores on both SCARED and SDQ Total scores.
Discussion and conclusions Children and adolescents with primary headache show an increased risk of psychopathology, especially emotional symptoms. Interestingly, girls with headache who are more prone to anxiety disorders, are described as affected also by relevant conduct problems.
A total of 12.4% of patients showed high scores on both SDQ and SCARED, thus representing probably the most suffering subjects who may need a complete psychiatric evaluation.
SDQ and SCARED may represent reliable, time-sparing and useful tools for screening psychopathological issues in children and adolescents affected by primary headache.
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PSYCHIATRIC COMORBIDITY IN PARENTS AND PRIMARY HEADACHE IN CHILDREN: INVESTIGATION IN 200 FAMILIES

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Background The psychiatric comorbidity (Psi-co) in headache arises questions on the likely common aetiological mechanism and direction of influence.
Objective To examine the relationship between headache and familial recurrence of psychiatric disorders by estimating the prevalence of mood, sleep and anxiety disorders in children diagnosed with headache compared to their parents' Psi-co.
Methods Headache history and symptomatology were collected in a clinical sample of 200 patients and their families, using a semi-structured interview which covered all items required for diagnosing headaches according to ICHD-II criteria (2004). The questionnaire was composed of different sections in which we assessed the Psi-co in parents, according to DSM-IV criteria. LRChi squares and Loglinear analysis were computed in order to analyse principle effects and interaction of variables.
Results A Loglinear analysis was computed in order to evaluate main effects and interactions between the following factors: headache subtypes (migraine/non-migraine) in children, headache (migraine/non-migraine-absent/present) in parents, headache (absent/present) in grandparents and psychiatric comorbidity (absent/present). Ninety-four mothers (47%) and 51 fathers (25.5%) had at least one psychiatric disorder, mainly mood and anxiety disorders. Considering the significant prevalence of Psi-co in children [69.03%; LR Chi-square=15.62; d.f.=1; $p<0.0001$], we compared it with the presence of familiarity for headache: a significant interaction has been found [LR Chi-square=5.03; d.f.=1; $p<0.05$] showing that migraineurs with high familial recurrence of headache had a higher percentage [74.65%] of psychiatric disorders, than non-migraineurs [52.17%]. Absence of headache familial loading seems to be related to psi-co only in non-migraine headache (87.5% *vs.* 45.5%).
Discussion The direction and characteristics of headache and psychiatric disorders is a matter of debate, and the familial recurrence of both of them has been documented over time. The different pattern characterising migraine and tension-type headache is a new finding that needs further studies, because of new elements emerging and adding to the debate (is psychiatric comordidity a cause or consequence of recurrent headache?).
Conclusions The occurrence of psychiatric disorders is high in children with headache, but a very different pattern seems to characterise migraine (familial co-transmission of migraine and Psi-Co?) if compared to non-migraine headache.

LOW CYCLIC ALTERNATING PATTERN RATE AS AN INDICATOR OF MIGRAINE WITHOUT AURA IN SCHOOL-AGED CHILDREN

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Introduction Primary headaches are closely related to sleep. Great modifications in the arousal patterns during sleep have been reported in migraine, especially in the nights preceding a headache attack.
Aim of the study was to evaluate the pattern of arousal from sleep in a group of migraine school-aged patients.
Materials and methods Population study consisted of 5 patients, (four females and one male), aged 8-15 years (mean 11.7 years, SD±2.43), affected by migraine without aura (MO), according to ICHD-II criteria, who referred to the third University Level Headache Centre for Developmental Age of the Department of Child and Adolescent Neuropsychiatry of the Second University of Naples.
All the mothers of the subjects were asked to fill in the Sleep Disturbances Scale for Children (SDSC) questionnaire to assess the presence of sleep troubles.
Patients underwent three overnight polysomnographic studies, following adaptation; arousal pattern was studied by the scoring of the cyclic alternating pattern (CAP).
Results Migraineurs showed a lower CAP rate in non-rapid eye movement (NREM) sleep (CAP rate mean value 14.875% *vs.* 24.56% of matched control, $p=0.005$) and, in particular, a lower number of A1 phases, as shown in a recent report in an adult population.
The reduction in the CAP rate indicates a lower level of arousal fluctuation in NREM sleep, suggesting a dysfunction in neural structures involved in both the control of REM sleep and the pathophysiology of migraine, such as the hypothalamus and the brainstem.
Discussion In the last 30 years, the intimate relationship between sleep and headache has been recognized even if the relationship remains clinically and nosologically complex, and widely obscure.
Headaches associated with nocturnal sleep have often been perceived as either the cause or result of disrupted sleep.
Recent biochemical and neurofunctional imaging studies in patients with primary headache disorders has lead to the identification of potential central generators which are also important for the regulation of normal sleep architecture and sleep microstructure and could be an important tool to clarify the relation between the two.
Conclusions The relationship between headaches and sleep disturbances is complex and difficult to analyse, but neurophysiological tools and sleep study (both macrostructural and microstructural) could be useful to clarify this obscure aspect of two so frequent clinical events, particularly in school-aged children.

PSYCHOLOGICAL TROUBLES ARE RELATED TO SLEEP PATTERN DISORDERS IN HEADACHE SCHOOL-AGED CHILDREN

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Introduction Headache is a common disorder in children and adolescents, associated with the presence of several disorders such as emotional, behavioural difficulties and sleep disorders.
Aim of the study was to verify the relationship between psychological troubles of headache patients and sleep patterns.
Materials and methods Population study consists of 64 subjects (27 females), aged 8-12 years (mean 9.4 years, SD±1.03), consecutively referred to the third University Level Headache Centre for Developmental Age of the Department of Child and Adolescent Neuropsychiatry of the Second University of Naples since January 2007.
All the mothers of the subjects were asked to fill in the Child Behaviour Checklist 4-18 (CBCL) and the Sleep Disturbances Scale for Children (SDSC) questionnaire to describe psychological profile and assess sleep troubles.
The SDSC is a sleep questionnaire that consists of 26 items subdivided into six sleep disorders subscales: disorders in initiating and maintaining sleep (DIMS), sleep breathing disorders (SBD), disorders of arousal (DA), sleep-wake transition disorders (SWTD), disorders of excessive somnolence (DES), and sleep hyperhydrosis (SHY), widely used in paediatric age both in its original and modified version.
To verify the relationship with psychological assessment, we considered only some of the scales of SDSC such as DIMS, DA, SWTD, and Total value.
Results According to ICHD-II criteria, headache subtype distribution was as follows: migraine without aura (71.87%), episodic tension-type headache (7.81%), and chronic tension-type headache (7.81%).
Psychological CBCL assessment (Total problems item) showed an

interesting relation with sleep disorders as DIMS and parasomnias (DA and SWTD) (respectively r=.37, p=0.019; r=.39, p=0.015; r=37, p=0.019).

Discussion As shown in recent medical literature, migraine children revealed a specific behavioural phenotype characterized by internalizing problems, as higher scores of behavioural and emotional symptoms, both of internalizing and externalizing type, than normal peers. Herein, temperament and sleep are important factors influencing all social aspects of life, both in adults and in children

Conclusions Several studies on headache in children outlined the contemporary presence of headaches and parasomnias. Few studies have focused on the whole sleepwake cycle and on the circadian aspects of headache to clarify the close relationship between the two.

Temperamental troubles should be considered not only for diagnostic and therapeutic purposes, but also from the aetiological aspect.

HEADACHES IN CHILDHOOD AND ADOLESCENCE II

PET THERAPY AND HEADACHES

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Within the framework of therapeutic psychological and psychiatric interventions, Pet Therapy has been used for some decades now, allowing patients to achieve therapeutic objectives [1].

Through what mechanisms does the relationship of man with animals perform a positive effect on human health? The most recent investigations are proving the prominent importance of emotions deriving from the relationship of man with animals and the research that is being carried out in Pet Therapy indicates several mechanisms able to enhance and strengthen each other, since they are often associated with one another (affective-emotional, psychological stimulation, game, physical and communicative mechanisms).

This therapy has been applied in several childhood psychiatric pathologies and defects. We have been using Pet Therapy for some years now for the treatment of childhood headache in which the main cause is related to psychological and social problems, with important results [2].

The aim of this study was to evaluate how the effects of this therapy have stabilised in headache sufferers.

The therapeutic course of Pet Therapy involved 20 weekly sessions of one hour each; the patients were divided into 3 groups aged 5–8 years; 9–11 years, 12–17 years.

The first three therapeutic groups which had undergone Pet Therapy for over one-year were re-evaluated in order to see, after a certain time, the characteristics of headache: T0, T26 T +52, both from the headache and psychological characteristics standpoints (CDI, FAB-C).

The study involved 41 children: 19 males, 22 females; age 14.9±3 years, range 7/18 years.

Diagnosis was: 21 (11 females, 10 males) migraine without aura; 17 (8 females, 9 males) episodic tension-type headache; and 3 females chronic tension-type headache. As to frequency, the values at the end of the therapeutic course remained stable (T0=6.1±0.8; T26=3.9±0.9; T+52=3.6±0.6-p<0.05). In regard to duration, there was a slight increase of the values at the end of the therapeutic course (T0=7.9±0.8; T26 =5.4±0.0; T+52=5.9±0.6-p<0.05). The psychological characteristics have, conversely, continued to improve.

Conclusions Pet Therapy may have acted on the patient's feeling of security, through constancy, trust, affection ensured by the animal and its effectiveness in acting as a transitional object, for autonomy, self-esteem, and self-control. But, also, by the continuing confrontation with the group of peers in a psycho-therapeutic setting.

We therefore consider that Pet Therapy may be an adequate instrument for handling those patients whose psychosomatic and psychiatric problems are considerable, since the relationship with the animal world, managed by competent personnel, helps patients emerge from their isolation, which is difficult to modify with common therapies.

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NEW EXPLANATORY APPROACH ON THE EFFECTIVENESS OF PET THERAPY IN CHILDHOOD HEADACHE

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Until now we have dealt with behavioural Pet Therapy for headache in childhood, in 259 children (159M, 100F) with the diagnosis of: MwoA, 99; MwA, 17; ETTH 81; CTTH, 30; and CDH, 32. In most cases the headache was remarkably diminished.

On this occasion we propose an appraisal of these results, starting from the concept that the methodology used is not based on linguistic communication (reduced to minimum terms).

The privilege during childhood of any form of communication related to one's own corporeity, poses researchers with the serious issue of the development of knowledge forms based on the cognitive ability of human beings to reproduce an action or a behaviour, even when this is just observed and not performed.

The studies on the mirror neurons and their functionality offer a valid epistemiological support to the study of the validity and effectiveness of the treatments based on the Pet Therapy technique.

In particular, we shall try to highlight how to develop the ability to attribute emotions, attitudes and willingness in the speaker (animal or human being), without previously experimenting or coding the same emotional condition.

In their interactive relationship with animals, children experience the basic cognitive ability of understanding the significance and emotional effect of their own actions on others, without referring to a linguistic dialogue.

The mechanisms that can immediately understand the meaning of the actions of others and even of their intentions without resorting to any kind of deductive logical reasoning appear clearly in the Pet Therapy treatments, where children label with emotional connotative interactions the effects of their interactions with the animals.

Mirror neurons provide a theoretical and experimental picture, as well as an epistemiological one, to determine the development of social (i.e., of many of our social behaviours) relationships, when one realizes the presence of a primitive and innate bodily ability to play again with others, even before developing the cognitive-linguistic ability, typical of the adult phase of the individual.

PET THERAPY IN CHILDHOOD WITH HEADACHE: REGION OF MARCHE PROJECT

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Introduction The therapeutic use of pets as companions has gained increasing attention in recent years for a wide variety of patients - people with AIDS or cancer, the elderly, and the mentally ill. It was born accidentally for the treatment of autism. Unlike people, with whom our interactions may be quite complex and unpredictable, animals provide a constant source of comfort and focus for attention. Animals bring out our nurturing instinct [1].

The psychosocial stress that may occur most frequently at school and within the family could be one of the most frequent causes of headache. Following the therapeutic use of Pet Therapy (PT) in people with psy-

chological, psychiatric and psycho-social problems, it was evaluated as a therapeutic approach in young headache patients arriving at the Salesi Hospital headache ambulatory [2].

Materials and methods We present preliminary results of the Region of Marche experimental project for children with headache treated with PT for 8 months. Our study included 15 children aged 9 to 13 years with diagnosis of primary headache (tensive headache or tensive/migraine) divided into 2 groups. A treatment cycle consisted in 18 sessions over 4 months of 1 hour each. PT in our group was conducted by 2 psychotherapists with 2 animals (dogs or/and cats) that were brought to the Centre by their owners/conductors. The psychological evaluation was made pre and post therapy by CDI, FAB-C, MACHOVER test, family test and clinical observations.

Conclusions From preliminary data we observed the improvement in the frequency of headache and in behaviour with a reduction in anxiety at the end of the 4 months treatment. These are preliminary data of few patients, but we believe that this therapy could be an important non drugs therapeutic approach for headache children.

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RIBOFLAVIN AND NIACIN IN THE PROPHYLACTIC TREATMENT OF MIGRAINE: PRELIMINARY DATA

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Background A decrease has recently been found in the phosphorylation potential in the brain and in the mitochondrions of headache suffering patients between crises. Even though this discovery is in line with the previous observations of the reduction in the phosphocreatine and phosphate ratio in the brain of migraine sufferers, the need for confirmation may represent the link between behavioural factors and the metabolism unbalance of brain oxygen, and the secondary activation of the trigeminalvascular system.

Patients with mitochondrial myopathies as well as encephalomyopathies have benefited from the use of riboflavin [1]. Also, in migraine, the lack of mitochondrial energy could be a triggering factor of the crisis, as such, the association of riboflavin and niacin, as essential behaviours for the operation of energy producing biochemical mechanisms, may have an important weight in the prophylaxis therapy of migraine.

This has led various authors (Schoenen et al., 1994, 1998; Boehnke et al., 2003) to use riboflavin in high dosages in the prophylaxis of migraine. Maizels (2004) has conversely proved the effectiveness also in low dosages [2]. There have also been attempts to use niacin (Prousky and Seely, 2005).

Objective The efficacy and tolerability of 50 mg of niacin + 2.5 mg riboflavin (NR) twice a day, was compared with placebo in a randomized double-blind, controlled trial.

Patients suffering from migraine without aura according to IHS criteria were treated for 26 weeks after a 4-week baseline period.

Methods The end point of this first study was to ascertain whether such preparation reduces the frequency of migraine attacks.

Forty-three patients (29 females, 14 males; average age 27±13 years, range 18/54 years, onset of headache 8.7 years) were included. The average monthly frequency was compared to T0 and T26 for the NR (n=23) and the placebo group (n=20).

Results The migraine frequency in the NR group decreased from 8.4 to 4.3 attacks per month, and in the placebo group from 8.2 to 6.1 attacks. The difference between treatment groups was statistical significant in favour of NR (p=0.0476) No side effects were found and no patients left the study.

Conclusions Riboflavin and niacin proved to be useful in reducing the frequency of migraine. These are only preliminary data, but if confirmed by further studies involving a higher number of patients, these drugs could be considered useful, in addition to being harmless, for the prophylaxis of migraine.

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CHILDHOOD IDIOPATHIC HEADACHE: RANDOMIZED COMPARISON OF BRIEF PSYCHODYNAMIC PSYCHOTHERAPY VERSUS USUAL-CARE TREATMENT

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Introduction The role and importance of psychological components in maintaining and influencing the course of headaches have been highlighted in recent literature [1]. Brief psychodynamic psychotherapy (PP) has demonstrated a favourable cost/effectiveness ratio for selected groups of children [2].

Objective To compare the efficacy of usual-care treatment with the efficacy of a time-limited combined individual and parent-focused PP in childhood idiopathic headache.

Methods Inclusion criteria were: (a) First specialist assessment for headache, (b) Diagnosis of headache according to the International Classification of Headache Disorders criteria modified for paediatric age, (c) Sufferers whose migraine the clinician is unsure how to treat (PP vs usual-care), (d) IQ in the normal range on the Wechsler Intelligence Scale for Children. Twenty children were enrolled and randomized to PP or usual-care treatment (PP group n=10; UC group n=10) at time 0 (T0). The psychotherapy protocol consisted of 11 weekly sessions. The sample included 14 females and 6 males, aged from 7 to 12 years (mean age 9.35±1.5). Follow-up visits were scheduled at 5 (T5), 8 (T8) and 12 (T12) months from randomization. Three questionnaires were used for data collection: a diary in which the patient recorded data relating to headache frequency; the Migraine Disability Assessment Questionnaire (MIDAS) that evaluates the degree of disability; and the Child Behavior Checklist (CBCL) that evaluates children's behavioral problems.

Results Patients in the PP group had a significantly lower number of attacks with respect to UC group patients, in all three time periods (p<0.05). The reduction in number of attacks within groups reached statistical significance during follow-up only in the PP group. This was observed comparing the number of attacks at T0 with T5 and T12. Comparison of MIDAS scores between groups did not show significant differences. However, within the PP group a significant reduction in disability was observed between T0 and T5 and between T0 and T12 (p<0.01). CBCL scores were significantly improved in the PP group at T5 and T12. The improvement regarded Total T, Internal T and External T scores together with Withdrawal, Anxious/depressive, Thought, Aggressive, and Total Competences scales. The within-group evaluation showed that significant improvement occurred in the time period between T0 and T5.

Conclusions Our data suggest that brief PP is more effective than usual-care treatment in childhood idiopathic headache. The improvement in CBCL scores in the PP group showed that PP could modify the psychopathologic component of childhood headache.

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CLUSTER-LIKE HEADACHE IN CHILDHOOD: A CASE RESISTANT TO SYMPTOMATIC THERAPY

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Cluster headache, the most painful of the primary headaches, is a disorder with well-known diagnostic criteria. The condition usually begins in the second decade of life; the prevalence of childhood onset is approximately 0.1%.
An 11-year-old male who suffered daily, in the last eight months, from severe strictly unilateral right orbital attacks lasting approximately 60-180 minutes associated with autonomic symptoms is reported herein. Frequency of attacks was 1-2/day, time locked (usually one at night). Until now, after 8 months he had no remission of attacks.
There was a family history for unspecified headache but not migraine or cluster headaches; physical and neurologic examinations and magnetic resonance imaging did not suggest any association with head trauma or vascular disorders. Blood tests, including study of coagulation and inflammatory indexes, showed no significant alterations.
At the age of 2.5 years he presented episodes of deviation of the right eye and esotropia, for which he was initially treated with occlusion therapy, and then at 9 years of age he underwent a surgical intervention of recession medial rectus and inferior oblique muscles in the right eye. After a negative indomethacin test, sumatriptan 6 mg s.c., octeotride 100 microg s.c. and Oxygen 7-8 l/min with mask, yielded only a partial efficacy. The same occurred with ketoprofen, paracetamol, codein, metamizole, ketorolac, and ibuprofen which proved inefficacy. Prophylactic treatment included citalopram, amitriptyline, dexamethasone, chyproheptadine, verapamil, and topiramate did not reduce the headache frequency and/or severity. Parents gave no consent to lithium therapy. According to the classification and diagnostic criteria for headache disorders of the International Headache Society the child fulfilled the criteria for episodic cluster headaches. Until now, after 8 months, he showed no remission of the frequency of attacks, thus indicating a possible chronic cluster headache from the beginning.
To the best of our knowledge this is the first described cluster-like headache with childhood onset resistant to symptomatic treatment and until now to prophylactic treatment.

CASE REPORTS

CLUSTER HEADACHE WITH AURA: A CASE REPORT

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Aura symptoms are occasionally reported in patients with cluster headache (CH). We report a case of episodic cluster headache with typical migrainous aura. A 43-year-old healthy man, with a history of migraine without aura (MO), developed stereotypic severe, unilateral headaches beginning at age 38. All were strictly right-sided, localized to the retro-orbital and temporal regions, lasted 90-120 min, and occurred 1-3 times a day. Associated symptoms included ipsilateral lacrimation, nasal congestion, conjunctival injection, ptosis, and sense of restlessness. The first cycle lasted 4 weeks and were followed by a remission of 48 months, the last cycle lasted 8 weeks. He always developed, before and during pain, visual (hemianoptic flashing lights, scotoma, on the right visual field) and sensory (paresthesias on the right side of the face, upper and lower limbs) symptoms, that lasted for 20-40 min. Visual and sensory aura occurred at the first attack and were invariably followed by the headache, which never had the migraine phenotype. Symptomatic administration of triptans was found to be beneficial. Both cluster cycles were treated with prednisone with resolution of the headache in a few days. There were no family history for CH, but the mother had MO. Brain MRI and MRA, carotid-Doppler and ophthalmology evaluation were normal. The relationship between CH and migrainous aura remains uncertain. Activation of the trigeminovascular pathways, resulting in the stimulation of the cranial parasympathetic outflow, is considered the basis for the expression of trigeminal pain and ipsilateral autonomic symptoms in CH. The presence of aura in CH suggests that in some cases, in addition to the supposed "cluster generator" within the hypothalamus, activation of brain cortical areas contributes to the generation of the pain attack.

CATARACT IN CLUSTER HEADACHE: REPORT OF 2 CASES

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Introduction Cluster headache (CH) is a form of primary headache, which consists of strictly unilateral headache, occurring in association with cranial autonomic symptoms and restlessness or agitation, which usually shows a striking circannual and circadian periodicity. Attacks of excruciating pain usually last less than 3 h, and occur in bouts of 1-2 months during which the patient has 1-2 crisis/day. Cataract is an eye disease, due to the opacification of the ocular lens, and that results in progressive visual impairment. Cataract prevalence increases with age, and this eye disease is relatively uncommon before the age of 60. Here, we report two cases of monolateral cataract in two patients affected by CH. We underline that the cataract occurred on the same side affected by CH.
Case 1 A 44-year-old man reported the first distinct episodes of CH when he was 21-year-old. Pain attacks (~90 min) localized at the left periorbital area with ipsilateral lacrimation and rhinorrhoea, and initially occurred sporadically, since 2005 the CH became chronic. At the age of 39 he was diagnosed with cataract in the left eye that was successfully treated by surgery. The only recognized risk factor for cataract was his cigarette smoking habit (30 cigarettes/day).
Case 2 A 53-year-old man experienced his first CH episode when he was 44 years of age. Cluster periods were characterized by 3-4 attacks/day of severe right-sided pain localized at the periorbital region, lasting ~45 minutes and associated to ipsilateral lacrimation. The CH was chronic from its onset. At the age of 52 he was diagnosed with cataract that was treated by surgery. Risk factors for cataract were his cigarette smoking habit (15 cigarettes/day) and hypertension (diagnosed at the age of 45).
Discussion To our knowledge this is the first report of cataract occurring in CH patients and particularly, in the same eye affected by the pain attack. It is noteworthy that the two patients, although not relatives, had the same rather uncommon last name, that we found concentrated in a defined area of North-Eastern Italy. They both developed cataract in a relatively young age, but after suffering for years from CH. The present observation suggests careful anamnesis and specific follow-up for cataract in CH patients. In addition, one may wonder whether, there is a causal relationship between repeated episodes of pain, inflammation and autonomic abnormalities, that are considered to contribute to the cluster headache attack, and the occurrence of the cataract in susceptible individuals prone to the disease, perhaps because of a common genetic background.

A CASE OF CHRONIC PAROXYSMAL HEMICRANIA IN PAEDIATRIC AGE

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Introduction Our aim was to describe the case of a child with headache non-responsive to most analgesic drugs.
Case report A 7-year-old male referred to our Headache Centre because of a headache begun 1 year earlier. Headache attacks were daily and lasted around 30 minutes. Pain was unilateral in the right orbito-frontal region and was associated with photophobia, vomiting and tearing of the right eye. Brain magnetic resonance imaging (MRI) was normal. Pain was not ameliorated by most analgesic drugs, including acetaminophen, ketoprofen, and aspirin. Prophylactic treatment with amitriptyline was attempted without any clinical improvement. Lastly, the child began psychological treatment.
Results Indomethacin 25 mg/day led to a significant improvement in headache frequency, reduced to 2-3 attacks per month. Moreover, pain attack was resolved by taking indomethacin 25 mg. After 6 months, the treatment was interrupted, but the headache worsened. Flunarizine 5 mg/day was attempted without any amelioration, while a satisfactory improvement was obtained after resuming indomethacin 25 mg/day (frequency: 6–7 attacks per month). Further reduction in frequency of the headache attacks (2–3 per months) was obtained when topiramate was added at the dose of 1.5 mg/kg/day.
Discussion The clinical characteristics of our child's headache and the positive response to indomethacin led us to propose the diagnosis of 'Chronic Paroxysmal Hemicrania'.
Conclusions Our child can be added to the very few cases of this Trigeminal Autonomic Cephalgia described in paediatric age.

PRIMARY OR SECONDARY HEADACHE IN A YOUNG PATIENT?

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Case report A 32-year-old hypertensive, dyslipidemic, and obese subject was admitted to our Department because of one-year recurrent episodes (three), characterized by hemispheric pulsating headache of abrupt onset associated with dysesthesias of the left arm with extension to the homolateral side of his face, followed by paresis. Motor deficit persisted for 3 days, than resolved spontaneously. Sudden and transient loss of consciousness was also part of the clinical presentation of one such episode. The patient was already under treatment with beta-blockers (nebivolol), calcium-antagonist (nifedipine) and statin (simvastatin) before the occurrence of these episodes.
The diagnostic work-up included: ultrasonographic investigation of the neck and cerebral (TCD) vessels, standard and polysomnographic EEG, transthoracic and trans-esophageal echocardiography, plain and perfusion brain CT scan, brain MRI-MRA as well as biochemical and genetic tests for thrombophilias. The results of such investigations were all unremarkable except for patent foramen ovale (PFO) and for lupus anticoagulant (confirmed by a further analysis performed three months apart). Genetic screenings for the known mutations of familial hemiplegic migraine were also negative. No further therapeutic strategy was adopted. Three months after, the patient complained of a new episode with the same clinical presentation except for a left eyelid ptosis and tearing, and a 20-day duration of the other symptoms (including motor impairment). During this symptomatic phase a brain Positron Emission Tomography (PET) was also performed, which showed no remarkable abnormalities. Because of the concomitant migraine without aura with a weekly frequency and because the patient had spontaneously discontinued taking nifedipine, we started a preventive therapy with nimodipine 90 mg per day, with a significant decrease in the frequency of migraine attacks, and no further episodes over one year.
Conclusions 1) Diagnostic criteria for primary headache do not meet the clinical presentation of this patient, 2) There are no findings which allow a definitive diagnosis of secondary headache.

OPHTHALMOPLEGIC MIGRAINE: A CASE REPORT AND FOLLOW-UP

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Introduction The incidence of childhood migraine in general has been estimated at between 2% and 5.7%. Ophthalmoplegic migraine is quite rare and constitutes 0.16% of childhood migraine. A typical clinical syndrome emerges in a child or young adult with periodic headache associated with ophthalmoplegia involving all functions of the third cranial nerve (CIII), beginning at the height of an attack of chephalalgia , which is primarily unilateral and in the orbital region; the paresis lasts for days to weeks following the cessation of headache; recovery is gradual and tends to be less complete after repeated attacks. MRI may show enhancement of the third nerve. Systemic steroids have shown promising results [1, 2].
Materials and methods We present a rare case of isolated recurrent ptosis with headache without motility or pupillary abnormalities as the sole manifestation of presumed ophthalmoplegic migraine in an otherwise healthy young girl.
The patient is a 5-year-old girl with a history of recurrent, isolated unilateral left upper eyelid ptosis and migraine. The initial episode occurred at age 21 months, with a complete ptosis and severe ipsilateral left-sided headache with pain in and around the eye with vomiting followed by sleep that resolved over 10 days with steroid therapy. The pain was not relieved with analgesic therapy.
Clinically, the eye examination was normal except for CIII left palsy.
During the following years, almost every month she complained of headache attacks located over the left eye, accompanied by nausea and sometimes vomiting, but no eye symptoms. These episodes completely resolved with analgesic therapy.
The differential diagnosis should include aneurysm, tumour, diabetes, sphenoid sinus mucocele, Tolosa-Hunt syndrome and myasthenia. Extensive clinical, neurophysiological and laboratory evaluation including testing for myasthenia gravis were unremarkable.
On high-resolution magnetic resonance imaging (MRI) and MR angiography (MRA), the left CIII was significantly thickened in its course and the nerve was enhanced following administration of gadolinium. No vascular malformations were found.
Discussion and conclusions The present case report is one of the rare cases of ophthalmoplegic migraine according to ICHD-2004 criteria. Ophthalmoplegic migraine is a diagnosis of exclusion, and noninvasive imaging tests such as MRI or MRA and many other neurophysiological and laboratory evaluations should be performed in all cases.
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A CASE REPORT THAT SUGGESTS A PROPER PLACE OF HEMICRANIA CONTINUA WITHIN THE CLASSIFICATION OF THE PRIMARY HEADACHE FORMS

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The recent ICHD-II classification has included hemicrania continua (HC) in chapter 4 "Other primary headaches", keeping it apart from the short-lasting trigeminal Autonomic cephalalgias (TACs). Unlike the other TACs, which are intermittent, short-lasting headaches, HC is

characterized by a continuous, strictly unilateral headache that varies in intensity, with superimposed exacerbations of more severe pain and complete response to indomethacin. Ipsilateral local autonomic symptoms may be present, but usually they are not as prominent as in cluster headache (CH) or chronic paroxysmal hemicrania (CPH).
We describe a case of a 49-year-old, right-handed male who presented with unilateral continuous headache with daily exacerbations that were accompanied by local autonomic signs, responsive to indomethacin. This headache met the ICHD-II criteria for HC, however, the clinical picture shared some features with other TACs. Indeed, the strict unilaterality of the pain, the presence of exacerbations (in which the pain is located in "trigeminal" areas) associated with oculocephalic autonomic symptoms, and the response to indomethacin seemed to suggest a clinical and pathophysiological affinity particularly with CH and CPH. This suggestion was further supported by the quick and complete response of the exacerbations to s.c. sumatriptan, coupled with the inefficacy of the oral route, by the improvement observed following the sphenopalatine ganglion block, by the possible role of alcohol as a trigger of the paroxysms at the beginning of the disease, as well as by the restless behaviour reported during particularly intense paroxysms.
Finally, our patient showed a temporary and partial response to prophylactic treatment with verapamil, which is the first-choice prophylactic drug for CH.
Hemicrania continua (HC) is an uncommon primary headache syndrome, which is a part of a larger spectrum of primary headache disorders with variable clinical overlapping and, for this reason, of controversial nosology. Our findings in this patient suggest that HC may be closer to the TACs than to the other primary headaches group included in part 4 of the ICHD-II classification. In addition, this report also highlights the need for better characterisation of exacerbations in terms of their pain characteristics, frequency, duration, and response to treatments. It seems likely that this additional information might allow a better nosographic framing of HC.

EFFECTIVENESS OF ANTIMIGRAINE THERAPY IN AN ADULT PATIENT WITH CYCLICAL ABDOMINAL PAIN, NAUSEA AND VOMITING

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A 71-year-old man came to our attention when he was 60 years old; he showed recurrent disorder characterised by episodic midline abdominal pain manifesting in attacks lasting several hours and recurring for days or weeks since he was 25 years old. Owing to abdominal symptoms our patient was submitted to repeated surgical investigations and to gastroenterologic examinations; several EGDS only showed chronic gastritis without any other significant data.
Often pain attacks had a cluster course and were completely disabling with repeated vomiting; they were followed by absence of pain even of long duration. There was no headache during the attacks while during one of these attacks the patient was submitted to partial gastroresection with transient improvement. Considering these stereotyped symptoms as a cyclic disturbance resembling those found in association with migraine headaches, we suggested a therapy with flunarizine for 3 months. There was a complete remission of symptoms. In the last 10 years in concomitance with the reappearance of recurrent abdominal pain, our patient underwent treatment with flunarizine for some months. Our patient during the pain attack found relief with indomethacin, alone or in combination, with triptans. During the attacks with nausea and vomiting our patient never complained of headache. The cyclic course, the presence of the symptoms even after gastroresection, the clinical effects of flunarizine, analgesics and triptans utilized during the pain attack, and the data collected from all the investigations, in particular, neuroimaging and electroencephalographic, revealed no abnormalities, allowing us to suggest the diagnosis of "abdominal headache" without headache.

TOPIRAMATE-INDUCED ACUTE MYOPIA

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A rare topiramate-induced side effect is acute myopia associated or not with acute angle-closure glaucoma; the etiopathogenesis seems to be related to oedematous effusion in the ciliocoroidal layer. Until April 2007, 7 cases have been described.
We report the case of a 27-year-old woman, E.M., who was treated with topiramate 25 mg per day for 10 days as prophylaxis for migraine; she had no history of myiopia. The patient came to our obsevation with sudden bilateral loss of vision and mild, pulsatile periorbital pain, particularly evident in the left eye. Ophthalmologic examination revealed a visual acuity of 20/100 in the right eye and 20/80 in the left eye; ocular pressure was 19 mmHg in both eyes. In the left eye a mild conjunctival chemosis was also noted. Topiramate was quickly discontinued. A further ophthalmologic evaluation 3 days later revealed visual acuity was 20/20 bilaterally; ocular pressure was 16 mmHg in both eyes. The patient reported subjective improvement of vision and no more periorbital pain. A one-week follow-up revealed normal vision and ocular parameters.

LATE-LIFE MIGRAINOUS ACCOMPANIMENTS ASSOCIATED WITH HEMORRHAGIC BRAIN DAMAGE: CASE DESCRIPTION AND REVIEW OF THE LITERATURE

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Late-life migraine accompaniments refer to transient focal neurological episodes, which are identical to the auras of migraine and are thought to have a similar underlying mechanism, but which are often not associated with headache. The diagnosis is not difficult when the spells have the clinical features described by Fisher. Generally, late-life migraine accompaniments represent a diagnosis of exclusion of TIAs. In patients with typical presentations and a normal neurological and neuro-ophthalmic examination, extensive diagnostic testing is not routinely indicated. Cerebral amyloid angiopathy, intracerebral tumours, demyelinating processes, metabolic disturbances and seizures must also be considered. One of the characteristic features that distinguish migraine accompaniments from TIAs is their benign course. However, there are reports of ischaemic and hemorrhagic cerebral infarction and subarachnoid hemorrhage associated with these spells. We report the case of a woman with migraine accompaniments who developed a cerebral hemorrhagic infarction associated with subdural hematoma. Flunarizine therapy was effective in stopping migraine accompaniments.

HEADACHE AND PSYCHIATRIC DISORDERS: TWO CLINICAL CASES

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Introduction From the literature and clinical experience it can be deduced that most headaches that appear in association with a psychiatric disorder are linked to it not by a relationship of cause and effect, but rather by one of comorbidity, probably related to a common biological substrate [1].
However, both literature and clinical experience suggest that, not exceptionally, headache that exclusively occurs during some kinds of psychiatric disorders, such as depressive and somatoform types, can be correctly imputed to these disorders.
We introduce two clinical cases that seem to confirm our assertion. The first case concerns a fifteen-year-old boy affected by anxiety disorder and consistent obsessive behaviour, who had experienced headaches of

a pulsating-constrictive type localised on the temporal sides for several months with daily frequency.
The second case concerns a fifteen-year-old girl affected by somatoform disorder who had showed sudden attacks of headache, several times a day, with a pulsating quality localized on the bitemporal side, accompanied by phonophobia and photophobia and not rarely by paresthesia and stiffening of the right pelvic limb.
Materials and methods Before admittance to our Department, a careful history, an accurate neurological examination, both clinical and instrumental, and an exhaustive psychiatric examination (also making use of projective techniques, such as Rorschach Test) were carried out.
Results The chosen diagnostic pathway placed the patients' symptomatology in a context of headache attributed to psychiatric disorders.
Discussion and conclusions The cases presented suggest that the diagnosis of headache attributed to psychiatric disorders can be reasonably made not just as a consequence of the temporal relationship between the two situations, but above all as a consequence of a complete neurological and psychiatric examination, and of the possibility to objectively demonstrate a clinical improvement, or even the resolution of the headache, when the psychiatric disorder is actually treated [2].
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MEDICATION-OVERUSE HEADACHE IN PITUITARY TUMOUR: A CASE REPORT

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Background Headache is a common and disabling aspect of pituitary disease. Chronic migraine (CM) with medication–overuse headache (MOH) according to the 2nd Edition of the classification (ICHD-II) [1] is a very disabling condition frequently associated with psychiatric comorbidity. Sometimes CM may be underestimated and expression of a different medical condition.
Case report We describe the case of a 41-year-old woman, who has been suffering for many years of an intolerable and severe headache with characteristics of CM which have transformed in the years into MOH. The onset of headache dates back to her adolescent years. During these years the patient underwent several investigations, hospitalisations, surgical ORL procedures and prophylactic treatment with an isolate period free of attacks only during pregnancy. Each symptomatic treatment was ineffective, the only method to reduce pain was the intake of glucose with a consequent important increase in weight body. Concomitant higher diastolic blood pressure and menstrual irregularity have suggested an endocrine disorder. The patient then underwent several endocrinological investigations without a definitive diagnosis.
At a recent observation at our Institute, the patient presented with severe and disabling headache with characteristics of hemicrania continua and overuse of symptomatic treatment.
The patient underwent neurological evaluation, blood tests and brain MR with pituitary details that showed a growth hormone (GH) secreting pituitary tumour. Her insulinlike growth factor (IGF) was elevated to 563 ng/mL (range 117–252), and a subsequent oral glucose tolerance-test (OGTT) confirmed active mild acromegaly (normal serum GH). Her prolactin (PRL) level, TSH, LH, FSH were normal.
The patient underwent a transsphenoidal resection and the istological diagnosis confirmed pituitary adenoma with pattern of diffuse growth.
Headache showed an important improvement without somatostin analogues treatment and had a frequency of one migraine attack during the month, responsive to common FANS.
The mechanism of pituitary tumour-associated headache in currently unknown.
Recent studies [2] showed that the improvement in headache following surgery is estimated in about 49% of cases and it implies a casual link between the tumour and presence of headache, however the elimination of headache in 64% of acromegalics with somatostatin analogues treatment suggests a link between tumours activity and headache.
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MIGRAINE–LIKE EPISODES FOLLOWING CRANIAL IRRADIATION OF POSTERIOR FOSSA MEDULLOBLASTOMA: FOUR PAEDIATRIC CASES AND REVIEW OF THE LITERATURE

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Introduction Complicated migraine–like episodes in children following cranial irradiation and systemic chemotherapy for brain tumours were first described in 1995 [1]. Recently, a reversible stroke-like migraine attacks after radiation therapy (SMART) syndrome has been recognized, particularly in adult patients [2].
Materials and methods We present a series of four girls with medulloblastoma who were treated, after initial gross-total resection, with whole-brain (36 Gy) and posterior fossa local boost (1.8 Gy) irradiation followed by cisplatin-, lomustine-, and vincristine-containing chemotherapy regimens. The mean age at diagnosis was 9 years (range 8 to 13 years).
Results At 4, 4.5, 6, and 11.5 years after diagnosis, while off-therapy and without evidence of disease, they had new onset of severe, intermittent throbbing headaches (lasting 2 to 24 hours) with nausea and/or vomiting associated with transient sensory or visual symptoms (homonymous hemianopsia, scintillating scotomas), aphasia and confusion (1 to 3 attacks) that spontaneously resolved after 6 to 24 hours and ceased at long-term follow-up.
At headache onset, head CT or MRI did not reveal acute ischemia or tumour recurrence; CSF cytology and interictal EEG were normal (only in one case the ictal EEG showed diffuse slow activity contralateral to neurological symptoms).
Discussion Migraine-like attacks - associated with reversible neurological symptoms, inconstant seizures, and transient posterior unilateral cortical gadolinium enhancement on MRI - have been reported in paediatric and adult patients who had previously undergone radiation therapy for brain tumours, without concomitant evidence of residual or recurrent disease or strokes [1, 2]. The clinical manifestations described in these patients are quite similar to those observed in the series reported, particularly in regards to the pattern of headache, the absence of personal or family history of migraine and the full spontaneous recovery [1].
Radiation-induced endovascular changes, prevalently in the posterior circulation, and/or injury of the trigeminovascular system, resulting in lower threshold for cortical spreading depression and migraine-like attacks, have been the etiopathogenic hypotheses proposed for these episodes.
This series, along with the other rare cases reported in the literature, suggests that a spectrum of migraine-like attacks - ranging from migraine with aura to the well-defined SMART syndrome [2] - can occur as a delayed consequence of cerebral irradiation for brain tumours.
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A PECULIAR HEADACHE AS FIRST MANIFESTATION OF NON-METASTATIC LUNG CANCER

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Isolated atypical facial pain may be, in rare cases, the presenting symptom of lung cancer. In these cases it is almost always unilateral, most commonly localized at the ear, jaw, and the temporal region, ipsilateral to the affected lung. Sarlani et al. described a case with attacks of debilitating facial pain, presenting as cluster headache [1]. Aggravation and expansion of the pain, digital clubbing, increased erythrocyte sedimentation rate, and hypertrophic osteopathy, may contribute to the diagnosis. Facial pain can preceded the diagnosis of lung cancer by 1 to 24 months [2]. Referred pain, due to invasion or compression of vagus nerve, as well as paraneoplastic syndrome seem to be implicated in the pathophysiology of this condition [1].
We observed a 45-year-old male, without a previous history of headache, suffering from a new-onset typical daily hypnic headache, rapidly evolving during 3-4 weeks from onset, into a clinical picture of clinostatic headache – diurnal/nocturnal – unresponsive to treatment with triptans and indomethacin. The head pain was severe, excruciating, bilateral with a slight prevalence on the left side, ipsilateral to the cancer localization. Neurologic examination and neuroimaging (brain and cervical spine MRI) were normal. Recent weight loss and elevation of sedimentation rate (ESR) were present.
Lung cancer should be considered in the diagnostic work-up of headache and atypical facial pain when refractory to treatment, associated with history of smoking, exposure to environmental factors, and elevated ESR.

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PSEUDO-PHEOCHROMOCYTOMA-RELATED HEADACHE MIMICKING TRIGEMINAL AUTONOMIC CEPHALALGIAS (TACS): A CASE REPORT

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Case report A 60-year-old previously healthy woman was admitted to our Department because of a 8-month history of headache, characterized by recurrent attacks (8-12 per day) of extremely severe pain, each lasting about 10 minutes, with a peri-orbital, unilateral location. The attacks were more frequent overnight. Tearing, sweating and mild confusional state were invariably associated to pain attacks. Over the first 6 months the attacks occurred in 15-days clusters every 2 months, then evolved into an almost daily headache. We first posed a diagnosis of probable trigeminal autonomic cephalalgia (TACs) based on negative neuroimaging investigations, non-response to therapy with verapamil, lamotrigine, indomethacin, and carbolithium, and because of some non specific clinical findings (frequency of attacks, symptoms duration, and autonomic signs).
Since we observed raised values of arterial blood pressure (>230/140 mmHg) during pain attacks, as opposed to normal values during the interictal phases, we suspected a pheochromocytoma and tested this hypothesis by measuring plasma and urine catecholamines and abdomen CT scan. These tests were all unremarkable, leading to the diagnosis of pseudo-pheochromocytoma according to standard diagnostic criteria. We thus started treating the patient with clonidine patch, in combination with atenolol and doxazosin, with consequent lowering of blood pressure values and significant reduction in the frequency of headache attacks.
Conclusions A secondary cause should always be suspected in those cases mimicking a TACs in which some atypical findings are observed. Pseudo-pheochromocytoma may be one of these unusual causes.

EPISODIC SUNCT SYNDROME ASSOCIATED WITH CEREBRAL MENINGIOMAS. CASE REPORT AND UPDATED REVIEW OF LITERATURE

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We report the case of an 85-year-old woman suffering from two cerebral meningiomas, located respectively in the falx cerebri (frontal lobe) and in the right ponto-cerebellar angle; she also presented severe dementia and a progressive impairment of walking and general conditions. Neurological examination did not show apparent focal deficit; she was confused and only partially collaborative. During her stay in the hospital she presented attacks of very severe pain in the right peri-orbital and maxillary region lasting 15–20 seconds, associated with ipsilateral conjunctival injection and profuse tearing, and recurring every 15–30 minutes. The pain could appear spontaneously but more frequently was triggered by touching the maxillar ipsilateral region. A supplement of the anamnestic data collected with the relatives revealed that the onset of pain was at the age of 81. The frequency of these episodes was irregular, with active periods lasting 2–3 months and treated with carbamazepine 200 mg b.i.d., alternated with remission periods of 2–3 months.
Neuroradiological investigations (cerebral CT scan with CE and MRI), apart the findings of cerebral atrophy and chronic vascular lesions, confirmed the presence of a 4 cm meningioma in the falx cerebri with an extensive oedema and an imposing mass effect on the frontal horns of lateral ventricles; another smaller meningioma was present in the right ponto-cerebellar angle.
Because of lack of efficacy of carbamazepine at the same dosage, we replaced it with lamotrigine 50 mg with disappearance of the symptoms within 4 days from the beginning of the therapy. The treatment was withdrawn after two months but its efficacy persisted for one month more until the death of the patient due to severe impairment of cardiac and general conditions.
This case may be diagnosed as SUNCT syndrome associated with an intracranial space-occupying process (first described case in association with meningiomas). Following this observation, we performed a literature review concerning SUNCT syndrome in association with other pathologies from 1991 to 2007. We found 22 papers reporting 23 cases (12 males, 11 females) associated with vascular and bone malformations, pituitary adenomas, traumas and other pathologies. Mean age at onset of headache was 40.61±18.60 years, while age at observation was 43.22±18.24 years. The concordance of the reported symptoms of each case with ICHD-II diagnostic criteria for SUNCT syndrome, and the features and locations of associated pathologies were fully evaluated.

A CASE OF SUNA-TRIGEMINAL NEURALGIA SYNDROME SECONDARY TO NEUROVASCULAR CONFLICT?

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Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) and trigeminal neuralgia (TN) are defined by diagnostic criteria in ICHD-II and in its Appendix [1]. SUNA is a rare primary headache syndrome, characterised by short-lasting attacks of unilateral pain that are accompanied by a spectrum of autonomic symptoms. Trigeminal neuralgia (TN) is a common unilateral disorder characterised by brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve; pain is commonly evoked by trivial stimuli including washing, shaving, smoking, talking and/or brushing teeth and frequently occurs spontaneously. To the best of our knowledge, in literature there are no case reports of concomitant SUNA syndrome and TN and of SUNA secondary to vascular loop [2].

We report the case of a 43-year-old female, suffering for 2 years of sporadic, recurrent attacks of TN pain localized in the first and second divisions of the trigeminal nerve, who came to our attention for a new paroxystic pain. She presented with attacks, started 20 days earlier, of severe, short-lasting (from seconds to 8-10 minutes) stabbing pain, localized in the upper teeth, in nose and orbital-temporal region, constantly on the right side, and associated in various combinations with ipsilateral conjunctival injection, tearing, redness of ipsilateral face, eyelid oedema, ptosis, nasal blockage and rhinorrhoea, with a mean of 20 attacks day. Some attacks were triggered by touching the face, talking, chewing and opening or closing both eyes. At admittance, general and neurological examinations were normal; complete blood count, ECG, chest X-rays and brain MRI with contrast were normal; angio-MRI showed the presence of a venous structure compressing the right trigeminal root in the "nerve entry zone". Initial treatment with carbamazepine was discontinued after a week because of the appearance of leucopoenia. We obtained good control of pain attacks with an association of 2400 mg of gabapentin and 75 mg of amitryptiline. At eight-month follow-up we found a persistent good control of attacks, which recur about once a month.

In conclusion, in our case a form of episodic SUNA coexists with trigeminal neuralgia in the presence of a vascular conflict, with a good response to medical treatment.

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SUNCT AND TRIGEMINAL NEURALGIA: THE DIFFICULTY OF A DIFFERENTIAL DIAGNOSIS (CASE REPORT)

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Introduction In the 2nd Edition of the ICHD Classification we find in chapter 3.3, SUNCT (Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing) and in chapter 13.1.1, Classical Trigeminal Neuralgia [1]. In some patients an overlap can occur between the two types of pain, making the differentiation and correct treatment difficult.

Case report A 61-year-old male was gender positive for unspecified headache disorder and a previous smoker. The patient was treated for arterial hypertension since the age of 55 with an association of delapril 30 mg and indapamide 2.5 mg/day. Since the age of 60 the patient referred periods of headache once a year, lasting from 10 to 15 days with 20 to 100 attacks/day, lasting from 1 to 10 seconds, strictly unilateral on the left side. Our observation revealed that pain started two months earlier. Pain was described as stabbing and excruciating, starting from the eye and spreading to the ipsilateral side of the nose and upper jaw, accompained by ipsilateral conjunctival injection, lacrimation and nasal obstruction. The pain was mostly provoked by eating or talking. Between crises the patient was completely symptom-free. Clinical and neurologic examinations were normal. Brain-MRI revealed few post-ischaemic areas bilaterally in the white matter. Angio-MRI of the brain, doppler study of the neck vessels and common blood tests were normal. Previous specialists diagnosed trigeminal neuralgia and prescribed different therapies with gabapentin 400 mg twice daily, carbamazepine 200 mg twice daily (stopped for diarrhea), cinnarizine 75 mg daily, pregabalin 75 mg twice daily, all without relief. Tramadol 50 mg oral and ketorolac 30 mg oral had no symptomatic effect. After our examination, we prescribed indomethacin 100 mg/day oral for seven days with no result. Oral verapamil at increasing doses up to 80 mg three times a day had no effect, so lamotrigine was started at 25 mg oral daily, increasing 25 mg/week to 100 mg daily with improvement of symptoms until the complete absence of crises 5 weeks after the beginning of therapy.

Conclusions The clinical features of our patient satisfy ICHD-II criteria for SUNCT, but some characteristics of trigeminal neuralgia are also present (triggering by chewing or talking, referred pain in upper jaw) with some difficulties regarding differential diagnosis (overlap between the two types of pain?). Remarkable is the response to prophylactic drugs: the inefficacy of carbamazepine and gabapentin makes the diagnosis of trigeminal neuralgia less probable.

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BAROTRAUMA AND TRIGEMINAL NEURALGIA: A CASE REPORT

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A 42-year-old woman had her first cranial nevralgia attack 4-months ago, following an airplane travel. All attacks had the same clinical characteristics. A severe stabbing pain suddenly developed in the left eye and nose wing during take-off. There were no accompanying symptoms of throbbing, lacrimation or conjunctival injection, blurry vision, nausea or vomiting. Attacks lasted few seconds and were elicited by local stimuli. She has no abnormality in her personal and familial history. Additionally, she has no other history of headache. Her neurological, ophthalmological and ear–nose–throat (ENT) examinations were normal. Routine blood analyses, cranial magnetic resonance (MR) and arterial and venous MR-angiography were normal. Paranasal sinus tomography showed a nasal septum deviation. Blink reflexes showed a significat delay on the left side. She was treated with oxacarbazepine 600mg/die with benefit.

In airplane headache, it has been claimed that barotrauma caused by pressure changes in the cabin during take-off could affect the ethmoidal nerves (branching from the ophthalmic branch of the trigeminal nerve) that carry the senses of the mucosa on the inner surface of the paranasal sinuses, and/or nociceptors in ethmoidal arteries, thereby activating the trigeminovascular system and leading to headache [1].

In this case, take-off seems to have elicited a "classical" trigeminal neuralgia, which does not disappear after landing, at a normal barometric pressure as occurs in airplane headache. It seems that the ethmoidal pressure change might have caused permanent damage in the ophthalmic branches of the trigeminal nerve as showed by the abnormal blink reflex. Blink reflexes have a high sensitivity and specificity in symptomatic trigeminal neuralgia [2]. The lack of any evidence demonstrating a neurovascular contact or other secondary causes, leads us to

conclude that barotraumas may be responsible for triggering trigeminal neuralgia which become permanent, therefore nolonger linked to barometric changes.

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NEUROPHYSIOLOGICAL ASPECTS AND NEUROIMAGING IN HEADACHES

REDUCED HABITUATION OF THE MMN AND P300 POTENTIALS IN CHILDREN WITH MIGRAINE AND TTH

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Introduction Our aim was to calculate the habituation of the auditory P300 and mismatch-negativity (MMN) responses in children with different types of headache and to compare it with healthy controls.

Materials and methods Eighteen migraineurs (mean age 10.2 years, range 7–14 years; 9 females, 9 males), eight children with tension-type headache (TTH) (mean age 11.5 years, range 8–16 years; 5 females, 3 males), and six healthy children (mean age 11.7 years, range 8–14 years; 4 females, 2 males) were recruited. To evaluate the evoked potential habituation, the P300 and MMN potentials were recorded to auditory stimuli in 3 successive trials, with an inter-trial interval of 5 minutes. **Results** No difference in both MMN latency and amplitude was found among the groups of subjects, while the P300 potential was lower in amplitude and slower in latency in both TTH and migraine patients, as compared to healthy controls. While in healthy children the MMN and P300 amplitudes showed a physiological habituation in the third trial, no MMN and P300 amplitude reduction was obtained in both migraine and TTH patients.

Discussion The abnormal P300 in children with headache might be related to a higher difficulty, as compared to healthy subjects, in keeping their attention focused on target stimuli. Moreover, the well-known phenomenon of the evoked potential reduced habituation cannot differentiate children with migraine from those with TTH.

Conclusions Our findings suggest that in the paediatric age, migraine and TTH are likely to represent a common disease.

CORRELATION BETWEEN REDUCED P300 HABITUATION AND BEHAVIOURAL DISORDERS IN CHILDREN WITH MIGRAINE

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Introduction Our aim was to assess the correlation between habituation of the auditory P300 and mismatch-negativity (MMN) responses in children with different types of headache and behaviour disorders.

Materials and methods Eighteen migraineurs (mean age 10.2 years, range 7–14 years; 9 females, 9 males), eight children with tension-type headache (TTH) (mean age 11.5 years, range 8-16 years; 5 females, 3 males), and six healthy children (mean age 11.7 years, range 8-14 years; 4 females, 2 males) were recruited. To evaluate the evoked potential habituation, the P300 and MMN potentials were recorded to auditory stimuli in 3 successive trials, with an inter-trial interval of 5 minutes. The behaviour of patients and healthy controls was assessed by means of the Child Behaviour Checklist (CBCL) administered to the mother.

Results No significant correlation was found between the MMN habituation and the CBCL scores in all groups. A significantly positive correlation was found between the reduced P300 habituation and the total CBCL score in migrainous children (p=0.01), but not in TTH patients and healthy subjects (p>0.05). In migraineurs, the reduced P300 habituation showed a significantly positive correlation with both the internalising (p=0.03) and the externalising (p=0.008) scores.

Discussion Our preliminary results suggest that in migrainous children the reduced P300 habituation may represent a neurophysiological marker of behavioural disorders, being higher in patients with worse externalising and internalising scores.

Conclusions To our knowledge, this is the first study showing in children with headache a correlation between neurophysiological and behavioural abnormalities.

REDUCED HABITUATION OF TRIGEMINAL REFLEXES IN PATIENTS WITH EPISODIC CLUSTER HEADACHE DURING CLUSTER PERIOD: A STRESS-LIKE STATE INDUCED BY HYPOTHALAMIC DYSFUNCTION?

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Introduction The aim of this study was to assess the trigeminal excitability in patients with both cluster headache (CH) and migraine evaluating the habituation phenomena of the R2 and R3 components of the blink reflex.

Methods Nineteen patients (2 females and 17 males; aged 24–67 years; mean age 33.8±9.4 years) suffering from episodic cluster headache (3.1.1, IHS, 2004) in a cluster period, 22 patients (14 females and 8 males; aged 23–58 years; mean age 35.5±10.0 years) with episodic migraine without aura (1.1, IHS, 2004) in interictal period and 20 healthy control subjects (15 females and 5 males; aged 23–49 years; mean age 31.02±6.6 years) were enrolled in the study. The blink reflex was elicited using a conventional configuration. R2 response habituation was assessed by delivering 3 blocks of 5 stimuli (1.3 Rth intensity) at different ISIs (frequencies 0.2 Hz, 0.3 Hz, 0.5 Hz, 0.7 Hz, 1 Hz) in random order. The mean size of the responses to the second and third block of stimuli, expressed as a percentage of the mean size of the first block responses, was taken as an index of habituation. For R3 response the habituation was assessed in series of 5 stimuli (1.3 Rth intensity) for longer sequences of stimulation at the longer intervals (15 and 30 s).

Results In patients with CH and migraine the BR habituation rate was abnormal. The R2 habituation rate was reduced at 0.3; 0.5; 0.7 and 1Hz (p<0.05) frequencies when compared with the controls. The R3 habituation was reduced at stimulation with longer intervals (15 and 30 sec) (p<0.05), compared with the control group. Patients with cluster headache revealed reduced R2 habituation at (1 Hz) intervals and R3 habituation at (15 and 30 sec) intervals compared with migraineurs (p<0.05).

Conclusions The main finding was the evidence of abnormal reduced habituation of R2 and R3 of the blink reflex in patients with cluster headache. Moreover, the habituation of R2 and particularly of R3 was significantly reduced not only versus healthy controls, but also versus migraineurs. The results suggested an abnormal activity of central trigeminal pathways mediating the reflex in cluster headache.

NOCICEPTIVE BLINK REFLEX AND CORTICAL TRIGEMINAL EVOKED POTENTIAL HABITUATIONS ARE CORRELATED IN MIGRAINE PATIENTS DURING THE INTERICTAL PHASE

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Background A positive correlation between visual evoked potential and nociceptive blink reflex (nBR) habituation deficit has been recently observed [1]. To better investigate the relationship between brainstem and cortical nociceptive responses we simultaneously recorded the nBR and the trigeminal nociceptive evoked potential (TNEP) in a group of migraine without aura patients (MO).
Materials and methods We recorded 9 healthy subjects (HS) and 14 MO patients between attacks according to the method described elsewhere [2]. Habituation of the brainstem and cortical nociceptive responses were defined as the percent change of the R2 response area-under-the-curve (AUC) for nBR and of the N-P amplitude for TNEP between the 1st and 2nd, and the 1st and 3rd block of five averaged responses, elicited by stimulating the right supraorbital region (Interstimulus intervals: 30 sec, Interblock intervals: 2 min).
Results No significant differences between HS and MO were observed in the sensory and pain thresholds, R2 nBR onset latency and AUC, N and P-wave TNEP latencies and amplitude in three successive blocks. We found a significant habituation deficit of the brainstem R2 nBR responses in migraineurs compared to HS (p=0.032 at the 2nd and p=0.033 at the 3rd block). As regards the cortical TNEP N-P amplitude, we found a progressive decrease of habituation in MO patients reaching statistical significance in the 3rd block (p=0.120 at the 2nd and p=0.05 at the 3rd block). A direct relationship was found between R2 nBR and N-P amplitude habituation deficit in MO patients (R=0.7, p<0.01).
Discussion We confirmed the presence of a lack of habituation of the R2 nBR responses in migraine patients interictally [1], furthermore we found the same deficit also in the cortical TNEP. In agreement with Ayzenberg [2] we found no differences between groups in nBR and TNEP absolute latency and amplitude values. Our results indicate that the processing of nociceptive impulses along the trigeminal pathways share the same habituation deficit, both at the brainstem and cortical levels.
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REDUCED CEREBELLAR INHIBITION IN MIGRAINE WITH AURA: A TRANSCRANIAL MAGNETIC STIMULATION (TMS) STUDY

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Introduction Evidence points to the involvement of cerebellum in migraine. Indeed, calcium channels are strongly expressed in cerebellar cortex and subtle clinical cerebellar alterations have been found in migraine with aura. Moreover, abnormalities in visual and motor cortex excitability consistent with a lack of inhibitory efficiency have been described in migraine and it is known that cerebellum exerts an inhibitory control on motor and non motor areas of cerebral cortex. The aim of the present study was to investigate if impairment of cerebellar activity on motor cortex, i.e., reduced inhibitory control, can be found in migraine.
Materials and methods Seven patients affected by migraine with aura and 8 healthy controls underwent an experimental protocol with transcranial magnetic stimulation (TMS) designed to investigate the cerebellar inhibitory drive on motor cortico-spinal pathways: a conditioning pulse on right cerebellar cortex was delivered 5, 7, 10, 15 msec before a test stimulus on contralateral motor cortex. The cerebellar conditioning stimulus inhibits the size of the motor evoked potential (MEP) produced by the test stimulus by approximately 30%–50%. Amplitude of conditioned (cerebellar stimulation) MEP is measured as a percentage of amplitude of MEP test alone.
Results Significant inhibition of motor cortex was induced by cerebellar stimulation, in healthy subjects (p<.01). On the contrary, no significant reduction of MEP test was found after cerebellum conditioning in migraine patients.
Discussion and conclusions Cerebellar inhibition is reduced in migraineurs; this could account for the reduced inhibitory efficiency of cerebral cortex showed in previous studies, suggesting a pathophysiological role of cerebellum in migraine.

BRAIN HYPEREXCITABILITY CAN BE REVERSED BY TOPIRAMATE IN CHILDREN WITH MIGRAINE

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Introduction We previously showed that in children with migraine the somatosensory system is hyperexcitable, as demonstrated by a shortened somatosensory evoked potential (SEP) recovery cycle [1]. In the present study, our aim was to evaluate the effect of topiramate treatment on headache clinical parameters and on somatosensory hyperexcitability.
Materials and methods Eleven children (mean age 11.5 years, range 8-15 years; 8 females, 3 males) were recruited. Somatosensory system excitability was assessed by calculating the SEP changes after paired electrical stimuli at 5 ms, 20 ms and 40 ms interstimulus intervals (ISIs), as compared with a single stimulus condition assumed as baseline. Brain excitability was measured before the therapy and after a 3-month treatment with topiramate at the average dose of 1.3 mg/kg/day.
Results In 9 patients who had a significant reduction in headache frequency (>50%) with topiramate use, the recovery cycles of the parietal P24 and the frontal N30 potentials were slowed (two-way ANOVA, p<0.05). On the contrary, in 2 migraineurs who did not show any improvement, the recovery cycles of the cortical SEP components were even shortened after pharmacological treatment.
Discussion Our results showed that topiramate can reduce the somatosensory cortex excitability in children with migraine only when it is effective on the clinical parameters.
Conclusions Our findings suggest that brain hyperexcitability in paediatric migraine is strictly related to pain attack frequency.
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A LASER EVOKED POTENTIAL STUDY IN PATIENTS WITH "PROBABLE MEDICATION OVERUSE HEADACHE"

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Objectives The physiopathology of "Medication-Overuse Headache" (MOH) is complex and includes central sensitization from repetitive activation of nociceptive pathways. Our aim was to assess the habituation to experimental pain in patients with "Probable MOH", before and after a detoxification scheme, by recording the scalp potentials evoked by CO_2 laser stimulation (laser evoked potentials – LEPs).
Methods We studied 5 patients affected by "Probable MOH" +

"Chronic Migraine" before and after a detoxification scheme (a corticosteroid course as a transitional support during acute medication withdrawal followed by 3-6 months of prophylactic treatment). LEPs were recorded to stimulation of both the right hand and the right periorbital region. The habituation of the negative-positive complex at the vertex (N2/P2) was assessed by measuring the LEP amplitude changes across three consecutive repetitions of 30 trials each.
Results In three patients with clinical improvement, LEP habituation, lacking before the treatment, was recovered after MOH had resolved. On the contrary, in the two patients who still had chronic daily headache and were still overusing acute medication at follow-up, LEPs still showed reduced habituation.
Conclusions The lack of habituation to repetitive stimuli is thought to be due to an abnormal excitability of the cortical areas devoted to pain processing. The LEP habituation recovery after successful withdrawal of acute medication and reduction of headache frequency is a probable indicator of normalization in the pain-processing mechanisms and of a "desensitization" of central nociceptive pathways.

"RED FLAGS" AND NEUROIMAGING IN PAEDIATRIC HEADACHES: PRELIMINARY RESULTS

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Introduction Headache is a common presenting complaint to the paediatric department, and although the majority of headaches are benign and self-limited, it can be the initial symptom of life-threatening disorders such as meningitis, brain tumours, cerebral vascular diseases or other dangerous illnesses. Most patients with intracranial pathology have clinical features that would raise a "red flag". There are several "red flags" in the patient's clinical history and general or neurological examinations that may provoke more attention and lead to several important diagnostic tests. "Red flags" could act as screening tools to help in identifying those patients presenting with headache who would benefit from the use of neuroimaging.
The aim of this study was to evaluate if the use of red flags in paediatric headaches may help as screening tools in selecting patients to undergo neuroimaging examination.
Methods Every child between 2 and 18 years of age who, after 1 April 2006, was admitted to our Unit because of headache and had one or more 39 defined "red flags", was included in this study [1]. Every child received one or more neuroimaging tests (CT, MRI, Angio-MRI) chosen by defined clinical criteria. The outcomes were defined as positive if abnormal radiological findings were found. We also examined if the abnormal radiological findings significantly changed the therapy or diagnosis of headache or was only incidental.
Results The selected population was included in the period between 1 April 2006 and 31 January 2007. A total of 35 children (14 males and 21 females) met the inclusion criteria. The mean age was 9.4±4.8 years (range 3 to 16 years). The more reported "red flags" were: daily headache <3 months, atypical aura and nocturnal headache. The neuroimaging tests (13 CT, 24 MRI, 5 Angio-MRI) were positive in 13 cases (37.15%). In 4 cases (11.42%) the abnormal findings led to a change in therapy or diagnosis (3 of sinusitis and 1 Arnold-Chiari type 1 with initial bulbar compression).
Discussion Our preliminary results show that paediatric headaches are usually benign, and even though "red flags" were used as screening tools, the significant abnormal radiological findings in paediatric headaches are few and rarely help to modify therapy. However, further study on a larger population is mandatory to better understand the utility of "red flags" and to identify the significant red flags.
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MIGRAINE WITHOUT AURA AND REVERSIBLE IMAGING ABNORMALITIES

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An 18-year-old man with a history of migraine without aura and normal physical and neurological examinations underwent a CT scan during a typical headache. CT scan demonstrated a left temporal-parietal-occipital hypodensity, and cerebral MRI, obtained five days later, showed no abnormalities.
Transient abnormalities on brain images have been reported in a few cases in basilar migraine.
The pathogenesis of migraine without aura remains unresolved. Three studies point to the possibility of a clinically silent cortical spreading depression (CSD) in migraine without aura. Based on this evidence, one might speculate that CSD leads to disruption of the blood-brain barrier by hypoperfusion-induced necrosis or hyperperfusion-induced pressure diapedesis at the arteriolar level in vulnerable regions. The relatively sparse sympathetic innervation of the vertebrobasilar circulation makes the cerebral areas of the posterior circulation most vulnerable. In contrast to persistent deep white matter lesions induced by hypoperfusion, hyperperfusion induces transient lesions due to the leakage of fluid into the interstitium and vasogenic edema.

f-MRI TIME AND SPACE SPREADING SENSIBLE POST-ANALYSIS OF THE VISUAL CORTEX IN MIGRAINE WITH AURA

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Introduction Functional Magnetic Resonance Imaging (fMRI) is applied to the study of the neuropathological mechanisms underlying migraine, still under debate in literature. The technique, being sensible to the blood oxygen level dependent (BOLD) signal, constitutes a straight link between the clinical assessment and the functional activation pattern. A time and space non-local analysis procedure, sensible to the spread of the activations during the functional exercise, is applied.
Materials and methods Nine patients suffering from migraine with aura (MA), seven without aura (MO) and six healthy volunteers (C), matching in age- and sex, underwent two 12 minutes long block designed fMRI scans (Philips Intera 1.5 T Gyroscan) using a flashing checkerboard visual stimulus. The functional activation pattern was analysed looking both for coherent activations and deactivations along the extended period of time (24 minutes), differences between the two scans, both intra- and inter-groups.
Results No patient developed a migraine attack during the fMRI scan. The introduction of time and space derivatives in the analysis highlighted a significantly different activation pattern between patients and C and, moreover, between MA and MO. In particular, MA and MO patients experienced a growing occipital excitability in spite of habituation, MA patients with a stronger spatial deactivation and a significant inter-subject delocalization.
Conclusions In conclusion, the application of a dynamic analysis procedure enhances the sensitivity of the analysis to differences in the physiological response to the visual stimulus in time and location and may open a future prospective in the study of the aura patho-physiology.
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f-MRI STUDY IN CHRONIC CLUSTER HEADACHE

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Introduction Until recently, primary headaches, such as migraine and cluster headache (CH), were described as vasomotor headaches. However, the great availability of neuroimaging techniques and clinical studies suggests that activation of central cerebral structures is mainly responsible for the onset of pain [1]. The obvious circadian rhythm of cluster headaches has favoured the hypothesis of a central origin. PET and f-MRI may be regarded as of little or no importance in a clinical context, but they introduce a great potential for the exploration of headache pathophysiology and the effects of pharmacological treatment [2]. To identify the cerebral activation area during an attack of chronic cluster headache we used f-MRI methodology.
Materials and methods We enrolled one male patient (45 years) suffering from chronic cluster headache (code 3.1.2 ICHD-II classification). The patient underwent an MRI recording that took place in one session with a mean duration of 180 min. In that period the recording previewed the anatomical and related functional data acquisition, at the asymptomatic stage, during the attack and after the administration of sumatriptan sucinate. MRI images were recorded with a scanner with a static 1.5 T magnetic field. The anatomical images were acquired with 3D sequences MP-RAGE and the functional data with EPI sequences. The data were converted into an activation map using the General Linear Model study. The statistical significance threshold was computed for $p<.05$ after Bonferroni adjustment.
Results We registered three attacks in the same recording session. After attack onset, at a 10 min interval, we administered sumatripan succinate s.c. Data analysis showed the presence of asymmetrical cerebral activation only in the hypothalamic region ipsilaterally to the pain.
Discussion and conclusions This study documents activation of the hypothalamic region homolaterally to the pain centre, as documented in previous functional studies realised with PET methodology. Until now, f-MRI has been used in the study of patients affected by SUNCT, but we have not noted any studies using this methodology on CH. Thus PET, like f-MRI, now amongst the most refined techniques for the in vivo visualisation of neuronal activity changes, has supplied relevant, clear information on the examined area from the source of CH attacks. If future studies confirm that its origin should be sought for in the central nervous system, we will obtain a better understanding of when and how to orient acute and preventive therapy.
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MAIN COMORBIDITIES AND COMPLICATIONS

PREVALENCE AND SIZE OF PATENT FORAMEN OVALE IN MIGRAINE WITH AND WITHOUT AURA AND CLUSTER HEADACHE AND RELATION WITH CLINICAL PHENOTYPE

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Background and objective To test the hypothesis that the link between cardiac interatrial patent foramen ovale (PFO) and migraine (both with and without aura; MA+/MA-) or cluster headache (CH) as well as migraine clinical phenotype are dependent on the size of the shunt.
Patients and methods Contrast enhanced transcranial Doppler examination with monitoring of the middle cerebral artery (MCA) was performed in a group of 260 consecutive patients with MA+, 74 with MA-, and 38 with CH, both at rest and after Valsalva maneuver. The size of the shunt was classified as small, medium or large, based on the number of spikes detected on MCA according to standard criteria.
Results Prevalence and size of PFO in each group were the following: 161 MA+ (61.9%), of which 86 (53.4%) small, 45 (27.9%) medium, 30 (18.7%) large; 12 MA- (16.2%), of which 8 (66.6%) small, 3 (25.0%) medium and 1 (8.4%) large; and 14 CH (36.8%), of which 11 (78.6%) small, 2 (14.2%) medium, and 1 (7.2%) large. There was no significant association of clinical variables (prevalence of autonomic symptoms, intensity and frequency of pain, frequency of aura and its clinical presentation) with presence and size of PFO in each subgroup.
Conclusions Our findings confirm the relation between PFO and MA+, but do not support the hypothesis of a pathogenic link between presence and size of PFO and MA+, given that the clinical phenotype of the disease is independent of such an association.

MIGRAINE AND ISCHAEMIC STROKE IN YOUNG PEOPLE: A NESTED CASE-CONTROL STUDY

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Objective To investigate the association between acute cerebral infarction in young people and history of migraine in a nested case-control study.
Patients and methods We conducted a prospective study on patients aged 16 to 44 years, who were consecutively admitted to our Unit from January 2000 to June 2006 because of a first-ever CT/MRI defined acute ischaemic stroke. Age- (±1 year) and gender-matched subjects, selected among partners or relatives of non-vascular and non-migrainous outpatients, were included as controls.
For both stroke and control subjects, treatment history for hypertension and/or diabetes mellitus, current smoking and alcohol habits, current use of the estro-progestinic pill, and history of typical migraine defined according to the criteria of the International Headache Society were recorded. Data were matched with univariate analyses. Thereafter, when indicated, significant results were entered into a logistic regression model to identify those data independently associated with stroke.
Results Two hundred ninety-six stroke patients and an equal number of control subjects were included. Both groups consisted of 153 women and 143 men, mean age 35 years. A history of migraine was found in 104 subjects (17.5%). Of these, 71 subjects (24.0%) were in the stroke group and 33 (11%) in the control group, with no statistically significant differences between groups ($p<0.0001$). However, when analyses were separated by sex, differences remained significant only in women. Precisely, 54 women had migraine in the stroke group (35%) *vs.* 21 in the control group (14%) ($p=0.0001$), whereas 17 men had migraine in the stroke group (12%) *vs.* 12 in the control group (8%) ($p=0.4333$). Logistic regression analysis for variables independently associated with ischaemic stroke in women selected migraine together with history of hypertension, smoking and current use of the estro-progestinic pill.
Conclusions In people aged 16 to 44 years, migraine appears to be associated with cerebral infarction only in women. The role of migraine seems to be independent of hypertension, smoking and use of the contraceptive pill.

MIGRAINE PROGNOSIS IN PATIENTS WITH PATENT FORAMEN OVALE TREATED WITH LOW DOSE OF ASPIRIN

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Patent foramen ovale (PFO), has been associated to migraine with aura [1], because of its high frequency in migraineurs with aura in respect to the general population and migraineurs without aura, and because migraine characteristics do change after PFO closure and its prognosis does seem to improve.

Aim of the study Considering that PFO is thought to be a risk factor for juvenile stroke, and for this reason these patients use antiplatelet drugs as chronic preventive treatment, and considering the fact that PFO closure mainly improves headache in patients suffering from it, we studied the prognosis of migraine with aura in patients with PFO that we treated with low doses of aspirin, in a prospective controlled observational study.

Patients and methods We recruited all the consecutive patients seen at the headache centre of our Hospital, along a 1-year period, affected by migraine with aura, according to the ICHD-2 classification for headache.

Each patient was visited by a neurologist specialized in headache disorders. All of them underwent: 1. a general blood, and hormonal screening, and screening for coagulation disorders; 2. echo-doppler of neck arteries; 3. MRI complete with intracranial arteries ANGIO MRI; 4. trans-thoracic echocardiography with contrast plus trans-cranial doppler, to look for PFO. Commonly used contrast was agitated with hemagel or saline solution. Migraine severity was expressed by a headache severity index calculated on numbers of day of headache and severity of each day expressed on a scale from 0 to 3 (0 no headache; 1 mild headache; 2 moderate headache, not disabling but requiring drug treatment; 3 severe).

Results We report the results referring only to patients screened for PFO and treated with antiplatelet drugs if PFO was detected.

Over a 1-year period we recruited 50 patients with migraine with aura. One was lost at follow-up, 2 patients have not yet undergone echocardiography, 5 patients refused the test.

Forty-two patients (8 men, 34 women) underwent all the diagnostic procedures. We found PFO in 24 patients (57%), 3 men and 21 women. Patients with PFO were slightly younger (mean 36 years vs 44 years of the other group), had a headache onset at a similar age compared to the group of patients without PFO (16 *vs.* 20), and also a similir index of headache severity at recruitment (21 *vs.* 25).

Patients with PFO were treated with low dose of aspirin (100 mg daily), only 2 patients used ticlopidine 250 mg daily. All of the patients showed an important improvement, only one patient needed to use topiramate as adjunctive therapy. The overall index of headache severity decreased to 6. The group of patients without PFO was treated with standard therapy for migraine prophylaxis and their headache severity index similarly decreased to 6.

Conclusions Considering the benefit of antiplatelet therapy on migraine with aura, we believe that performing trans-echocardiography with contrast can become a useful standard procedure in patients suffering from migraine with aura. This procedure is well tolerated by the patients and can give important information for the treatment of migraine, but also for the prevention of PFO complications such as stroke [2].

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PERSONALITY AND MOOD DISORDERS IN EPISODIC CLUSTER HEADACHE

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Several studies have demonstrated a comorbidity of psychiatric disorders and cluster headache (CH). A higher prevalence of anxiety [1], hysteria and neuroticism has been reported; some Authors also suggest that these patients are more likely to develop depressive symptoms. In this regard, Hsieh and colleagues found a specific activation of brain structures involved in the affective and cognitive processes, such as the hypothalamus and the anterior cingulate cortex; the importance of hypothalamic function is also emphasized by May et al. who demonstrated that CNS dysfunction in the region of the hypothalamus plays a crucial role in the pathophysiology of CH. In particular, this structure is intriguing for the typical clinical cyclical course of the CH. There is also evidence of an involvement of the central serotonergic system in the pathogenesis of CH. Serotoninergic system plays a central role in the modulation of pain threshold and vascular reactivity. D'Andrea et al. [2] suggest that CH is characterized by an increase of plasma 5–HT metabolism; Afra et al. demonstrated a diminished serotonergic activity in raphe-hypothalamic serotonergic pathways using intensity dependence of auditory evoked potentials (IDAP) as a marker of central 5-HT activity. As a matter of fact, CH patients have a cyclic disorder involving brain structures and neurotransmitter pathways associated with affective and personality disorders. With this in view, we are performing a case-control study aimed to investigate personality traits and mood disorders in CH patients. The study protocol plans to recruit 30 patients with CH, according to the ICHD-II criteria, excluding those with other primary headaches or family history of mood and personality disorders, and 60 healthy matched controls. All patients will undergo neurological examination, brain neuroimaging (CT or MR), routine blood test and thyroid function, neuropsychological and psychiatric evaluation (including a structured interview, MMPI, MCMI, SCID-II, VRS, TPQ, TAS 20, BDI, STAI, BDHI). Central serotonergic neurotransmission is assed by using the intensity dependence of auditory evoked potentials (IDAP). To date, 17 patients and 30 controls have been studied. Preliminary results do not seem to show significant differences between CH patients and controls.

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PREVALENCE OF PRIMARY HEADACHES IN EPILEPTIC PATIENTS: PRELIMINARY DATA FROM A CLINICAL STUDY

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Introduction Epilepsy and migraine are two distinct neurological conditions with a possible common pathological mechanism in relation with cortical hyperexcitability. In previous studies, the prevalence of migraine in epileptic populations ranges from 8% to 24% [1]; it has been found that migraine has a negative effect on the prognosis of epilepsy [2].
Materials and methods We conducted a clinical study on a consecutive series of patients referred to our Epileptic Centre with the aim to identify the prevalence of primary headaches. Epileptic syndromes were classified according to the Classification of Epilepsies and Epileptic Syndromes proposed by ILAE (1989). The diagnosis of primary headaches was made according to ICHD-II criteria.
Results We recruited 94 patients (51 females, 43 males; age 48+18 years, ranged from 16 to 85 years) with diagnosis of epilepsy. Of these patients, we found 50 (53.2%) with cryptogenetic focal epilepsy (CFE), 26 (27.6%) with symptomatic focal epilepsy (SFE), 16 (17.1%) with idiopathic generalized epilepsy (IGE), 1 undetermined whether focal or generalized, and 1 with diagnosis of migraine-triggered seizures (in the past referred to as "migralepsy"). In this population, we identified 40 (42.6%) patients with primary headaches: 16 (17.1%) with migraine (13 females, 3 males, age 48±19 years), of whom 14 without aura (MO), 1 with aura (MA), 1 with migraine-triggered seizures; 22 (23,4%) with tension-type headache (9 females, 13 males, age 44±16 years), of whom 21 episodic (ETTH), 1 chronic (CTTH); 1 primary stabbing headache, and 1 new daily-persistent headache. In relation to the diagnosis of epilepsy, in the CFE group we found 7 MO (14%), 1 MA (2%), 13 ETTH (26%), and 1 primary stabbing headache (2%); in the SFE group 4 MO (15.3%), 4 ETTH (15.3%), 1 CTTH (3.8%), 1 new daily-persistent headache (3.8%); in the IGE group 3 MO (18.8%), and 3 ETTH (18.8%).
Discussion and conclusions The literature to date has given conflicting data concerning the association of epilepsy and migraine, but most of the previously published studies were done before the ICHD-II or the diagnosis does not fullfil its criteria; moreover, previous studies do not consider the prevalence of different primary headaches. Our preliminary study, at the present limited by the small number of cases and relative to the patients referred to an epilepsy centre, shows a prevalence of migraine higher than in the general population; moreover, our results seem to indicate that the association between migraine and epilepsy is similar for CFE, SFE, IGE.
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COMORBIDITY HEADACHE - EPILEPSY: COGNITIVE AND ELETTROENCEPHALOGRAPHIC EVALUATION

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Introduction Several studies show memory deficit in adults suffering from migraine. Data concerning children are few and recent. Conflicting data on cognitive defects in migraine could be explained by differences in the clinical variables of the samples studied. The memory defects, both on visuo-spatial and verbal cognitive tasks are attributed to impaired recall mechanisms, or may be related to strategically and organizationally defective aspects of learning. Also, performance in patients with right-sided pain seems to support a right hemisphere dysfunction hypothesis. However, in children the findings are few and controversial.
Materials and methods In this study we carried out an investigation on 80 randomly selected patients with headache, aged 8-16 years: 20 suffering from migraine with aura, 20 from migraine without aura, and 20 from tension-type headache according to the International Headache Society criteria, ICHD-II, 2004. They underwent a comprehensive battery of neuropsychological tests: Rey complex figure (1959), WISCH- R (1986), TEMA test (1997), and were grouped according to EEG characteristics. Patients were compared on the basis of EEG anomalies.
Results Migraineurs with and without aura did not show significant differences in verbal and visual memory, with no differences between migraine groups. The Rey test was <25° on 20% of migraineurs with aura and 30% in migraineurs without aura. The memory defects, both on visuo-spatial and on verbal cognitive tasks, were present in children with centrotemporal and occipital Spikes.
Conclusions In this study EEG anomalies are the factor conditioning the different behaviour of cognitive tests in children with migraine and tension-type headache.

OLFACTORY HALLUCINATIONS AND MIGRAINE

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Introduction Olfactory epileptic auras, consisting in a sudden unexplained sensation of smell, are well recognized. Olfactory hallucinations (OHs) have also been rarely described as a migraine aura, in some instances combined with visual or sensitive aura. In literature, nineteen descriptions of this clinical condition have been reported. We present a case of OHs in a migraine patient, with a review of the literature.
Case history A 34-year-old man reported a 25-year history of migraine without aura (MO). At the age of 33 he started to experience, just before some migraine attacks, OHs described as nauseating, gas-like odour lasting less than two minutes. During OHs he also experienced cognitive-dysmnestic phenomena, in particular he was "unable to remember his schedule". In one year he presented six of these attacks. In addition, he reported one attack per month of MO. After about one year, during a migraine attack preceded by OHs, he had an episode of loss of consciousness, lasting about two minutes. Afterwards, he presented confusion and subsequent amnesia for about two hours. Admitted to the ED, he underwent cerebral CT and MRI with gadolinium, which were both normal. The EEG showed aspecific alterations. In the following five months, he presented about twelve migraine attacks, four of which with OHs. In the last one, which occurred about a month ago, migraine was already present at the moment of awakening, and became severe at lunch time, when the patient experienced repeated OHs for a few minutes. In the early afternoon, withstanding his headache, he was found by his wife staring, presenting an absence and masticatory automatisms, lasting a few seconds, followed by deep sleep and retrograde amnesia. At dinner time (headache was still present) he had a generalized tonic-clonic seizure lasting a few minutes. After an hour, at the ED, he presented again an episode of loss of consciousness with tonic contraction of upper limbs and jaw. During the night the headache continued and he had four episodes of absence with staring and masticatory automatisms. The EEG confirmed the previous findings. Brought to our attention a therapy with valproic acid 300 mg bid was started and, so far, he is asymptomatic with reference to headache, OHs, temporal and generalized seizures.
Discussion The literature review has identified nineteen cases of OHs associated with migraine attacks, mostly unpleasant odours, lasting from a few minutes to 24 hours. When performed, cerebral CT and EEG were normal. The limited number of described cases were not submitted to MRI [1, 2], useful to detect temporal lobe lesions or mesial sclerosis, which were absent in our peculiar case of "migralepsy".
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FIBROMYALGIA COMORBIDITY IN PRIMARY HEADACHES

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Aims To test the frequency of fibromyalgia and its influence on clinical outcome in a cohort of primary headache outpatients, compared with a population of healthy non-headache suffering subjects.
Methods Two hundreds consecutive primary headache outpatients were enrolled at the Headache Centre of our Department. The frequency of fibromyalgia was evaluated [1], and compared with 200 age- and sex-matched non headache suffering healthy subjects. In addition, in all patients Total Tenderness score (TTS), anxiety and depression scales (SAS and SDS by Zung), MIDAS score, allodynia questionnaire, Short Form 36 Health Survey (SF36), MOS (Medical Outcomes Study-Sleep Scale) and MAF (Multidimensional Assessment of Fatigue) were evaluated.
Results Forty-two per cent of headache patients presented fibromyalgic symptoms, in respect with 5.5% of non headache people (chi square test: $p<0.001$). The tension-type headache prevailed in patients with concomitant fibromyalgia, in respect with migraine and other forms of primary headaches (chi square test $p<0.01$). The TTS and allodynia were more severe in patients with fibromyalgia, while the MIDAS, SAS and SDS scores were similar across headache patients.
Conclusions Primary headache is a risk factor for fibromyalgia, which prevails in patients with tension-type headache in respect with migraine patients. Fibromyalgia is not associated with a more severe outcome of headache, though its comorbidity influences higher levels of pericranial muscular tenderness in both tension-type headache and migraine patients and allodynia in migraine patients.
Primary headaches and fibromyalgia may share a common disorder of pain modulation system.
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HEREDITARY HEMOCHROMATOSIS (HFE) DIAGNOSTIC PROTOCOL IN THE STUDY OF PRIMARY HEADACHES

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Background Hereditary Hemochromatosis (HFE), a common hereditary disease in the Caucasian population, is characterised by progressive tissue iron overload which leads to irreversible organ damage. Recent developments have radically improved the understanding of the physiopathology and diagnosis of this disease in particular genetic testing for the C282Y mutation of the HFE gene. However, transferrin saturation and serum ferritin are still the most reliable tests for identifying subjects with HFE. Recent studies have suggested that iron metabolism may be involved in the pathogenesis of migraine, in particular iron overload may alter neuronal excitability and thereby lower the threshold for triggering headache.
Objective The aims of this study are: to evaluate the HFE frequency in a primary headache population with definite clinical criteria and features; and to look for a simple diagnostic protocol to study primary headache suspected of HFE.
Methods We observed 100 patients with primary headache according to ICHD-II criteria, and selected subjects according to these methods: A) diagnosis of headache disorders for more than five years; B) high frequency of attacks, evaluated with migraine diary compilation; C) moderate-severe intensity of the attacks (in accordance to the Tfelt-Hansen scale); and D) index of disability of 3-4 (in accordance to the MIDAS scale). Each subject underwent laboratory analysis, biochemical iron parameters, and neuroradiological investigation (RM/TC brain). Patients with secondary headaches and subjects with overload of ferritin in presence of normal transferrin saturation (expression of secondary form) were excluded. The remaining subjects (16/100) were investigated for the three principal HFE mutations. DNA was extracted from PBMC using the automated MagnaPure system (Roche), amplified using the Mutagel HFE kit (ListarFish) and analysed by elettrophoresis.
Results Patients selected (2 males, 14 females; mean age: 35.8 years, range: 28–56) had diagnosis of: migraine without aura with episodic tension-type headache in 9/16, migraine without aura in 5/16, tension-type headache in 1/16, and migraine with aura in 1/16. The frequency of attacks is 9 per month. In 3/16 subjects iron indexes confirmed iron overload (1 transferrin saturation and 2 serum iron). The mutation C282Y was present in homozygous state in 1/16 and in heterozygous state in 1/16 subjects. One presented the genotype H63D/H63D and two were heterozygous for S65C.
Discussion Our data support the hypothesis that mutation of the HFE gene is not directly responsible for the neurological pathology such as headache, but has to be taken into account for patients with suggestive anamnestic and diagnostic parameters.
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THERAPEUTIC STRATEGIES I

LOW TRIPTAN USE IN THE ITALIAN POPULATION

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Introduction Studies performed in migraine patients show that the percentage of triptan use varies with the countries. Few studies on triptan use in the general population have been performed. This study was aimed at establishing the pattern of triptan use in a large sample of the Italian population.
Materials and methods The patterns of triptan prescriptions dispensed during 2006 in the population of 33 Italian Health Authorities were investigated. In one of these Authorities an accurate analysis was performed on the prescriptions from 2005.
Results Of a total of 5 549 731 residents, subjects receiving triptan treatment were 32 584 (0.6% of the population), 22.3% males and 77.7% females. Males and females aged 15–44 years received 51.4% of total prescriptions, those aged 45-65 received 38.7% of prescriptions, and patients over 65 years received 7.8% of prescriptions. The total number of triptan packages prescribed was 312 337. The percentage of triptans prescribed was: rizatriptan 26%, sumatriptan 20.1%, almotriptan 17.3%, zolmitriptan 13.9%, eletriptan 12.6%, and frovatriptan 10%. The DDD/1000 inhabitants/day were: 0.004 (0–14 years), 0.813 (15–44 years), 1.324 (45–64 years), 0.446 (65–74 years), 0.216 (75–84 years), and 0.122 (>85 years).
The outcome of an analysis performed on the prescriptions from 2005, in one of the Italian Health Authorities with a resident population of 224 065, showed that the percentage of triptan use was 0.55% of the population, and that the age- and sex-distributions were also the same as those from the 2006 study. Oral and soluble tablets accounted for 94% of prescriptions. In 57.7% of triptan users only 1–2 packages were prescribed. We identified 3.2% of triptan users who received more than

120 dosage units in tablet form during the year (potential triptan abusers), while 5.7% of patients received 40% of packages.
Discussion and conclusions This was a large study on triptan use involving about one-tenth of the Italian population. Considering that migraine prevalence in Italy is about 12%, our study showed a very low triptan use: only 5% of migraine patients were treated with triptans. Moreover, about 60% of triptan users received only 1-2 packages in one year. Further study is needed to explain why a small percentage of migraine patients use triptans and, when they do, why in such small amounts.

THE USE OF VITEX – AGNUS CASTUS IN MIGRAINOUS WOMEN WITH PREMENSTRUAL SYNDROME

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Objectives The association between migraine and menstruation is well known; moreover, headache is considered to be part of the premenstrual syndrome (PMS). A number of treatments were proposed for PMS, also with herbal medicines, including vitex, derived from agnus castus (verbenae), which was reported to be very effective on PMS. We assessed the influence of a prolonged vitex treatment on headache frequency and duration in migrainous women with PMS.
Methods Seventy-two women were enrolled in the study. Headache information regarding the previous three months was obtained with the use of a diary. The mean number of monthly headache attacks was 4.23 (±1.77); the mean number of headache days/month was 7.55 (±4). Each subject received an in-label treatment for PMS and/or dysmenorrhoea with vitex (40 mg/day) for three months.
Results Sixty-eight patients completed the 3-month treatment period. Data from the last month, obtained from the diary, were compared with pre-treatment data. A reduction >50% of headache attacks was recorded by 26 women (38.2%), and a reduction >50% of headache days/month by 36 women (52.9%). Patients with a null, or worsening effect on headache were 13 (19.1%). No major side effects were noted. After treatment, the mean number of headache attacks/month was 2.83 (±1.78, p=1.6*10^{-9}); the mean number of headache days/month was 4 (±2.72, p=1.5*10^{-13}). A reduction in headache was observed in both menstrual and non-menstrual attacks.
Conclusions Vitex appears to be effective as headache treatment in women with PMS. The effectiveness could be due to the biological action of vitex, that is, as a dopaminergic, estrogenic, and opiatergic agonist. Placebo-controlled trials on larger numbers of patients are necessary to confirm our findings.

NEW ASPIRIN FORMULATION IN ACUTE CONTROL OF TENSION-TYPE HEADACHE

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Acetylsalicylic acid (ASA, Aspirin) is among the most used drugs worldwide. At present, Aspirin represents a quite versatile drug employed in the control of pain sympthomatologies and in situations such as prevention of both ischaemic stroke and cardiovascular events. Aspirin causes inhibition of prostaglandin (PG) synthesis by inactivation of the cyclooxygenase (COX) enzyme. ASA constitutes the focus of new developments explaining more widely Aspirin's control of inflammation. The induction of lipoxins endogenous epimers (Aspirin-triggered 15-epi-lipoxins, ATLs) represents one of the most recent achievements. This particular feature of Aspirin is not shared by other NSAIDs.
ASA is well-known as a headache medication, figuring as a possible treatment choice in tension-type headache but also in acute migraine attacks. Furthermore, a new aspirin formulation with a greater rapidity of action has been introduced.
In conclusion, little information exists on the subject and more studies are required.
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EFFECT OF A COGNITIVE AND PHYSICAL PROGRAM ON MIGRAINE AND TENSION-TYPE HEADACHE WITH OR WITHOUT CERVICAL PAIN AND PSYCHIATRIC COMORBIDITY: A LONGITUDINAL CONTROLLED STUDY

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Objectives This study was aimed at examining the effects of a cognitive and exercise program on migraine (M) and tension-type headache (TTH) in subjects with or without cervical pain and psychiatric comorbidity.
Methods Three hundred forty-four employees of the city of Turin were divided into two groups: study group (n=169) and control group (n=175). After history, psychological assessment with a structured interview and clinical examination were completed, the following diagnoses were made: M (n=53 and 58 in the study and control groups, respectively), TTH (33.52), M + TTH (51.44). Cervical pain was also present in 94 and 118 subjects, and psychiatric comorbidity (depression and/or GAD) in 44 and 49 subjects, respectively, in the study and control groups. All participants were given a diary to record daily from March 2005 (month 1) to October 2007 (month 8) frequency and severity of the headache episodes. At month 3, a program of instructions of how to relax and reduce muscle contraction and how to perform simple shoulder and neck exercises was administered to the study group. For each subject, the difference (Delta) in the frequency of headache episodes between months 7-8 and baseline (months 1–2) was calculated; the Deltas between the three headache categories (M, TTH, M+TTH) of the study group and those of the control group were compared using ANCOVA, adjusted for age, gender and baseline values. Differences between the two groups were also assessed accounting for the presence or absence of cervical pain and psychiatric comorbidity.
Results A significant improvement was found in all three headache categories of the study group with respect to those of the control group. Mean treatment effect (headache frequency of last two months vs baseline) was for: M, -2.99 days (95% CI -4.71 to -1.26); TTH, -2.56 (-4.63 to -0.49); M+TTH, -3.67 (-6.23 to -1.11). The data were improved if cervical pain or psychiatric disorders were present as comorbid factors. Mean treatment effect in the study group was - 3.76 (-5.20 to -2.32) if cervical pain was present and -6.46 (-8.89 to -4.03) if depression or anxiety were present.
Conclusions The applied program significantly decreases the frequency of different headache types in a working community. The considerable improvement found in subjects with comorbid cervical pain confirms that this may be a relevant pathogenic factor in TTH and M. The high response of subjects with anxiety or depression may be explained by the relevant cognitive component of the program.

WHEN CARE OF HEADACHE PATIENTS BECOMES A CHALLENGE FOR THE SPECIALIST: NEUROBIOLOGICAL ASPECTS IN HEADACHE SUFFERERS WITH SLEEP DISORDERS AND MENTAL DISORDERS

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So far, much clinical evidence has been collected that shows a frequent association of headache, sleep disorders and/or mental disorders. A very complex scenario may present which explains this clinical finding: really, abnormalities of several neurotransmitters and neuromodulators may account for this association. An impairment of noradrenergic and/or serotoninergic activity has been shown in the pathophysiology of headache as well as depression; so the administration of drugs implementing these neurotransmitters, such as SSRI or NSRI can improve both diseases. SSRI can be used also when headache is associated with obsessive-compulsive disorders likely due to the important role of serotonine in exerting a continuous inhibition on dopaminergic neurons in basal ganglia [1]. The antidepressants with sedative side effects can be choosen when a sleep difficulty is associated to headache and depression: in the case of amitriptyline, sleep facilitation depends on an inhibition of cholinergic-muscarinic and histaminergic receptors, whereas acetilcholine and histamine are strongly implicated in the mechanisms of arousal. An excess of excitatory glutamate-mediated transmission has been hypothesized both in migraine and in some anxiety disorders such as panic disorder: since an inhibition of glutamate pool is induced by some anticonvulsivants, these drugs can be efficaciously used in migraineurs with panic disorder; moreover, glutamate is one of the wake system neurotransmitters, so a modulation of this substance can be useful also in insomnia. Due to a postulated functional abnormality of GABA receptors in panic disorders [1] and to the importance of GABA-mediated transmission in the mechanisms of sleep, benzodiazepines can be choosen too, but the risk of tolerance in a long-term treatment must be taken into acccount. One more neurobiological base for the association between sleep disorders and pain is given by recent findings pointing to a role of orexines, neuropeptides of the wake system, in nociception; the orexinergic neurons have been shown to exert a direct inhibitory action on nociceptive neurons in the dorsal horne and in the trigeminal nuclei as well as an indirect inhibitory action by means of activation of serotoninergic descending pain-modulating pathways in midbrain structures such as PAG and raphe nuclei [2].
The knowledege of the neurobiological bases underlying the comorbidity of headache with sleep disorders and/or mental disorders can surely help the headache specialist in the choice of a drug which can possibly improve all three diseases, or, if it is difficult to obtain, at least a careful combination of drugs that cannot counteract each other or worsen any one of the problems affecting the patient. So, it becomes less difficult to accept the challenge of such a complex association of disorders and to gain a therapeutical success also in these "resistent" patients.

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POSSIBLE ROLE OF CAFFEINE IN THE PROPHYLAXIS OF HYPNIC HEADACHE

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Introduction Hypnic headache (HH) is a rare primary pain disorder originally described by Raskin in 1988 and characterised, according to the International Classification of Headache Disorder 2nd edition (ICHD-II), by a dull headache without autonomic symptoms, which awakens the patient from sleep many times a month, lasts for more than 15 minutes, and tends to start after the age of 50. HH is idiopathic in nature, although a few symptomatic cases have been described. A number of agents have been employed for HH prophylaxis, including lithium, indomethacin, tricyclic antidepressants, beta-blockers and others, with inconsistent results and/or significant side effects [1]. Caffeine has been demonstrated to be of some relief in single clinical reports. To better understand the possible therapeutic role of caffeine we performed a retrospective analysis of the caffeine response in our cohort of HH patients.
Methods All patients affected by HH according to ICHD-II diagnostic criteria who were administered caffeine as monotherapy as well as add-on therapy were studied. Caffeine was given as one or two cups of coffee, corresponding to about 80 to 160 mg of caffeine, at bedtime. The therapy was prescribed for at least one month and the patients were considered responders if a reduction of 50% or more in headache frequency was achieved as compared to baseline conditions. Side effects and patient judgment were also considered.
Results Of 23 consecutive HH patients admitted to our headache facilities from 1998 to 2007, eleven were prescribed caffeine as headache prophylaxis. Their mean age was 65.1 years (median, 61 y), with a mean duration of illness of 50.5 months (median, 24 mo.). Four patients exhibited the typical 'chronic' pattern of illness, while 7 suffered from a remitting (or 'episodic' [2]) form. Seven of 11 patients took caffeine as monotherapy, while the other 4 took it as add-on therapy (with lithium in two cases, verapamil in one, and lithium at the beginning and indomethacin thereafter in one patient). Five of 7 patients (71%) who were given caffeine as monotherapy reported a reduction in frequency >50% (>75% in most of them). All four patients who took caffeine as add-on therapy achieved a reduction in frequency >50%. In all these patients caffeine induced a significant clinical improvement compared to the previous monotherapies. Two of 11 patients presented sleep disruption, with drug withdrawal in one case. Two additional patients took caffeine during their spells as symptomatic therapy with complete relief within 30 minutes.
Discussion In this open-label study, caffeine appears to be an efficacious and well-tolerated treatment in the majority of patients with HH as monotherapy, as well as add-on therapy. Caffeine could be regarded as a first-line treatment for HH.

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PREVENTATIVE TREATMENT OF CHRONIC DAILY HEADACHE WITH BOTULINUM TOXIN TYPE A

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Botulinum toxin type A (BoNT-A) has been recently suggested as prophylaxis therapy for the treatment of primary headache chronic forms. Several studies on its efficacy are available, but results are often contradictory and not univocal. BoNT-A has been investigated on chronic forms of both tension-type headache and migraine.
In this study we introduce our five-year long experience with BoNT-A (BOTOX®, Allergan, Irvine CA). The employed dosage was of 100 U and the Fixed Sites - Fixed Doses (FSFD) protocol was used.
The period of study was carried out between April 2001 and July 2006 and 1 350 patients suffering from chronic daily headache (CDH) underwent treatment.
We registered in these patients the number of headache days per month and observed their reduction in relation to the number of injections. The best results were found after 12 months of treatment, with patients being free of attacks 23 days per month.
The BoNT-A treatment resulted safe and well-tolerated, as only 1.6% of patients reported adverse events, and they were all mild and tran-

sient.
In conclusion, BoNT-A therapy appears to be an efficacious new therapeutic choice in the prophylaxis of CDH, especially for patients not responding to previous prophylactic treatments.
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LOW-DOSAGE TOPIRAMATE IN PROPHYLAXIS OF MIGRAINE: RESULTS OF A RETROSPECTIVE STUDY ON 490 PATIENTS

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Introduction Topiramate received relevant evidence of efficacy for prophylaxis of migraine. In the majority of the trials the effective dosage was 100 mg/daily. However, some recent studies report efficacy of topiramate in migraine prevention also at lower (50-75 mg daily) dosages. Here we show results of a large retrospective chart study including 490 patients referred to our outpatients service at the Department of Clinical Neuroscience, University of Palermo in the last 3 years, effectively treated for at least six months with low-dose topiramate.
Methods We reviewed the charts of our headache outpatients treated by topiramate. Patients were followed for at least 6 months, with at least 2 follow-up visits, were considered eligible for the study. Four hundred and ninety patients were recruited. Fifty percent of them were affected by chronic, 40% by migraine without aura and 10% by migraine with aura. The drug was slowly titrated with dose increase of 25 mg every 10 days till final dosage of 50 mg/daily; dosage was increased to 75–100 mg/day if necessary at the follow-up visits. Monthly attack frequency was the primary end-point for efficacy; secondary outcomes were: responders rate and MIDAS score.
Results In about 80% of the treated patients, topiramate was effective at the dosage of 50 mg/day with more than 50% attack frequency reduction after 3 months of treatment; the effect was very consistent over time with only 5% of patients requiring dosage increase at 6 months and 7% after 1 year. Patients showed also relevant and significant reduction of MIDAS scores, over time. Topiramate was quite equally effective in all groups (chronic, migraine with and without aura). Topiramate was also well tolerated: the most frequent side effects being: paresthesias (10%), insomnia (4%), nervousness (3%), and somnolence (3%). Only 3 patients asked to discontinue treatment because of intense somnolence after 3 months.
Discussion and conclusions Topiramate is a safe and effective treatment for migraine prophylaxis. Daily dosages lower than 100 mg/day (the recommended dose) can be equally effective and consistent over time, reducing the side effects and optimizing patient compliance.

MIGRAINE OUTCOME AFTER MENOPAUSE: A POSSIBLE PREDICTIVE FACTOR

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Background Throughout reproductive life cycle, as hormonal levels change, many women experience significant headache changes [1]. Although migraine prevalence decreases with advancing age, migraine can either regress or worsen or remain unchanged at menopause [2]. Up to now, no data exists, predicting the outcome of the illness after the onset of menopause.
Objective In order to find out some predictive factors about the development of the illness, we studied the course of postmenopausal migraine in a number of mothers and daughters, with the idea that, since migraine is nowadays thought to have a genetic basis, a link could be identified.
Methods One hundred and thirty-three women (age 42-75 years) suffering from migraine according to ICHD-II criteria, referring for the first time to the Headache Centre of the University of Turin, in the years 2000-2005, whose mothers suffered from the same illness, were studied. We asked these women if and how the characteristics of their migraine changed during menopause, then the same questions about migraine were posed to the mothers. Then we compared the results.
The data were statistically analysed using the c2 test.
Results Forty-eight (36.09%) patients improved after menopause, 69 (51.87%) worsened, and for 16 (12.03%) of them, migraine remained unchanged. While 55 (41.35%) mothers improved after menopause, 15 (11.27%) worsened, and for 35 (26.31%) of them, migraine remained unchanged and for 28 (21.05%) no data were found.
In particular, it was observed that 26 (47.27%) daughters improved out of 55 mothers with the same tendency, while 22 (40.00%) worsened and only 7 (12.72%) remained the same. Eleven (73.33%) daughters worsened out of 15 mothers, while 2 (13.33%) improved and 2 (13.33%) remained unchanged. In the group of the 35 mothers who showed no changes, 11 (31.42%) daughters improved, 19 (54.28%) worsened and just 5 (14.28%) remained the same. Respectively, 9 daughters improved, 17 worsened and 2 remained unchanged, in the group with no data about the mothers (*p*: ns).
Conclusions On the basis of these data, in the majority of cases after the onset of menopause the daughters' migraine seemed to follow their mothers' pattern. In fact, there was more often an improvement, where daughters are concerned, if that had been the mother's pattern, and if the mother showed a worsening of the symptoms, the same aspect was a characteristic of the majority of the daughters. Since at present there are little or no data on this particular aspect of the illness, more studies are needed to assess this tendency.
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FROVATRIPTAN VS TRANSDERMAL ESTROGENS OR NAPROXEN SODIUM FOR SHORT-TERM PROPHYLAXIS OF MENSTRUAL MIGRAINE

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Introduction Sixty percent of migrainous women suffer an increase of frequency in menstrual period (menstrual window), defined as the time of 2-3 days before and 2-5 days after onset of bleeding. Some attacks are exclusively present during bleeding (true menstrual migraine: TMM), while others are only related to the menstrual period (menstrually-related migraine: MRM). In both conditions, acute treatment of migraine attack is often incomplete and unsatisfactory, and short-term prophylaxis of the menstrual window may be needed for decreasing frequency and severity of the attack.
Methods In this pilot, open-labelled, non-randomized, parallel group study we evaluated in 38 women affected by menstrual migraine, the efficacy of frovatriptan (n=14) 2.5 mg per os, or transdermal estrogens (n=10) 25 mcg, or naproxen sodium (n=14) 500 mg once-daily for the short-term prevention of migraine. The three treatments were given in the morning for 7 days, beginning 2 days before the expected onset of menstrual bleeding. All patients were asked to complete a diary card, in the absence of headache (baseline) and under treatment, to score headache severity.
Results All women reported al least one episode of menstrual migraine

at baseline. During treatment, all patients taking estrogens or naproxen and 13 of 14 patients (93%) taking frovatriptan had at least one migraine attack (p=0.424). Daily incidence of migraine was significantly lower with frovatriptan than with transdermal estrogens or naproxen (p=0.047).
At baseline, the overall median score of headache severity was 4.6, 4.2, and 4.3 in the group treated, respectively, with frovatriptan, transdermal estrogens and naproxen (p=0.819). During treatment, the median score was significantly lower with frovatriptan (1.9) than with transdermal estrogens (3.7) and naproxen (3.6) (p=0.033). This was also evident for each single day of observation (p=0.014). Among treatments, the differences were particularly evident for the subgroup of patients with TMM (n=22) and for frovatriptan vs naproxen.
Conclusions Our study suggests that short-term prophylaxis for menstrual migraine with frovatriptan may be more effective than that based on transdermal estrogens and naproxen.

THERAPEUTIC STRATEGIES II

ATENOLOL AND PROPRANOLOL SEEM TO SHOW EQUIVALENT EFFICACY IN MIGRAINE PROPHYLAXIS: AN OPEN-LABEL TWO-PERIODS CLINICAL STUDY

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Introduction The beta-adrenergic blocking agents are the most thoroughly studied and most widely used of all migraine preventive agents. The body of evidence is greater for propranolol and timolol then for atenolol. Their mechanism of action is still unknown. The selectivity of the beta blocking agents does not seem to be a major factor since both non-selective agents (propranolol, nadolol and timolol) and cardioselective agents (atenolol and metoprolol) can be effective. In addition, their lipid solubility, the ability to cross the blood-brain barrier and to stabilize membranes, and effects on platelets do not seem to be decisive in determining their efficacy in the prevention of migraine. The only important factor seems to be the lack of intrinsic sympathomimetic activity. The aim of the study was to investigate the difference between propranolol and atenolol in migraine prophylaxis, based on the reduction of monthly attacks, and intake of symptomatic agents (FANS) per month.
Materials and methods Twelve patients (3 males, 9 females; mean age 33.5 years; mean duration of migraine 15.22 years) were enrolled in the study, and were administered atenolol 50 mg daily for 2 months, and propranolol 60 mg daily for the subsequent 2 months.
Results At baseline patients suffered from a mean of 9.67 attacks per month, with the use of 13.33 doses of FANS per month; after atenolol 5.75 attacks per month with the use of 6 doses of FANS per month; after propranolol 5.42 attacks per month with the use of 5.58 doses of FANS per month. Both drugs significantly reduced blood pressure, with a comparable effect. A paired t-test did not show a difference between atenolol and propranolol in the reduction of monthly attacks (reduction in attacks with atenolol – reduction in attacks with propranolol = 0.33; p=0.305) or in the reduction of monthly use of FANS (reduction in doses of FANS with atenolol – reduction in doses of FANS with propranolol = 0.42; p=0.241).
Conclusions The corresponding 95% C.I. (-0.348, 1.015 for the difference in the reduction of attacks, and -0.323, 1.156 for the difference in the reduction of intake of doses of FANS) are sufficiently narrow to suggest an equivalence between the two drugs, and a further cross-over study, specifically planned to investigate equivalence, is recommended.

LEVETIRACETAM MONOTHERAPY IN MIGRAINE PREVENTION AND EPILEPSY: A NEW OPEN-LABEL STUDY

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Purpose To evaluate the efficacy of levetiracetam (Lev) as monotherapy in migraine prevention and epilepsy.
Methods Eighteen patients (13 females and 5 males) with an established history of migraine without aura, according to ICHD-II criteria, and epilepsy were enrolled in this prospective, open-label study. The median duration of epilepsy was 2.6 years (range 1-44 yrs). A total of 9/18 patients were taking AEDs: 1 topiramate (TPM), 5 valproic acid (VPA), 2 phenobarbital (PB), 1 carbamazepine (CBZ). Nine patients were newly diagnosed for epilepsy; 5 patients took drugs as migraine prophylaxis: 3 flunarizine, 1 pizotifen, 1 TPM. We decided to switch all patients to Lev as monotherapy, both for epilepsy treatment and migraine treatment, because of adverse events (weight gain with flunarizine e pizotifen, sedation with TPM) and lack of efficacy for patients treated with AEDs. Levetiracetam was introduced (starting dose 500 mg bid, increased over 4 weeks to the target dose of 3000 mg/day, fixed for 6 months, the evaluation period of the study), while the old AED was slowly tapered off.
Results 11/18 (61%) patients achieved total freedom from seizures; 7/18 (38.8%) showed a 94% reduction in epileptic seizures; 10/18 patients (55.5%) showed a reduction in monthly migraine frequency.
The global clinical impression was excellent or good in 16/18 (88.8%) patients. All adverse events associated with levetiracetam were mild and transient: 1 rash, 1 dizziness, 2 nausea, 1 diarrhoea, 1 increased behavioural abnormality.
Conclusions Our data confirm the effectiveness of levetiracetam as monotherapy in the treatment of partial and generalized seizures and suggest levetiracetam monotherapy treatment in the prevention of migraine.

LEVETIRACETAM IN PROPHYLAXIS OF MIGRAINE WITH AND WITHOUT AURA: AN OPEN-LABEL STUDY

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Background Migraine is actually considered a complex neurovascular disorder with paroxysmal disturbances in neurovascular function that may reflect primary or secondary disorders in the maintenance of ionic gradients. Since levetiracetam (LEV) induces a partial inhibition of N-type voltage-gated calcium channels, a reduction of inhibition of GABA/glycine-gated currents and a modulation of neural transmission by influencing activity of synaptic vescicle protein (SV2A), this well-tolerated new antiepileptic drug may be effective as a prophylactic agent in migraine [1]. The aim of this open-label study is to evaluate the efficacy of LEV in the prevention of migraine both with (MA) and without aura (MO).
Materials and methods At least 1-year after previous unsuccessful treatments with β-blockers and calcium antagonists, 40 consecutive patients with a diagnosis of MA or MO according to ICHD-II criteria were included. After a 1-month run-in period for titration of drug (250 mg/day for the first week, increased by 250 mg/week to a final dosage of 1000 mg/day), frequency, duration and severity of pain with VAS scale was evaluated at 6 months with paired t test.
Results Five patients dropped out because of adverse events (somnolence, dizziness) and lack of compliance. MO was diagnosed in 21 patients (7 men, 14 women) while MA in 14 (3 men, 11 women) (mean age of 29.1±5.4 years). Evaluation at 6 months presented: headache frequency decreased from 5.6±1.5 to 1.1±1.6 mean episodes per month (p<0.001), attack duration from 39.5±13.3 to 12.4±11.1 hours (p<0.001) and pain intensity from 7.9±1.4 to 3.6±1.8 (p=0.0014) by

VAS; 11 (27.5%) patients were completely headache free at 6 months. In the patients with residual attacks, the mean VAS score was more significantly decreased in MA patients (from 5.6±0.3 to 1.1±0.15; $p<0.0001$) than in MO subjects (from 6.9±1.2 to 3.1±0.15; $p<0.005$). No statistically significant differences were observed in relation to age, sex, migraine subtypes and disease duration.

Discussion As previously reported in few open-label studies, LEV reduced both frequency and severity of MO and MA with modest side-effects. According to Brighina et al., the reduction of MA attacks suggests a possible role on physiopathology of cortical spreading depression [1]. LEV efficacy on MO also points to the presence of silent cortical spreading depression as an underlying mechanism [2]. These results may warrant a double-blind placebo-controlled trial of LEV in migraine prophylaxis.

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EFFECTS OF A DETOXIFICATION THERAPY REGIMEN IN MEDICATION-OVERUSE HEADACHE

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Introduction Medication-overuse headache (MOH) is becoming an increasingly frequent occurrence in the headache population but controlled trials and guidelines for the treatment of this condition are not currently available [1, 2]. This study evaluated the effects of a detoxification therapy protocol on painful symptoms in patients diagnosed with MOH according to the last revision of IHS criteria, ICHD-II.

Materials and methods Twenty-five patients were considered (13 women and 12 men, aged 33-74 years, mean age: 47.16±12.3 SD), who had been suffering from migraine without aura [+/- tension-type headache] (n 24) or cluster headache (n 1) for 7-44 years (19.32±10.4 years). They had been under medication overuse (triptans and/or NSAIDs) for 1-10 years (3.28±2.13 years) and were no longer responsive to prophylactic therapy. They underwent a detoxification program over a period of 2 months in a mixed regimen (Day Hospital + Home therapy) involving: abrupt withdrawal of the abused drug [2] and treatment (i.v. and oral) with: - prednisone at scalar doses; -glycerol; - benzodiazepines; - metoclopramide; - H2-receptor antagonists. Acetaminophen + codeine was the only symptomatic drug admitted for the crises. All patients underwent systematic evaluation of symptoms through the headache diary [for each month: number of crises, peak intensity of pain (via Visual Analogue Scale – VAS), symptomatic drug use] before and after therapy. At the end of the program, prophylaxis was started again in all of them.

Results At a six-month follow-up after the end of the detoxification program, the percentage of patients presenting a stable improvement of symptoms (72% - n 18) was significantly higher than that of patients with partial/transitory improvement (only during the first month post-therapy) (12% - n 3) and those without any improvement (non-responders, 16%, n 4) (chi-square test: $0.0001<p<0.0003$). Patients with a stable improvement showed a highly significant decrease in the mean monthly number of crises (from 23.9 ±7.1 to 9.9 ± 7), peak pain intensity (from 8.1±1.1 to 4.8±1.7 cm) and symptomatic drug use (from 22.5±8.2 to 7.2±5.3)($p<0.001$, Student's t-test).

Conclusions An adequate detoxification program proves effective for the vast majority of patients with MOH. Patients with scarce or no response are possible candidates for a repetition of the program combined with an earlier start of prophylactic medication in the course of treatment [1].

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REHABILITATION ROUTES OF MEDICATION-OVERUSE HEADACHE

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The impact of headache on the person and society represents a public health issue. Recently, a study evaluated 51% of headache's prevalence in Europe, of which 14% is affected by migraine. Also, 4% of the adult population is affected by chronic forms, which constitute therefore an even more relevant problem in terms of health and social policies. The International Classification of Headache Disorders, II version (ICHD-II) recognises 24 types of chronic headache and states primary episodic headaches as chronic when attacks appear for more than 15 days per month, for at least three months.

Headache given by drug overuse, defined by ICDH-II in 2004 (and revised in 2005) as medication-overuse headache (MOH), is associated with overuse of a combination of analgesics, barbiturates, opioids, ergot alkaloids, aspirin, AINS, caffeine and triptans. Patients affected by MOH present reduced working performance and a significant alteration in the quality of life.

Furthermore, some psychological and behavioural states seem particularly important in promoting and sustaining drug abuse.

The management and rehabilitation of patients affected by CDH, abusing symptomatic drugs, consists in the withdrawal and/or gradual reduction of their assumption, because of tolerance and addiction possibilities.

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"NERIT (NEUROMUSCULAR EMOTIONAL RELAXING INTEGRATED TREATMENT): A NEW THERAPEUTIC METHOD IN TENSION-TYPE HEADACHE"

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Introduction Twenty female subjects, aged 35 to 50, underwent NERIT (Neuromuscular Emotional Relaxing Integrated Treatment). We considered a possible positive function of this new method: on the reduction in frequency and intensity of headache attacks and, in particular, the reduction in disability on working, social and family levels and, therefore, improvement in the quality of life.

Methodology Forty middle-aged female subjects underwent a Psychodiagnostic evaluation before enrolment in the study through the administration of the following scales: MIDAS, MSQOL, MQoLQ, HIT, and MSQ. In this study we utilised the MIDAS scale (an instrument which objectively measures the gravity of a headache attack, specifies the level of disability, and is suitable for identifying the appropriate therapy based on the degree of gravity of each patient). MIDAS scores resulted between 6 and 10; therefore, our patients did not undergo therapy that used antimigraine drugs, excluding headaches with mild (level 1) and grave disability (levels 3–4).

Afterwards, the study group of 20 subjects underwent NERIT (Neuromuscular Emotional Relaxing Integrated Treatment) every week for three months, followed by an extended period of treatment: initially, every fifteen days for another three months, then, every month for an additional three months. A control group, instead, of equal number, did

not undergo any treatment programme. After nine months, both the study and control groups, a total of 40 subjects, underwent another evaluation.

Results Comparison of the first and last MIDAS scores in the study group showed a decrease of 5 points in 10% of the cases, 4 points in 20%, 3 points in 15%, 2 points in 25%, and no change in 30%. In contrast, comparison of the first and last MIDAS scores in the control group showed no significant decrease. Thus, results were achieved only for those patients who underwent NERIT. They should improve quality of life, reduce the negative working, social and family effect of the headache attacks and of the consequent unpleasant personal experience lived by our tested patients.

Conclusions On the basis of the results, we can assert that in the study group, submitted to NERIT, life quality, valued through the MIDAS scale, is improved significantly. This is a noteworthy result, above all, if we compare it with the changeless one of the check group. NERIT, seems to have a positive function in the reduction of the headache attacks frequency and the alleviation of their seriousness.

EFFECTIVENESS OF ACUPUNCTURE AND RATIONAL EMOTIVE BEHAVIOUR THERAPY IN CHRONIC TENSION-TYPE HEADACHE

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Introduction Tension headache (TH) is a common condition affecting a large part of the active population producing significant reduction in social activities and work capacity. The importance of emotional distress in the development and maintenance of pain induced us to use a non pharmacological approach to tension headache management. Acupuncture is commonly used for the relief of tension-type headache. Rational Emotive Behaviour Therapy (REBT), reducing anxiety levels, decreases anxiety related to pain sensation. The aim of this study was to evaluate the efficacy of acupuncture or REBT in the treatment of patients with TH.

Materials and methods Twenty-eight patients (M/F=7/21, aged 21-54 years) with TH, diagnosed according to ICHD-II criteria, were enrolled in the study, after informed consent. All patients were randomized into two groups: ACU group (14) received acupuncture treatment twice weekly for 5 weeks, and the REBT group (14), previous preliminary psychological profile performed by a psychologist, was submitted to cognitive, emotional and behavioural techniques with a weekly therapy for 3 months. Selection of acupoints was done according to criteria of traditional Chinese medicine. All patients could use usual symptomatic drugs if needed during treatment. The study included also an evaluation of the quality of life (Short Form-36).

Results The frequency of attacks, the average headache severity, and the rate of rescue dosage significantly decreased during treatment in both groups although at different time point. Thus, the ACU group reported a rapid response in lowering headache pain score during the treatment period, compared to the REBT group. Nevertheless, progressive pain relief registered in the REBT group resulted to be more stable at 6 months follow-up. Acupuncture showed good efficacy and tolerability especially after reaching the halfway point of treatment. Finally, in the REBT group the emotional condition improved with a sensible reduction of depression, anxiety and hostility levels.

Discussion Our results confirm that the perception of pain is influenced by cognitive, affective and behavioural factors, therefore intervention based on REBT seems to be the appropriate treatment for chronic pain in tension-type headache. In addition, acupuncture is effective in pain relief affecting more positively improvement in daily functioning compared to REBT.

Conclusions Acupuncture and REBT can offer benefits in the treatment of tension headache. These treatments are safe or minimally invasive procedures, and may specifically benefit those patients who cannot tolerate prolonged therapy often burdened with adverse effects.

THERAPEUTIC STRATEGIES III

IMPACT OF LOW DOSE CARBOHYDRATE DIET ON HEADACHE SEVERITY IN MIGRAINEURS

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Migraine is characterized by a complex biochemical dysfunction attributed to a disorder of the trigeminal and hypothalamic pathways. Impairment of glucose and insulin metabolism has been reported in migraine, and insulin alteration seems to be specific to migraineurs [1].

Objective Following our previous study [1], that reported how about 80% of migraineurs had high insulin plasma levels, we began a prospective observational controlled study to evaluate the prognosis of migraine in those patients who followed the diet to treat hyperinsulinism.

Patients and methods The study lasted 2 years (2005-2006). All the consecutive patients visited at our headache centre were evaluated with a general blood test, hormonal screening, and a standard oral glucose tolerance test (OGTT) after a 12-hour fasting period, measuring levels of glucose and insulin. Those patients who had metabolic alterations in OGTT were visited and followed up by our endocrinologist (AR). At the first visit for headache they were asked about headache characteristics and underwent a brain MRI. Results of OGTT were recorded together with body mass index (BMI); a neurological visit and OGTT and BMI were performed after 3-6 months after the beginning of diet. Migraine severity was expressed by a headache severity index calculated on numbers of day of headache per month and severity of each day expressed on a scale from 0 to 3 (0 no headache; 1 mild headache; 2 moderate headache, not disabling but requiring drug treatment; 3 severe). The diet was the one usually used for hyperinsulinism, i.e., simple sugar was avoided, an average of 6 small meals were distributed throughout the day, each consisting of a small quantity of carbohydrates, together with protein and lipids. A light proteinic meal was suggested before sleeping. Percentage of carbohydrates should have been 45% of daily intake.

Results Over a 2-year period, 319 migraineurs had been visited at our headache centre. They were 63 men and 257 women. The mean age was 40 years. Among these patients, 251 suffered from migraine without aura, and 68 from migraine with aura. The group of patients with a normal metabolic profile was used as the control group to evaluate efficacy of diet on migraine prognosis. Fourteen patients were lost at follow-up, 217 (68%) showed glucidic-insulinemic metabolic alterations and 89 patients (22%) had a normal glicaemic-insulinemic metabolism. Among patients with metabolic alterations, there were 39 men and 178 women. Mean age was 40 years. Index of headache severity was similar in the metabolic altered group (30) and in the control group (31). At the end of follow-up, the diet group had a severity headache index of 10, just like the control group (9). BMI at baseline was similar in the two groups, i.e., 25 in the diet group and 23 in the control group. After the diet the BMI slightly decreased in the diet group (24). During follow-up the metabolic profiles improved in the majority of patients, proportionally to clinical improvement, but with less significance.

Conclusions A proper diet therapy seems a useful non-pharmacological treatment for migraine, just as useful as a traditional pharmacological treatment commonly used for migraine prophylaxis. It is less expensive and easy to perform.

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EFFICACY AND TOLERABILITY OF PREGABALIN IN PROPHYLAXIS OF CHRONIC AND REFRACTORY MIGRAINE

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Introduction Chronic migraine often represents a relevant therapeutic challenge. In recent years, antiepileptic drugs have been effectively employed in prevention of migraine. Pregabalin is a new antiepileptic drug that showed efficacy also in the treatment of neuropathic pain syndromes. We evaluated efficacy and tolerability of pregabalin for prophylaxis in patient with chronic, refractory migraine.
Materials and methods Sixteen patients (10 females/6 males, mean age 34±4 years) with chronic migraine were selected. They were all previously unsuccessfully treated with at least 4 prophylactic drugs (including also topiramate or valproate). Patients were treated for six months with pregabalin that was slowly titrated (in 15 days) till final doses of at least 450 mg/daily; this dose was eventually increased to 600 mg/day after one month, if necessary.
Primary efficacy endpoint was attack frequency per month; secondary endpoints were: attack duration and intensity, number of symptomatic drugs per month, percentage of responders and disability assessed by score at Migraine Disability Assessment Scale (MIDAS) at the beginning of the study and then every three months.
Results Pregabalin was well tolerated and no relevant side effects were reported. No drop out was observed. Two patients complained of somnolence; three reported dizziness. No other relevant side effects were observed. Pregabalin showed also good efficacy, significantly reducing attack frequency after one month ($p<.01$); attack frequency was further reduced at third and sixth month; secondary endpoints were all significantly reduced at third and sixth month of treatment with responder rate at 50% and 55%, respectively.
Discussion and conclusions If confirmed by studies in larger patient samples, pregabalin may represent a new option for prophylactic treament of chronic migraine, giving patients one more chance to manage chronic refractory headaches.

USE OF PREGABALIN IN THE THERAPY OF PAROXYSMAL HEMICRANIA

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Paroxysmal hemicrania is a new primary headache included in the trigeminal-autonomic cephalalgias (TACs). TACs are rare, but very disabling conditions which cause the involvement of trigeminovascular nociceptive pathways and reflex cranial autonomic activation (ICHD-II 2004) [1].
The character and localization of pain, and also the associated autonomic symptoms are very similar, although less severe, to those observed in cluster headache. In contrast to cluster headache the attacks of paroxysmal hemicrania are shorter (2–30 minutes) and more frequent (5 attacks per day). The age of onset is between 20–40 years; and female to male ratio is 3:1.
The only therapy, well recognized in International Guidelines, for this headache is indomethacin (225 mg daily); in fact, the complete response to indomethacin is the most important criterion for diagnosis of paroxysmal hemicrania.
We report two cases that fulfil the diagnostic criteria for chronic paroxysmal hemicrania who were successfully treated with a low dose of pregabalin (75 mg daily dose), a drug recently introduced in therapy for its anticonvulsivant, anxiolytic and analgesic activity [2]. The efficacy of drug was evident within two days after administration and lasted six months. In one case, pregabalin was discontinued and, about a couple of weeks later, headache attacks started again and the reuse of the drug was successful. The patients were in therapy for 8-10 months respectively. Presently, both patients are free of pain and have not referred significant side effects.
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RESPONSIVENESS TO PREGABALIN IN HEMICRANIA CONTINUA

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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 a case fulfilling ICHD-II criteria for HC, whose initial response to indomethacin was not sustained. The patient had a subsequent complete and prolonged response to pregabalin.
Materials and methods We have conducted a prospective follow-up study of a 46-year-old man suffering from HC. At the onset of headache, the patient underwent extensive investigations, including cerebrospinal fluid examination, brain MRI and Angio-MRI, which were normal.
Results When the patient was 43 years old, he presented with severe, continuous, strictly unilateral left-sided headaches, located in the ocular and frontal regions, associated with nasal congestion. Treatment with intravenous indomethacin 200 mg daily resulted in an immediate response, but when it was withdrawn, the headaches recurred with a continuous course and moderate intensity. The patient thus began oral indomethacin 150 mg daily followed by prompt easing of the pain. However, after 4 months, his response to indomethacin appeared to fade and gastric discomfort was reported. Indomethacin was replaced by pregabalin that was titrated up to the dose of 600 mg daily. The patient reported a significant improvement in headache pain on pregabalin 300 mg daily and became completely headache free on pregabalin 600 mg daily. He was thereafter followed for over 8 months and has remained pain free. Attempts to lower the dosage of pregabalin resulted in a return of the headache within 48 hours. The tolerability of the drug was excellent, since the patient did not report any significant adverse events.
Discussion HC has a prompt and enduring response to indomethacin 25–300 mg daily. The complete response to this medication is a prerequisite for diagnosis by the classification criteria of the International Headache Society. Unfortunately, a significant proportion of treated patients develop gastrointestinal adverse events 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-cyclodextrin and rofecoxib, verapamil, melatonin and neuromodulators, such as topiramate and gabapentin. This is the first report of the responsiveness to pregabalin in the treatment of HC.

THERAPEUTIC EFFECTS OF PREGABALIN IN TENSION-TYPE HEADACHE

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Introduction We administered to ten subjects, aged between 25 and 40 years of age, with tension-type headache, a pharmacological treatment

with pregabalin at 150 mg/day. We tried to consider a possible positive effect on the reduction in frequency and intensity of the headache attacks.
Methods Twenty subjects underwent psychodiagnostic evaluation, before follow-up, with the use of the MIDAS scale. With a MIDAS score between 6 and 10, therefore, our patients were not administered any therapy, which used antimigraine drugs, excluding the headaches with slight (level 1) and severe disability (levels 3–4).
Afterwards, the study group, including ten subjects, was administered pregabalin at 150 mg/day for six months. A control group with the same number of people did not undergo any pharmacological therapy. At the end of six months, both the study and control groups, twenty patients in total, underwent another evaluation.
Results The score obtained compared to the first MIDAS values showed a decrease of 7 points in 15% of patients, 5 points in 25%, 3 points in 20%, and 2 points in 15%, with an unchanged condition in 25% of cases for the study group. In the control group, the points achieved, compared to the first MIDAS evaluation, did not reveal any significant decrease. The results, therefore, were achieved only in the patients who underwent pharmacological treatment with pregabalin at 150 mg/day, improving their quality of life and reducing the frequency and intensity of headache attacks.
Conclusions In the study group that underwent pharmacological treatment with pregabalin, the quality of life, evaluated through the MIDAS scale, improved significantly. It is noteworthy the results obtained with the use of pregabalin in the reduction of headache attack frequency and alleviation of their seriousness.

TREATMENT STRATEGIES IN COMORBID PRIMARY HEADACHES-MOOD DISORDERS

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Introduction Numerous epidemiological and community studies reveal the greater frequency of psychiatric disorders among recurrent headache patients than the general population; the prevalence increases and is over-represented in clinical populations.
Regarding comorbidity of migraine-mood disorders, large-scale population-based studies show that:
1) migraineurs are more likely to have Major Depression (OR 2.2 to 4.0), Bipolar disorders (OR 2.9 to 7.3) (Hamelsky & Lipton, 2006) - in particular, strong association with Bipolar II disorders (Fasmer & Oedegaard, 2004); 2) the prevalence is significantly higher in women (3:1), migraine with aura (Oedegaard et al, 2006); transformed migraine; high frequency of attacks; 3) the lifetime prevalence applies to a broad age range (Breslau et al, 2000).
Furthermore, a "non casual" association between migraine and mood-disorders is suggested by several lines of evidences: epidemiological (bidirectional and specific relationship, Breslau et al, 2003; Torelli & D'Amico, 2004); clinical (similar clinical features, Fasmer et al, 2004); genetic (association with particular polymorphisms); neurobiological (dysregulation in monoaminergic systems, nociception-induced neuroplasticity at the cortico-limbic level, Rome et al, 2000; Cady et al. 2005); behavioural (role of learned helplessness, Seligman, 1975).
Psychiatric comorbidity complicates headache management, requesting sometimes more intensive multidisciplinary approaches.
Methods The fundamental treatment strategies are represented by pharmacological therapy, behavioural and psychotherapeutic approaches, alone or combined.
Pharmacological treatment includes use of antidepressants,whose efficacy in chronic headache pain - documented by a series of controlled studies (with a lot of methodological limits) - is represented by the analgesic effect.
Criteria for the choice of antidepressants in the preventive treatment of comorbid primary headaches-mood disorders are fundamentally clinical (patient history, clinical features of comorbid disorders) and pharmacological (specificity of antidepressant's pharmacological profile, in particular, chemical structure and biochemical profile of principle).
A meta-analysis by Onghena et al (1992) demonstrates a series of clinical features of the analgesic efficacy of antidepressants in chronic pain. Some of the main strategies are represented by the use of tricyclics and/or SSRIs; other medications such as mirtazapine, venlafaxine, buproprion; or antiepileptic drugs (valproate, topiramate); a treatment target, based on presenting symptoms and behaviours as specific neurotransmitter dysregulation (Slaby & Tancredi, 2001).
Behavioural approaches include type A modification, locus of control, stress management, and patient education. Useful in our experience is the "stick of dynamite" educational model (Sheftell et al, 2002).
Psychotherapeutic treatment comprises psychological aid therapy, familiar therapy, and support groups.
Results and conclusions Comparison between behavioural and pharmacological therapies in chronic tension-type headaches shows that the combined approach is responsible for mean headache improvement superior to each technique alone (Holroyd et al, 2001).
Moreover, it is fundamental to take "each case into account", considering the headache patient as "individual and specific", and avoiding from seeing him behind the abstract dimension of illness.

REVERSAL OF HEADACHE AND COMA FROM SPONTANEOUS INTRACRANIAL HYPOTENSION BY TRENDELENBURG POSITION AND BY LUMBAR EPIDURAL BLOOD PATCH IN TRENDELENBURG POSITION

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Objective Treatment of spontaneous intracranial hypotension (SIH) resulting in coma.
Background Spontaneous intracranial hypotension (SIH) is characterized by orthostatic headaches, low CSF pressure and distinct abnormalities on MRI [1]. Rarely, SIH may cause coma.
Materials and methods We report one case of coma from SIH.
Results A 62-year-old man developed severe, diffuse, orthostatic headache with nausea and vomiting. After 15 days he became progressively obtunded. Brain CT revealed mild bilateral chronic subdural haematomas (BCSE) and increased attenuation in the sylvian fissures. Cerebral angiography was normal. He underwent an evacuation of BCSE. Two days later the patient became comatose (GCS: state 5). Subsequently, he developed three episodes of respiratory distress and was intubated.
Brain MRI, 12 days after the operation, showed diffuse pachymeningeal enhancement, basilar cistern obliteration, and descent of midbrain structures. These features were consistent with SIH and severe resultant diencephalic compression. Spinal and myelo-MRI failed to demonstrate a CSF leak. He was placed in the Trendelenburg position (TP) at about 30° and awoke within 8 hours. The day after, the patient underwent lumbar autologous epidural blood patch (EBP) with 35 cc of blood mixed with gadolinium. Spinal MRI post-EBP showed only a little quantity of blood in the lumbar epidural space. He was sitting in bed 24 hours after EBP when he again became stuporous. Another EBP was given under fluoroscopy guidance with 30 cc of blood mixed with contrast medium. Multi-slice spiral spinal CT (MSSCT) post-EBP showed little quantity of blood in the lumbar epidural space. He progressively improved in 15 days, at which time he again became stuporous. We performed another EBP (27 days after the second EBP) with 30 cc of blood. MSSCT post-EBP showed blood in the epidural space from the level of L3 to C7-D1. After 24 hours the headache disappeared and he improved. The patient maintained TP during and 24 hours after the EBPs. After 6 months of follow-up the patient was in good health.
Discussion and conclusions Our case suggests that placing a patient with rostrocaudal herniation by SIH in TP can be life saving and that TP can favour the spread of blood in the epidural space from the lumbar to

cervico-dorsal level [2].
Furthermore, the case showed the efficacy of EBP to treat cases of SIH resulting in coma. Sometimes, it can appear inefficacious because of the incorrect execution of this procedure. Therefore, it is necessary to perform a neuroimaging examination post-EBP to confirm the correct execution.

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CARE MODELS

HEADACHE AT AN EMERGENCY UNIT

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Introduction To evaluate the final diagnosis of patients referred to a tertiary medical care unit in 2005 as a means of critically evaluating primary care previously provided in the region of Calabria.
Materials and methods We reviewed the medical records of patients who came to the Emergency Unit of the Hospital "Pugliese-Ciaccio" of Catanzaro with headache as the major complaint. Those who stayed more than 12 h in the hospital environment were automatically considered to have been admitted.
Results Of the 1 454 patients seen (54% women), 1 375 (94%) were discharged after the administration of parenteral analgesics and not more than 12 h in the hospital because they had no pain and their clinical-neurological examination was normal. Only 96 patients (8.7%) stayed in the hospital more than 12 h. In the first group, 71.5% had migraine or tension-type headache and did not require additional examination for diagnosis. Among those who stayed more than 12 h, 70.3% had secondary headaches and 51.5% required additional examination.
Discussion Primary care for headache in the Calabria region is unsatisfactory. Many patients with primary headaches are referred to tertiary medical services, overloading the already precarious care for acute cases in these services, which indicates the need to disseminate the diagnostic criteria of the International Headache Society among general practitioners.
Conclusions When the headache crisis does not improve with the administration of regular parenteral analgesics, the probability of the presence of a secondary headache and the need for additional examinations increases.

CLINICAL PRACTICE GUIDELINES AND HEADACHE PATIENT MANAGEMENT BY GENERAL PRACTITIONERS

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Introduction This study explores the awareness of technical terms used in Evidence-Based Medicine (EBM) and the manner of treating patients with migraine among a random sample of 500 General Practitioners (GPs). EBM for chronic headache management for primary care physicians has been developed in many countries. Their objectives include: demonstrating how to make a diagnosis, recommending what medications to use, what to use when the medications do not work, and when it is appropriate to refer the patient to somebody with greater expertise.
Materials and methods During the period October to December 2002, a survey was conducted on a random sample of 500 GPs in Calabria. A mailed questionnaire included questions on GPs' demographics and practice characteristics, awareness of EBM, sources of information about migraine and EBM, and patient's treatment behaviour.
Results Of 500 questionnaires distributed, responses were received from 455, a response rate of 91%. 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. For two-thirds of GPs, disability is equivalent to the diagnosis of illness, 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. In addition, the clinical approach to migraine required an evaluation of clinical effectiveness in those who treated a lower number of headache patients who were older, and who did not use guidelines. Most GPs (93.1%) felt that it is important to integrate clinical practice with the best available evidence.
Discussion This behaviour was more frequent in those who agreed that the clinical approach to migraine requires an evaluation of clinical effectiveness. In addition, clinical trials are needed to evaluate the efficacy of migraine treatments and in those who attended EBM courses. In contrast, when scientific evidence indicates that a current treatment is less efficacious or more expensive than the new treatment, only 14% and 3.1%, respectively, of GPs would modify the treatment.
Conclusions Additional training and continuing educational programmes on guidelines for treatment of headache for GPs are strongly needed.

ADOPTION OF AN ANAMNESTIC QUESTIONNAIRE: WHAT'S CHANGED IN A CENTRE FOR THE STUDY, CARE AND DIAGNOSIS OF HEADACHES

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Discussion For over a year we adopted an anamnestic questionnaire at our centre for the study, care and diagnosis of headaches.
The questionnaire contained all information necessary for establishing the diagnosis according to ICHD-II, 2004 classification.
Use of this questionnaire conformed to the diagnostic and international standards for headaches and better followed SISC guidelines.
Moreover, it allowed diffusion of essential criteria for the diagnosis and care of paediatric headaches among Hospital paediatricians.

FREQUENCY OF CRISES AND PAIN: EFFICACY OF THE INTEGRATED APPROACH IN PATIENTS SUFFERING FROM CHRONIC TENSION-TYPE HEADACHE FOLLOWING PHARMACOLOGICAL PROPHYLACTIC THERAPY

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Introduction A retrospective study was conducted on patients from our clinics suffering from chronic tension-type headache (CTTH), diagnosed according to ICHD-II classification criteria, code 2.3 (OMS G44.2). The objective of this study was to demonstrate the efficacy of prophylactic therapy on an integrated approach (pharmacological and psychotherapeutic) compared to an exclusively pharmacological one.
Materials and methods We selected 7 patients suffering from CTTH, 1 M and 6 F, mean age 31 years (range 22– 49), who used the integrated approach as prophylactic therapy (Group AI) compared with 7 patients suffering from CTTH, 3 M and 4 F, mean age 31 years (range 22–39), who used prophylaxis only with pharmacological therapy (Group F). Observations were carried out for 20 months. In the beginning, patient group AI had an average percentage of 100% of days/month with headache. They were treated with a daily pharmacological therapy of prophylaxis with amitriptyline (daily average dosage

25 – 40 mg) and a weekly session of relational systemic psychotherapy with individual and familiar meetings. The patients of group F had, in the beginning, an average percentage of 75% of headache days/month. They were treated only with the same pharmacological therapy of group AI. The clinical headache diary was evaluated in the beginning (T0) and after 20 months of treatment (T1). The experience of pain was evaluated using the VRS (Verbal Rating Scale) at T1.

Results The patients of Group AI showed a monthly average headache symptomatology of 9%, with a decrease of 91%. The patients of Group F showed a monthly average headache symptomatology of 13%, with a decrease of 80%. Comparison between the two treatments showed a moderate statistical significance ($p<0.05$). The results obtained from VRS (Verbal Rating Scale) showed a medium level of pain equal to 4 in group F and 2 in group AI, with an average value related to headache of the last 24 hours, respectively, of 6 and 3.

Discussion and conclusions In the prophylaxis of patients suffering from CTTH the integrated approach produces results that are more effective than only pharmacological therapy, affecting the monthly frequency of headache and pain perception.

PATIENTS SEEKING TELEADVICE FOR HEADACHE: IDENTITY, CLINICAL PROBLEMS, COMMUNICATION ISSUES, MOTIVATION, AND EXPECTATIONS AS EXPRESSED IN E-MAILS SENT TO PHYSICIANS

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Aim of the study Electronic communication with physicians in the absence of a patient-physician relationship is a growing phenomenon about which little is known. The aim of this study was to analyse the identity, clinical problems, motivation, and expectations of patients seeking teleadvice to an ask-the-doctor service for headache and to evaluate the appropriateness of their requests and the potential for teleadvice to improve medical assistance for headache.

Methods *Design and setting*: exploratory survey and quantitative content analysis of the e-mails sent to an ask-the-doctor service on a website dedicated to headache from September 2005 to August 2006. Main *Outcome Measures*: identity and headache subtype of the writers, previous contacts with live physicians, content analysis of e-mails, motivation for contacting a virtual physician, possibility to answer without visiting.

Results A total of 332 e-mails were received in the study period, of which 69% were sent directly by the patients and 29% by first-degree relatives. Approximately 50% of the writers were aged between 15 and 35 years. Fifty-four percent of the writers reported a headache diagnosis (migraine 27.2%, cluster headache 24%, MOH 13%), while almost 50% of those not reporting a diagnosis cited use of symptomatic medication on an almost daily basis. Seventy-four percent of the writers declared to have seen a physician before. On content analysis the most frequent reasons to write were information about visits/physicians, general advice, information about therapy, and advice about therapy. Forty percent of the writers expressed frustration or disappointment about previous physicians, whereas 68% of the e-mails were judged as suitable to be answered via e-mail.

Seeking teleadvice is not a frequent activity (1/15000 website contacts). It is overused by young patients suffering from chronic or highly demanding headaches, frustrated by previous medical experience, in different stages of their decision-making process regarding their need for medical help. E-mails supplement rather than replace the traditional visit and have the potential to improve several aspects of the medical support for headache.

"THE HEADACHE DAYS" A NEW TOOL TO REDUCE BURDEN OF MIGRAINE INCREASING PATIENT INFORMATION: DEFINITIVE RESULTS ON 220 PATIENTS

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Objective In 2005, through "The Headache Week" (a free informative point for a week in a headache centre) we found that 78% of participating patients, affected by severe headache, did not know where to refer for their headache. Our aim was to extend and give continuity to initiatives for patient information by increasing the sites (more headache centres) and their overall period of activity.

Methods To favour the participation of more headache centres, we reduced the activity of each information site to 1-2 days calling the initiative "The Headache Days".

Nine headache centres in the city and province of Palermo participated, covering a period of three months (May, June and October 2006). The initiative was advertised in local newspapers, television and on the headache national websites. Participating patients were examined by a headache specialist, received informative materials and filled in a questionnaire about physicians visited, knowledge and usage of symptomatic (triptans) and preventive treatments.

Results Two hundred and twenty patients participated (migraine: 75%; tension-type: 18%; cluster: 4%; other: 3%); about 70% of migraineurs never used triptans while these drugs were erroneously taken by 15% of patients with tension-type headache; about 70% of migraine and tension-type headache patients never received prophylaxis; about 50% of patients receiving preventive treatment, and chose non conventional approaches (acupuncture, homeopathic medicines, etc.).

Conclusions Lack of information represents a major cause of poor recognition and treatment of migraine in the population. Giving continuity to initiatives like "headache days" can increase patients' knowledge about headache with the final goal (through more appropriate diagnosis and treatment) to reduce disability and burden of migraine.