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Proceedings of the XXII National Congress of the Italian Society for the Study of Headaches

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On behalf of the Italian Society for the Study of Headaches (SISC), it gives us great pleasure to present the abstracts of all the scientific contributions that will be presented at the XXII National Congress of our Society, held in Turin from October 2 to October 4, 2008.

The Congress takes place under the auspices of the World Federation of Neurology, the International Headache Society and the European Headache Federation and is the main way in which our Society fulfils its aim to provide a forum for physicians involved in all aspects of headache, including research, clinical practice, and professional and lay education.

The city of Turin was chosen in order to remember and recognize its very important role in the history of our Nation but, also, in the history of modern Italian Medicine. The Scientific Program Committee has put together an exciting program that will cover the full range of interests of headaches, from molecular genetics to recent advances in therapy. Of relevance, the space dedicated towards the integrated activities with other scientific Societies, like the Italian Society for the Study of Hypertension and the Italian Society of Psychopathology, whom promote clinical and scientific research activity of common interest with our Society. Participants will also enjoy a full social program that will introduce them to the unique historical location of the town.

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

Lorenzo Pinessi
President of the Italian Society for the Study of Headaches
President of the XXII National SISC Congress

Biochemical and neurophysiology in headache and facial pain

Role of cortical inhibition on habituation to visual evoked potentials explored through combined effects of light deprivation and repetitive transcranial magnetic stimulation in healthy subjects: new insights for pathophysiology of migraine?

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Introduction Habituation, i.e., the decremental response to repeated sensorial stimulation, is studied in humans through evoked potential stimulation. Mechanisms underlying habituation are not yet clear, even if inhibitory circuits are hypothesized to play an important role. The investigation of neural processes that are at the basis of the habituation could be important in understanding the mechanisms of migraine pathophysiology since habituation has been shown to be impaired in this disease [1], but also because there is increasing evidence about deficiency of cortical inhibitory circuits in migraine [2]. Light deprivation (LD) increases visual cortical excitability likely through down-regulation of GABA-circuits. We previously found that high-frequency rTMS (hf-rTMS) can revert these facilitatory effects likely restoring activity of inhibitory circuits [3].

Objective The aim of the present study was to investigate the effects of LD and rTMS on habituation of visual evoked potentials (VEPs) as a potential model to explore the role of cortical inhibition. The hypothesis was that if the inhibitory circuits have a role in habituation, then LD, that down-regulates GABA-circuits, should impair habituation that in turn should be restored by hf-rTMS. This could also help our understanding of migraine pathophysiology establishing a link between reduced inhibition and impaired habituation and opening the way to new therapeutic perspectives.

Methods Six healthy subjects underwent VEPs recording (10 trains of 50 stimuli each) in the following conditions: 1) baseline (without LD); 2) LD alone (without rTMS); 3) LD and 1 Hz rTMS; 4) LD and 10 Hz rTMS. rTMS was applied to the optimal scalp position for induction of phosphenes after 45 min LD, at a phosphene threshold intensity (as assessed before LD).

Results Habituation (i.e., decremental VEP amplitude) observed at baseline (without LD) was significantly impaired after LD, whereas 10 Hz but not 1 Hz rTMS was able to restore normal habituation phenomena.

Discussion and conclusions VEPs-habituation is impaired by LD but it could be restored if hf-rTMS is given during LD. As LD acts reducing GABA circuits activity and hf-rTMS likely up-regulates such circuits, these data support the hypothesis that cortical inhibition can play a relevant role in mechanisms underlying habituation. Therefore, the impaired habituation observed in migraine could be the consequence of the reduced activity of cortical inhibitory circuits that have been consistently reported in migraine. Conversely, the restoring effects of hf-rTMS that likely act through up-regulation of inhibitory circuits, could establish a new therapeutic approach.

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Modulation of pain-related evoked responses by hormonal influences in menstrually-related migraine

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Introduction While contradictory results were found about changes of psychophysical pain features during the menstrual cycle, there is evidence of an association between oestrogen “withdrawal” and attacks of migraine without aura [1]. Nociceptive cortex activation has been observed during menstrual cycle [2]. Migraine is characterized by an abnormal modulation and habituation of cortical responses evoked by nociceptive laser stimulus [3]. The aim of the study was to examine the features of laser evoked potentials (LEPs), including habituation, in women suffering from migraine without aura vs. healthy controls, during the late follicular and late luteal phases.

Methods Eight migraine without aura (menstrually-related migraine without aura) women (MA), aged 25–38 years, and eight non-migraine healthy controls, aged 26–36 years, (N) were selected and evaluated during the late follicular phase (confirmed by basal temperature) and late luteal phase, as determined by the first day of menses. LEPs were recorded during the inter-critical phase, in the 72 hours following the previous attack. The laser stimulus was settled at 7.5 W intensity and 25 ms duration. LEPs were recorded by Fz, Cz, Pz electrodes referred to the nose and by a T3-T4 referred to Fz derivation. The right supraorbital zone and the dorsum of the right hand were stimulated. Three consecutive series of 20 laser stimuli, with 10 sec ISI and 5 min inter-series interval, were obtained for each stimulation site. Laser pain perception was rated by a 0–100 VAS after each stimulation series.

Results In both groups, the N2-P2 amplitude was significantly enhanced during the late luteal vs. the late follicular phase, for both the hand and face stimulation (ANOVA with the phase as factor: $F=19$ p 0.0001). In MA patients, a significant reduction of N2-P2 habituation was observed in the late luteal phase, compared with N women (ANOVA with repetitions x cases x phases as factor: $F=4.15$ p 0.04). In both groups the pain perception was significantly increased during the late luteal phase (phases as factor $F=4.60$ p 0.034).

Discussion and conclusions In both migraine and healthy women, the late luteal phase was characterized by increased pain sensitivity and enhanced cortical responses to laser stimuli, expressing an increase of nociceptive cortex activation. The dishabituation pattern of nociceptive cortical responses is also enhanced in migraine in the menstrual phase, confirming that migraine susceptibility may be modulated under hormonal fluctuations.

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Evidence of increased plasma matrix metalloproteinase-9 levels during migraine attack: correlation with increased IL-1 β , IL-6 and TNF- α plasma levels

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Introduction Previous reports have shown that plasma levels of matrix metalloproteinase-9 (MMP-9) are increased in patients with migraine both ictally and interictally. This has been related to proteolytic degradation of the blood-brain barrier (BBB) consequent to cortical spreading depression (CSD), which is believed to underlie the pathogenic events not only of migraine with aura (MA) but also migraine without aura (MwA) [1]. The present study investigated plasma levels of MMP-9 during migraine attacks in MwA and MA patients, and correlated them to the proinflammatory cytokines interleukin (IL)-1 β and tumor necrosis factor (TNF)- α .

Materials and methods Thirty-five migraineurs, attending the Perugia Headache Centre, participated in the study. Twenty suffered from MwA and 15 from MA according to the diagnostic criteria of the International Classification of Headache Disorders II. Twenty healthy subjects without headache were included as controls. Blood samples were taken at 1, 2, 4, and 12 hours after attack onset, and 2–4 days after its termination. The levels of MMP-9 and proinflammatory cytokines were measured with ELISA.

Results We found increased MMP-9 plasma levels during the entire migraine attack in both MwA and MA patients, with higher levels detected at 6 and 9 hours after onset, compared to controls ($p < 0.005$ and $p < 0.003$, respectively) and headache-free periods, independently of the symptomatic drugs taken ($p < 0.01$ and $p < 0.002$). MMP-9 levels in patients responding to symptomatic drugs were lower than those with a partial or unsatisfactory response without differences between MwA and MA. Increased MMP-9 levels were preceded by a transient increase of IL-1 β , IL-6 and TNF- α , which reached maximum at 2 hours and tended to decrease successively, although they remained higher than those measured during the headache-free period until the end of attacks.

Discussion and conclusions Our results suggest that increased plasma MMP-9 in migraineurs could be related to neurogenic inflammation and/or CSD underlying migraine attacks. The correlation with a transient inflammatory response is suggested by the increase of IL-1 β , IL-6 and TNF- α in both MA and MwA. This is further supported by experimental data demonstrating that inflammatory stimuli, such as IL-1, IL-6, TNF- α , and sources of reactive oxygen species (as free radicals), increase MMP-9 expression in models of CSD and meningeal neurogenic inflammation [2]. The predominant sources of MMP-9 detected

in the circulation, however, are unknown. It cannot be excluded that MMP-9 is released by circulating immune cells rather than being derived from brain endothelial cells, astrocytes and microglia.

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Plasma concentrations of glutamate in patients suffering from chronic migraine overusing acute medication, before and after withdrawal treatment

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Background and objectives A dysfunction of the glutamatergic system seems to play an essential role in the pathogenetic mechanism of migraine. Glutamate is implicated in cortical spreading depression, trigeminovascular activation, and central sensitization [1]. Glutamate levels higher than those of healthy controls have been found in plasma and platelets of migraine patients [2] and in cerebrospinal fluid of chronic migraine patients [3]. Our aim was to verify whether the plasma levels of glutamate in patients with chronic migraine overusing acute medications were different from those in control subjects, and also whether the plasma levels of glutamate in chronic migraine patients changed after withdrawal from the overused medication.

Methods We studied 12 patients (F 10, M 2; mean age: 50.3 \pm 9.8 years) with diagnosis of chronic migraine, according to ICHD-II criteria, overusing acute medications, and 15 healthy subjects as controls (females 2, males 3; mean age: 48.2 \pm 7.3 years). Patients were studied twice, before and after 15 days of standardized inpatient withdrawal treatment. Venous blood samples for the assay of glutamate concentrations were taken in the morning, after overnight fasting. Glutamate concentrations were measured by means of a fluorimetric detection high pressure liquid chromatographic (HPLC/FD) method.

Results Plasma concentrations of glutamate were significantly higher in chronic migraine patients either before (62.5 \pm 5.1 μ mol/L) or after treatment (27.7 \pm 11.3 μ mol/L) than in control subjects (7.3 \pm 2.9 μ mol/L) ($p < 0.05$, ANOVA followed by Student-Newman-Keul's test). However, after 15 days of in-patient withdrawal treatment, once overuse was interrupted and the frequency of headache reduced, plasma glutamate concentrations were significantly lower in the same patient with respect to the prior level ($p < 0.0001$, Student's t-test for paired data), irrespective of the kind of medication overused.

Conclusions Elevated plasma levels of glutamate in chronic migraine sufferers could support the role of this excitatory aminoacid in the process of central sensitization. The decline in glutamate plasma concentrations is associated with medication-overuse discontinuation and reduced headache frequency; thus, plasma glutamate levels monitoring in chronic migraine might serve as a biomarker of clinical improvement.

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Experimental models

Antiepileptic drugs on calcium currents recorded from cortical and periaqueductal gray (PAG) neurons: therapeutic implications for migraine

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Objective Some antiepileptic drugs (AEDs) are effective in the prevention of migraine. A rationale for this use is the hypothesis that migraine and epilepsy share several pathogenetic mechanisms. Abnormal neuronal activity of Ca²⁺ channels can represent one of the major targets of AEDs in migraine. Ca²⁺ channels in the PAG (periaqueductal gray) modulate trigeminal nociception and dysfunctional activity of these channels influences migraine pathophysiology. Thus, an altered activity of Ca²⁺ channels in both cortical and PAG neurons can represent a target of AEDs showing efficacy in migraine prevention [1]. In this study we have analysed the differential expression of various subtypes of high voltage-activated (HVA) Ca²⁺ channels in neurons isolated from cortex and PAG. We also have compared the efficacy and the potency of four different AEDs such as topiramate (TPM), valproic acid (VPA), lamotrigine (LTG) and levetiracetam (LEV) in inhibiting the various subtypes of Ca²⁺ channels in cortical and PAG neurons.

Methods Slices from frontal cortex, and PAG were chosen for preparation of acutely dissociated neurons and for whole-cell patch-clamp recordings. ANOVA test was used to statistic analysis.

Results In cortical neurons the modulation of TPM was mediated by L and P type Ca²⁺ channels. Conversely, in PAG neurons, the modulation of TPM was mediated by N, L and P type channels. Moreover, in these neurons the inhibitory action of TPM was more potent and effective than the one observed in cortical neurons. N-type and P-type channels are primarily involved in the action of LTG in cortical neurons. On the contrary, a selective N-type HVA blocker fully occluded the inhibitory action of LTG (100µM) in PAG neurons. The same results were obtained in the presence of LEV. VPA, at all the concentrations tested, failed to affect HVA Ca²⁺ currents.

Discussion The reasons why only a few compounds among the various AEDs are effective in the prophylactic treatment of migraine is still unknown. We found that while TPM significantly reduced L-type Ca²⁺ currents (in addition to P- and Q-type Ca²⁺ currents, respectively), LEV and LTG decreased N-type but not L-type Ca²⁺ currents.

Conclusions It is possible that the effects of TPM in the prophylactic treatment of migraine are mainly explained by its potency and efficacy in selectively inhibiting HVA Ca²⁺ currents in PAG neurons.

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Alteration of the endocannabinoid system in an animal model of migraine: evaluation in specific cerebral areas of rat

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Cannabinoids have demonstrated ability to block spinal, peripheral and gastrointestinal mechanisms that promote pain in migraine. Anandamide (AEA), a cannabinoid (CB) receptor agonist, is tonically released to play a modulator role in the trigeminovascular system. Systemic nitroglycerin (NTG) provokes spontaneous-like migraine attacks in migraine sufferers and induces a condition of hyperalgesia in the rat, 4 hours after its administration. In the present study we investigated the role of the endocannabinoids system in an animal model of migraine, based on the administration of NTG. Male Sprague-Dawley rats were injected with NTG (10 mg/kg, i.p.) or vehicle and sacrificed 4 hours later. The mesencephalon, the lower brainstem and hypothalamus were dissected out and utilized for the evaluation of regulators of the endogenous levels of AEA and 2-arachidonoylglycerol (2-AG) *in vivo*: fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). In the same areas, we also evaluated the density of CB receptors by means of receptor binding. The results obtained have shown that NTG is able to increase the activity of hydrolases and the density of CB receptors in the mesencephalon, when compared with the control group. In the lower brainstem, NTG induced an isolated increase in the activity of FAAH, while, in the hypothalamus, it caused a marked enhancement of FAAH activity associated with an increase in CB receptors density and other possible AEA-binding sites. These data support the potential involvement of a dysfunction of the endocannabinoid system in the cerebral areas of the rat implicated in the modulation of cephalic pain evoked by NTG administration.

Effect of the fatty acid amide hydrolase inhibitor URB597 in nitroglycerin-induced hyperalgesia in the rat

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Systemic nitroglycerin (NTG) provokes spontaneous-like migraine attacks in migraine sufferers and induces in the rat a significant reduction in the latency of the tail flick, 2 and 4 hours after systemic administration. Studies of the endogenous endocannabinoids have demonstrated that they are present in most tissues and that, in some pain states, their levels are elevated at key sites involved in pain processing. Fatty acid amide hydrolase (FAAH) is the main enzyme responsible for the metabolism of several endogenous fatty acid amides, such as anandamide (AEA). The aim of this study was to determine whether systemic inhibition of FAAH may alter the nociceptive response to tail flick in baseline conditions and during NTG-induced hyperalgesia. The tail flick test - a model of phasic

pain - was performed in male Sprague-Dawley rats. The animals were pre-injected with NTG (10mg/kg, i.p.) or saline (4 hours before the test) and treated with a FAAH inhibitor, URB597 (2mg/kg, i.p.) or vehicle 30 minutes before the tail flick. URB597 induced a significant increase in the tail flick latency in the animals treated with vehicle and it abolished NTG-induced hyperalgesia. The data obtained suggest that inhibition of FAAH activity may elevate spinal cord AEA content, therefore suggesting a possible role for FAAH inhibitors as targets of analgesic drug development also in migraine.

Epidemiology and social impact of headaches

Prevalence and prevention of headache in working communities

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Objectives To evaluate the effectiveness of a workplace educational and physical programme in reducing headache and neck and shoulder pain a 14-month controlled trial was performed.

Methods Central registry office employees (n=192; study group) and 192 peripheral registry office and central tax office employees (controls) in the city of Turin, Italy were given diaries for the daily recording of pain episodes. After 2 months, only the study group began the educational and physical programme. Two studies were performed [1, 2]. Primary end-point of the first study was the change in frequency of headache and neck and shoulder pain expressed as the number of days per month with pain, and as the proportion of subjects with a $\geq 50\%$ reduction of frequency (responder rate) at month 8. The number of days of analgesic drug consumption was also recorded. To confirm the long-term benefits of the programme in the second study the period of follow-up after intervention was extended from the initial 6-month period to 12 months. The same outcome measures were analysed at months 13–14 and compared to the baseline (months 1–2).

Results At month 8, diaries completed for the whole 8 months were available for 169 subjects in the study group and 175 controls. The baseline frequency of headache (days per month) was 5.87 and 6.30 in the study group and in controls; frequency of neck and shoulder pain was 7.12 and 7.79, respectively. Mean treatment effects [days per month, 95% confidence interval (CI)] when comparing the last 2 months vs. baseline were: headache frequency -2.45 (-3.48, -1.43); frequency of neck pain -2.62 (-4.09, -1.16); responder rates (odds ratio, 95% CI) 5.51 (2.75, 11) for headache, 3.10 (1.65, 5.81) for neck and shoulder pain, and 3.08 (1.06, 8.90) for days with analgesic drug consumption. At months 13–14 the number of days per month that subjects of the study group experienced headache was 3.11 ($p < 0.001$); for neck and shoulder pain frequency was 3.88 ($p < 0.001$); and for analgesic consumption was 0.86 days/month ($p < 0.001$). The proportion of responders was 58.8% (95% CI=47.1–70.5) for headache, 60.9% (49.4–72.4) for neck and shoulder pain and 68.2% (48.7–87.6) for drug consumption.

Conclusions These results show the effectiveness of our intervention programme and the high degree of subject compliance in a large, random, working population, and illustrate the stable positive effects of intervention following an extended period without treatment.

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Lessons from epidemiology and social impact of headache disorders

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Headache is one of the most common disorders of the nervous system and several of its subtypes cause substantial levels of disability. Yet, throughout the world, headache has been and continues to be underestimated in scope and scale, and headache disorders remain underrecognized and undertreated everywhere. Sufficient studies have been conducted to establish that headache disorders affect people of all ages, races, income levels, and geographical areas. Globally, the percentage of the adult population with an active headache disorder is 47% for headache in general, 10% for migraine, 38% for tension-type headache, and 3% for chronic headache that lasts for more than 15 days per month. Headache disorders are disabling: worldwide, WHO ranks migraine alone at 19th among all causes of years of life lost to disability (YLDs). Collectively, all headache disorders probably account for double this burden, which would put them among the ten top causes of disability. The prevalence of headache disorders has important economic implications. In the United States, for example, the annual economic burden imposed by migraine has been estimated at \$14 billion however, only 7% of that amount is attributed to direct medical costs. The remainder stems from indirect costs, in the form of missed work-days and reduced productivity: thus the burden of migraine disproportionately falls on the patients and their employers. Furthermore, relatively little is known about the costs of tension-type or cluster headache and the available studies fail to capture the full impact of headache disorders. Cost estimates, in fact, measure only headache related medical costs and disability without taking into account associated disorders, the effect of headache on families, the "lost productivity" of those individuals who do not work (children, students, retirees), and the "economic losses" related to the effect of headache on nonvocational aspects of life (leisure time, academic studies, child rearing, sexual life). In a world of limited resources for healthcare services and health related research, reliable data on the individual and societal impact of different disorders are crucial for a rational distribution of means. Epidemiological studies may be used to identify causes, risk factors, and lifestyle associations for headache disorders which may lead to identify specific preventive modalities still lacking and develop strategies to reduce the risk of progression. Epidemiological studies can provide effective and efficacious tools to drive the economic choices between options when there is scarcity of resources and this, in turn, can help to overcome clinical, social, political and economic barriers to care, and reduce markedly headache-related costs and disability.

Management of patients with primary headache by headache centres improves quality of life

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Background and aims Primary headaches may have a major impact on how sufferers' live, disrupting daily activities and heavily impairing health-related quality of life (HRQOL). Improvement of HRQOL and reduction of functional disability are therefore fundamental goals of primary headache management. The effect of headache management by specialised centres on HRQOL and disability, however, is little known. Most studies that have evaluated HRQOL, in fact, were focused on migraine and acute attack treatment. This study was aimed to evaluate the occurrence of changes in HRQOL and functional disability after management of patients with primary headaches by headache centres.

Patients and methods Participants were recruited from among patients attending for the first time 9 specialists working in headache centres (including academic centres, hospital-based centres and private practice) of the Emilia-Romagna Region in northern Italy. Patients with primary headaches of any type were included in the study. At baseline visit (V1), the following data were collected: i) social and demographic data; ii) ICHD-II diagnosis of primary headache(s); iii) main headache(s) features (frequency and duration of headache, intensity of pain); iv) some information about the examining physician. Patients completed the Migraine Disability Assessment Score (MIDAS) questionnaire for the evaluation of headache-related disability and the Short Form 36 (SF-36) survey for measuring HRQOL. Each patient was then given a headache diary card. At the follow-up visit (V2), three months later, the diaries were reviewed and the MIDAS and SF-36 forms were completed a second time. Changes in SF-36 scales and MIDAS total score between V1 and V2 were compared using paired Student's t-test.

Results One hundred and seventy-four patients were enrolled; 145 of them (83.3%; F 79.3%; mean age: 37.1±11.41 years) completed the study. Most patients had migraine without aura (74.3%), whilst tension-type headache accounted for 22.2% of the diagnoses; 27 patients (18.5%) presented two primary headache types. A symptomatic treatment was prescribed to almost all the patients, while a prophylactic therapy was given to two thirds of them. As regards to SF-36 scales, all of them improved at V2 in comparison with V1, most significantly: Physical Functioning: $p=0.04$; Physical Role: $p<0.0001$; Bodily Pain: $p<0.0001$; General Health: $p=0.07$; Vitality: $p<0.0001$; Social Functioning: $p<0.0001$; Role Emotional: $p<0.0001$; Mental Health: $p=0.03$. MIDAS total score passed from 30.7±38.73 at V1 to 18.5±42.46 at V2 $p<0.0001$.

Conclusions Management of patients with primary headaches by headache specialists improves HRQOL and reduces headache-related disability.

Genetics and pharmacogenetics in primary headaches

New approaches to migraine genetics

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Migraine is a common, heterogeneous neurovascular disorder that is transmitted as a complex genetic trait. The success of Familial Hemiplegic Migraine regarding the discovery of genetic defects

associated with the disease remains elusive in common forms of migraine and causative genes have not yet been identified. Thus, additional approaches for analysing the genetic basis of this disorder have been suggested. Within the past decade, using a genome-wide screen approach, several susceptibility gene loci that predispose to migraine have been identified. So far, only the locus on 4q has been replicated but no specific, disease-causing mutations have been described. New phenotyping strategies, such as latent class analysis and trait component analysis, found significant evidence of linkage of migraine to chromosome 5q21 and this region was associated with symptoms of the migraine attack such as phonophobia and photophobia. Migraine with and without aura also can be associated with rare monogenic neurovascular syndromes such as CADASIL (*NOTCH3* mutations), retinal arteriolar tortuosity and leucoencephalopathy (*COL4A1* mutations), retinal vasculopathy with cerebral leukodystrophy (RVCL: *TREX1* mutations) and familial advanced sleep phase syndrome (FASPS: CK1 d-T44A mutation). The functional characterization of these disease gene mutations is underway and may lead to new insights in the molecular pathways involved in the disease. Migraine has been noted to be comorbid with a large variety of illnesses and a genetic explanation of this association has been proposed. The association between migraine and epilepsy suggests that a genetically determined dysfunction of ion channels underlies both paroxysmal disorders. Dissecting the complex genetics of migraine and the continuing identification of proteins potentially involved in the disease will help to unravel the mechanisms underlying migraine pathophysiology. Given the co-morbidity of migraine with vascular and psychiatric disorders, the knowledge of the causes of migraine may also contribute to our understanding of these disorders.

Assessing the contribution of mitochondrial alterations in migraine headache

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Introduction: The array of clinical phenotypes associated with oxidative phosphorylation (OXPHOS) defects has expanded enormously shortly after the identification of the first mutations and deletions in the small 25th chromosome, the mitochondrial genome (mtDNA) in 1988. In the past 20 years, more common disorders of the brain with possible or established mitochondrial energy failure, including Parkinson disease and Amyotrophic Lateral Sclerosis, have long been studied but seldom associated with definitively pathogenic mtDNA variants. As primary headache disorders are often referred as "mitochondrial" in origin, we decided to study in depth the contribution of deficient OXPHOS in a subset of patients. **Materials and methods** After revisiting past and more recent literature on the putative association of OXPHOS defects in primary headache disorders, we analysed the whole mitochondrial genome in 50 patients, including 14 children, suffering from migraine with or without aura and allegedly inherited in a maternal fashion. Patients were referred from specialized Headache Clinics. Total DNA was purified from peripheral blood and whole mtDNA sequences were tested by the mitoSEQ™ resequencing system (Applied Biosystems, Foster City, CA). Due to the double genetic

origin of OXPPOS subunits, we also scanned by denaturing high performance liquid chromatography and direct sequencing the coding exons and flanking intronic sequences of the single mitochondrial DNA polymerase.

Results A number of new and already reported variants were observed in a subset of cases with migraine with aura. Combination of those “mutations” seems to define disease-related haplogroups.

Conclusions While our data propose to consider mitochondrial alterations in a limited number of cases, we conclude that more functional approaches to study OXPPOS deficiency in primary headache disorders are needed.

Mitochondrial DNA influences response to riboflavin in migraineurs

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Introduction More than 50% of migraineurs are found to be “responders” to a high-dose riboflavin prophylactic treatment [1]. It has been hypothesized that this efficacy could be related to the improvement of mitochondrial oxidative metabolism, supposed to be reduced in migraine patient [2]. To improve our knowledge about mechanisms involved in response to riboflavin in migraine prophylaxis, we analysed the role played by specific mitochondrial DNA (mtDNA) genotype.

Materials and methods Sixty-seven migraineurs completed a 4-month open trial with riboflavin (400 mg/day). Whole mtDNA sequence was performed to assess the mutation rate, the divergence from the reference Cambridge sequence, and the specific haplogroup.

Results Forty patients responded to riboflavin treatment (monthly frequency of attacks reduced more than 50%), and 27 were non-responders (NR). Thirty-one cases harboured the mtDNA H haplogroup and 36 harboured other, non-H, haplogroups (“Rest” group). Rate of overall mtDNA mutations ($t=2.821$; $p=0.006$) and, more specifically, variations in the sequences encoding subunits of Complex I ($t=3.546$; $p=0.001$) appeared to be related to riboflavin response. Responders harboured mostly in the Rest group (67.5%). Conversely, NR were mostly H (66.7%) with a significant association to low riboflavin response ($\chi^2=7.57$; $p=0.006$; OR= 0.24; C.I. (95%)=0.09–0.68).

Discussion Mutation rate in mtDNA sequences appears to be directly related to possible dysfunctions in mitochondrial oxidative metabolism. Riboflavin resulted to be more effective in patients in whom there was a higher mutation rate, and consequently a higher mitochondrial impairment [3]. Our findings show that a high mutation rate in mitochondrial Complex I and a non-H mtDNA haplogroup are the two significant genetic markers of riboflavin response in migraineurs.

Conclusions We further corroborated the efficacy of riboflavin in migraineurs. We also showed for the first time that response to treatment might be influenced genetically by a combination of variants in the mtDNA genome.

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Aquaporin 4 gene and migraine: an association study

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Introduction The pathophysiology of migraine is complex and not completely understood. Recent studies suggested a possible alteration of the blood-brain barrier (BBB) in migraine attacks. In patients with familial hemiplegic migraine, a significant BBB opening limited to the cortex and preceding cortical edema was revealed by MRI. In addition, the concentrations of matrix metalloproteinase 9 (MMP-9), a proteolytic zinc-dependent enzyme that disrupts the BBB and promotes brain edema, resulted significantly increased in migraine patients both during the attacks and in the interictal phase. The aquaporins are a family of water-selective membrane channels. Aquaporin 4 (AQP4), the main water channel in the brain, is expressed in pericapillary astrocyte foot processes, glial limiting membranes, and ependyma. This distribution suggests the involvement of AQP4 in the movement of water in the brain across the blood-brain barrier and cerebrospinal fluid-brain interface. AQP4 has therefore an important role in water homeostasis of human brain and a dysfunction of AQP4 could induce pathological conditions in neuronal activity. The purpose of our work was to evaluate the association of a biallelic polymorphism in the *AQP4* gene with the risk and the clinical features of the disease.

Methods A total of 292 consecutive patients and 257 age- and sex-matched healthy controls of Caucasian origin were involved in the study. The diagnosis of migraine was made according to the ICHD-II criteria. Patients and controls were genotyped for the biallelic (A>G) rs 3763043 SNP, selected from SNPs database of NCBI, located in the 3' UTR region of *AQP4* gene. Statistical analyses were performed using Genepop and SigmaStat.

Results Hardy-Weinberg equilibrium was verified for all tested populations. No significant difference in the distribution of *AQP4* genotypic ($\chi^2=0.748$, $p=0.69$) and allelic frequencies ($\chi^2=0.229$, $p=0.632$) between cases and controls was found. When patients were subdivided into subgroups (migraine with aura and migraine without aura), *AQP4* alleles were similarly distributed. Comparison of the clinical features of the disease according to different *AQP4* genotypes showed no significant difference.

Conclusions We found no evidence of association between a polymorphism in the 3' UTR region of *AQP4* gene and migraine in a cohort of Italian patients. Thus, our data do not support the hypothesis that the *AQP4* gene could represent a genetic susceptibility factor for migraine. Additional studies in different populations are needed in order to evaluate the precise role of the *AQP4* gene in migraine pathogenesis.

Genetic investigation methods in familiar and sporadic headache

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Recent advances in molecular medicine have provided powerful tools to identify DNA mutations responsible for different types of genetic headaches. Recent molecular techniques are applied in two main fields of genetics: the search for unknown gene mutations and the identification of mutations already characterized. The identification of new gene mutations is based mainly on three types of approaches: 1) the analysis of linkage through genome-wide scanning; 2) case-control association studies; 3) the sequence of candidate genes. Genome-wide scan studies are performed using families with a clear mendelian inheritance of the disease (parametric linkage) or through the analysis of a large number of small families in which at least two patients are affected (non-parametric linkage). The identification of genomic loci is usually followed by sequencing of the genes located in the candidate region. Functional studies are then performed in order to obtain evidence of the possible biological effect of the discovered DNA mutation. The study of mutations already known is usually performed for diagnostic purposes or to perform a genotype-phenotype correlation in order to clarify the clinical implications of the mutations. The techniques used in this type of study can be different. Point mutations can be analysed by gene sequencing, RFLP analysis with enzymatic digestion or DHPLC. Deletions and duplication in the gene can be identified by MLPA, FISH, real time PCR or Array CGH. Any chromosomal rearrangements can be analysed with standard karyotype analysis. The technical progress in the understanding of the molecular mechanisms involved in the genesis of headaches allow the development of new genetic tests for the early detection and clinical management of patients.

Neuroimaging in migraine and cluster headache

MRI in migraine and cerebrovascular disease

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The role of magnetic resonance imaging (MRI) in migraine and stroke has been already hypothesized. Migraine is a benign disorder that usually starts in young people characterized by recurrent attacks of disabling headache, sometimes preceded by transient neurological disturbances and autonomic nervous system dysfunction; the diagnosis is supported by the International Classification of Headache Disorders [1]. Generally, no brain abnormalities are present at MRI, but the occurrence of cerebral white matter lesions (WMLs) has been described [2]. WMLs are common findings in migraineurs, specially in aura patients and in younger individuals without co-occurring cerebrovascular disease risk factors. Otherwise, migraine is considered an additional risk factor for cerebrovascular disease [3], both in women and in men, and could be a direct cause of stroke; migraine and stroke seem to have the same pathological substrate. Both in migraine and stroke, conventional MRI has to be scheduled as part of clinic-radiological protocol evaluation. During migraine and stroke attack, advanced MRI techniques, like diffusion (DWI) and perfusion (PWI), could be useful in the diagnosis and in the evaluation of treatment efficacy. In fact, according to the "time is brain" concept, differential diagnosis of

acute stroke and prolonged migrainous aura is of vital importance in this era of systemic thrombolysis for acute cerebral ischemia.

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Functional magnetic resonance imaging in episodic cluster headache

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We investigated the cerebral activation centre in four patients with episodic cluster headache (CH) by functional Magnetic Resonance Imaging (f-MRI). The patients underwent a MR recording that previewed the anatomical and functional data acquisition: (1) at asymptomatic state, (2) during the attack, and (3) after subcutaneous administration of sumatriptan. The anatomical images were acquired with 3D-MPRAGE sequences and the f-MRI images were obtained with echo-planar imaging. The data were analysed with the use of software BrainVoyager QX, version 1.7. 81. In all the patients, the data showed a significant activation of the hypothalamus ipsilateral to the pain side, ascribable to a headache attack. Up to now, f-MRI has been used in the study of patients affected by other trigeminal autonomic cephalalgias but not in CH. Overall, we demonstrated the anatomical location of the central nervous system activation with a f-MRI study in CH. The rate at which a technique acquires an image determines its temporal resolution. Across f-MRI studies, the sampling rate typically varies from a few hundred milliseconds to a few seconds, which is much faster than positron emission tomography (PET) studies that integrated brain activity over intervals of about a minute or even longer. There is a great need to investigate CH and other related idiopathic headache syndromes by using f-MRI. f-MRI presents some advantages in comparison with the PET that cannot be overlooked: (a) it does not use radioisotope administrative tracers (intravenously), but endogenous tracers (deoxy-hemoglobin); (b) the anatomical and functional acquisitions could be effected in the same recording session; and (c) there is less management expenses, in comparison with the PET, which needs to have a cyclotron and a skilled staff. Taking into account these considerations and the fact that the f-MRI provides a good balance of spatial and temporal resolution, this method of study appears appropriate for investigating the pathogenetic aspects of primary headaches, in particular in analysing the symptoms that precede the onset of the headache attack. 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 physiopathology and the effects of pharmacological treatment.

Fourier space analysis on the fMRI-bold signal in the primary visual cortex in migraine with aura

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Functional Magnetic Resonance Imaging (fMRI) is widely applied to the study of the neuropathological aura processes, in particular when searching for systematic differences in the BOLD signal in the primary visual cortex. Six patients suffering from migraine aura (MA), nine without aura (MO) and ten healthy volunteers (C), matching in age and sex, underwent two block designed fMRI scans using visual stimuli, lasting 12 minutes each, with a Philips Intera 1.5 T Gyroscan. The fMRI-BOLD signal from the primary visual cortex (both splitted into right and left hemisphere and considered as a whole), as identified on an anatomical scan coregistered to the fMRI EPIs, was analysed along the extended period of time (24 minutes) and for the two scans independently in Fourier space. The relative intensity of the resonances was calculated from the power spectrum and an ad-hoc hemodynamic response function (HRF) was derived for each group. No patient developed a migraine attack during the fMRI scan. The Fourier space analysis showed a significantly different pattern of activation between patients and C and, moreover, between MA and MO. Specifically, MA showed stronger variability of the signal with respect to both the other groups and between scans. The derived HRF differed significantly between groups, raising the problem of the consistency of an fMRI analysis with predetermined basis functions. The different shape of the HRF for the three groups considered reflects a significant difference in the coupling of the neural activation with the blood flow, which may either rise from altered blood dynamics or reflect the timing of the microscopic neural activation. The Fourier space analysis, together with information about the physical source of the fMRI-BOLD signal, helps to elucidate the phenomenon.

Treatment in migraine

Combination therapy in the acute treatment of migraine headache

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Over the past decade migraine care has been greatly optimized by the discovery of drugs able to act at various levels in the migraine pathophysiology process. Monotherapeutic approaches to migraine do not provide rapid, consistent and complete relief in all migraineurs with a severe impact on daily life and disability. The major issue is that no single agent currently exists that targets all the hypothesized mechanisms involved in the complexity migraine pathophysiology. Combination therapy is based on a multimechanistic approach that targets different aspects of the pathophysiological mechanism, taking advantage of pharmacodynamic interactions to improve outcome. Furthermore, drug administration, because of pharmacokinetic interactions, may modify absorption, distribution, metabolism or excretion of the drugs combined. A synergic mechanism is exemplified by a combination between triptan and non-steroidal anti-inflammatory drugs (NSAIDs). Triptans are believed to interrupt the migraine process in 3 ways: by direct vasoconstriction

of meningeal vessels, by reducing neurogenic inflammation and by inhibiting central transmission of nerve impulses to the trigeminal nucleus caudalis (TNC). NSAIDs may also inhibit neurogenic inflammation by blocking formation of prostaglandins in the meninges, but additionally, they may have the capacity to interrupt established central sensitization since they may interfere with the glial production of prostaglandins. A pharmacokinetic interaction between triptans and NSAIDs may also play a role since coadministration of sumatriptan and naproxen appears to slow the elimination of naproxen from plasma. In the acute treatment of pain, caffeine has been shown to enhance the effect of a variety of analgesics and increases the rate or extent of absorption of aspirin, ergotamine and acetaminophen. The mechanism responsible for this pharmacokinetic mechanism is not fully known whereas any potential pharmacodynamic (multimechanistic) effect of caffeine may be related to its ability to block adenosine receptors. Metoclopramide is a prokinetic agent that stimulates gastric motility and accelerates gastric emptying; its prokinetic effects are thought to be mediated primarily by actions at the serotonin 5-HT₄ receptors in the upper gastrointestinal tract. Metoclopramide also has an antiemetic effect that stems from blockade of dopamine D₂ receptors in the CNS. Both effects may contribute to the added efficacy that has been seen with metoclopramide combinations. A pharmacokinetic interaction would be produced by the increased gastric motility since the coadministered agent would be absorbed more rapidly, while the antiemetic effects of metoclopramide would reduce nausea and vomiting. In conclusion, combination therapy can induce an increase in effectiveness of drugs administration and reduction in adverse events.

Triptans: what is the clinical importance of kinetic differences?

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Triptans, selective antagonists of 5-HT_{1B/1D} receptor, are effective and safe drugs for acute migraine treatment. Their marketing has improved the methodologies of clinical trials, and has allowed defining which characteristics should have the ideal medication according to patients: pain-free response within 2 hours, no recurrence or need for other drugs, consistency of response, oral administration, good tolerability, safety, and no drug-drug interactions. Triptans do not always correspond to these parameters. In particular, the maximum response after oral administration, measured as pain-free after 2 hours, is approximately 70% in clinical trials and up to 40% of attacks fail to respond to a particular triptan. Furthermore, less than 2/3 of patients respond to a triptan in 3/3 attacks [1]. In Italy, 6 triptans with similar mechanism of action are available, but with different kinetic profiles. In alphabetical order, the first one is almotriptan. Its oral bioavailability is 70%-80%, T_{max} is about 1 to 4 hours, and elimination half-life is 3 to 4 hours. Oral bioavailability of eletriptan is 50%, its elimination half-life is 4 to 5 hours, and T_{max} is about 1.3 hours. Frovatriptan presents long half-life (25 hours), but a relatively low bioavailability of 24% to 30%, and T_{max} is 2 to 4 hours. Elimination half-life of rizatriptan is 2–3 hours, bioavailability is 40%-50%, and T_{max} is about 1–1.5 hours. Sumatriptan undergoes first-pass metabolism. Its bioavailability following subcutaneous administration is much higher (96%) than after oral (14%) administration, and elimination half-life is about 2 hours. Half-life of zolmitriptan is 2.5 to 3 hours, and its oral bioavailability is approximately 40%. The clinical importance of pharmacokinetic differences

after oral administration has not been established yet. There are no elements to foresee which triptan works best for any given patients [2]. As far as sumatriptan is concerned, the highest therapeutic gain (headache response at 2 hours on active medication minus headache response on placebo) is obtained by venous administration, followed by subcutaneous and then oral, nasal, and rectal administration. Therapeutic gain does not depend on the quantity of sumatriptan in the circulation, measured as $AUC_{0-1\text{st}}$. It has been suggested that pharmacokinetics during early post-dose interval (0–2 hours) is the most important one for clinical response and that the initial rate of absorption and the height of the plasma levels reached may be closely related to headache relief [3]. A slow and reduced early absorption after oral administration could therefore explain the poor response reported by some patients.

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Allodynia and the autonomic system activation as a possible cause of a lack of response of migraine attack to triptans

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Background and objective To test the hypothesis that the activation of the autonomic nervous system during a migraine attack without aura and the manifestation of allodynia influence the response to triptans.

Patients and methods The presence of autonomic symptoms was carefully evaluated in 126 consecutive subjects (M/F 52/74; mean age: 38.2±8.4) with a history of MA- by both a structured interview and telethermographic investigation. Based on these findings, the entire group was dichotomized into a subgroup with autonomic symptoms (A+; n=54) and a subgroup without (A-; n=72). The two subgroups were comparable for demographic characteristics and other clinical variables, including pain severity. Clinical response to triptans (eletriptan 40-mg tablets) during 3 consecutive migraine attacks was recorded in each subject. End points were pain-relief and pain-free response at 1 and 2 hours when considering both the entire group of patients and the number of crises.

Results Pain-relief was reported in 48.1% and 62.5% of migraine attacks at 1 hour and in 64.8% and 78% at 2 hours, while pain-free was observed in 29.2% and 39.6% at 1 hour and 25.3% and 41.0% at 2 hours in the A+ and A- subgroup, respectively. Response to treatment turned out to be related to the co-existence and the complexity of autonomic symptoms. In particular, the more complex the autonomic activation, the less evident the benefit of treatment. A significant difference between the two subgroups was observed in pain-relief at 1 hour and in pain-free at 2 hours.

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

Trigger factors in migraine and tension-type headache

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Primary headaches are widespread neurological diseases, and therapy is not always satisfactory. An important topic is the identification of trigger factors (TF) of the attacks, to avoid them in order to reduce the onset of related crises. The objective of this study was to identify and evaluate TF, by using different questionnaires, in a group of 398 patients (74% women, 26% men) visited at our Headache Centre from January 2007 to December 2007, affected by migraine with (MA, n=39), and without aura (MO, n=327) and episodic tension-type headache (ETTH, n=32). One group (221) received an open questionnaire, where they indicated possible TF of attacks; another group (177) received a structured questionnaire, listing 40 different triggers, which summed up those considered in previous studies on this topic [1–3]. We considered the number of TF related to the type of administered questionnaire, sex, diagnosis, history of headache, the latency between the exposure to the trigger and the onset of the attack. Moreover, we evaluated if there were differences between “naive” patients and those previously visited in other specialized structures. TF more frequently reported were stress (56%), menstruation (32%), and sleeping deprivation (26%). We found a very significant difference between the number of TF identified with the structured questionnaire (7.2±4.6) than with the open one (1.7±1.8). There were no significant differences between the number of triggers reported by naive patient and those previously visited. Women recognized more trigger factors than men (3.9±4.0 vs. 3.6±4.3). The number of trigger factors was not related to the length of headache history, nor to the intensity of the attacks. Latency time between the exposure to the trigger and the onset of attack was less than 6 hours in almost 68% of the patients. Triggers which characterized these two primary headaches were eyestrain and reading for ETTH, and smells for MO. We conclude that a structured questionnaire is much more suitable than an open one to identify TF. We stress the relevance of its use as a part of the history taking in a Headache Centre.

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New perspectives in the prophylaxis of headache

Body weight gain in migraine prophylaxis with flunarizine, amitriptyline and topiramate

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Drugs used in the prophylactic therapy of primary headaches may have an effect on body weight. This study considers weight variations with flunarizine (5 and 10 mg), amitriptyline (20 and 40 mg) and topiramate (100 mg) used in monotherapy for a period of three months, in relation to the dose and type of drug, age, gender, initial Body Mass Index (BMI), appetite modification, and effectiveness of therapy. Return to initial body weight after drug withdrawal was also evaluated. A total of 174 patients were enrolled in the study (152 F, 22 M; age 37±13 years), suffering from migraine with (MA, n=20) or without aura (MO, n=129) or episodic tension-type headache (ETTH, n=25). Patients were not following prophylactic therapy, nor were they affected by pathologies that could cause body weight variations. In an outpatient setting, weight and height were evaluated; thereafter, weight was monitored weekly by the patient at home for three months of prophylactic therapy and for an additional three months after prophylaxis discontinuation. The control sample consisted of 70 subjects of both genders (72% F, 28% M; age 38±10 years), who followed only attack therapy. A weight increase was recorded in 90% of patients treated with flunarizine 10 mg (n=12), in 56% with flunarizine 5 mg (n=61), in 45 % with amitriptyline 40 mg (n=18), and in 42% with amitriptyline 20 mg (n=59); a weight loss (2.5±1.3 kg) was recorded in 71% of patients treated with topiramate (n=24). Flunarizine 10 mg caused the greater weight increase (5.9±4.2 kg), followed by flunarizine 5 mg (4.0±1.9 kg). The percentage of patients who returned to their initial weight three months after prophylactic treatment discontinuation varied from 62% for amitriptyline 20 mg, to 52% for amitriptyline 40 mg, to 35% and 30%, respectively, for flunarizine 10 and 5 mg. No statistically significant differences were found for age, gender, BMI or headache improvement. A drug-induced appetite change seems to be relevant in determining weight modification. An increased appetite is more manifest in patients (49%) treated with flunarizine 5 mg compared with those (29%) treated with amitriptyline 20 mg. Topiramate determines an appetite reduction in 46% of patients. Our data indicate that the use of flunarizine, compared to amitriptyline, is associated with a greater risk of weight gain in terms of percentage of patients, mean weight gain and failure to return to initial weight three months after discontinuation of therapy, in particular at the dosage of 10 mg. When appropriate, alternating a course of amitriptyline or flunarizine with topiramate could be of help in managing body weight modification.

Low-dose ASA in the prophylaxis of migraine with aura: a retrospective study

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Migraine with aura (MA), a primary headache affecting a significant minority (30%) of migraine patients, even if less frequent than migraine without aura, may often cause severe anxiety and distress. According to the studies of the last years, MA seems to be a risk factor for cardio-vascular diseases (CVD) which are the leading cause of death in Western countries. It has been hypothesized to have a neurovascular basis and several studies suggest an association between MA, ischemic stroke and an adverse cardiovascular risk profile. A better understanding of the

mechanisms underlying the aura will increase our insight into the mechanisms by which migraine headaches are initiated and may hopefully lead to more effective therapies, aimed at preventing migraine headaches before they start. The therapeutic prophylaxis options for this form of migraine are very few and not always tailored to prevent the neurological symptoms. Aim of this study is to evaluate the efficacy and tolerability of acetylsalicylic acid (ASA) for MA prophylaxis in patients attending our Headache Centre. We reviewed the charts of adult patients with MA according to the ICHD-II criteria treated for a period of at least 4 months with ASA. Patients began taking ASA at a dosage of 300 mg/day for minimum 4 months, then reduced the dosage to 200 and 100 mg/day before stopping. Headache frequency, duration, intensity, disability, accompanying symptoms duration and intensity of the aura were evaluated before beginning the treatment and after it ended. A noticeable reduction in the frequency of the attacks and in duration and intensity of the auras was observed in the majority of the patients. Very few adverse events (mainly gastric pain) were reported by very few patients. On the basis of the data of this retrospective analysis ASA seems to be a very effective prophylactic treatment for MA. Up to now, ASA is the most widely prescribed medication for prevention and treatment of CVD and related atherothrombotic events and is one of the most widely used pharmacologic agents in the world. On the basis of these observations ASA seems to be particularly indicated in the prophylactic treatment of MA considering also that it has a very good tolerability profile in particular when compared to the other pharmacological prophylaxis treatment actually used for MA.

Improving care through health economics analyses: cost of illness and headache

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The impact of headache disorders is a problem of enormous proportions, both for the individual and the society. The medical literature tried to assess the effects on individuals, by examining prevalence, distribution, attack frequency and duration, and headache-related disability, as well as effects on society, by looking at the socio-economic burden of headache disorders (Rasmussen, 1999, Lanteri-Minet et al., 2003). The issue of costs represents an important problem too, concerning both direct and indirect cost. Direct costs concern mainly expenses for drugs. Migraine has a considerable impact on functional capacity, resulting in disrupted work and social activities: many migraineurs do not seek medical attention because they have not been accurately diagnosed by a physician or do not use prescription medication (Solomon et al., 1997). Indirect costs associated with reduced productivity represent a substantial proportion of the total cost of migraine as well. Migraine has a major impact on the working sector of the population therefore determining that indirect costs outweigh the direct costs. The study will explain the notion of cost of illness, examining how it could be applied in such a framework. Then, an overview of the studies aimed at measuring direct and indirect costs of migraine and headache disorders will be carried out, later shifting on the relationship between costs and quality of life for people affected by headache disorders. Finally, a brief review on advantages of new pharmaceuticals and preventive treatments for migraine for patients and society will outline improvements in the context of cost-effectiveness and cost-utility analysis.

Headache in children

Hyperreactivity and migraine risk: an 18-year follow-up study

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This study represents an attempt of detecting a connection between migraine and early hyperreactivity, considered as an early temperamental characteristic. Hyperreactive (HPR) newborns show a low threshold of sensory stimulation and a lack of habituation to stimuli. Studies by visual and auditory evoked potentials and event-related responses, suggested that the lack of habituation is the main abnormality of sensory processing in migraineurs. It also seems that migraineurs' children are more "stress-reactive" than others, with lower thresholds of physiological reaction. In this study we evaluated, after at least 18 years, the prevalence of primary headache in HPR infants. We contacted 100 children (males=60, females=40; mean age: 17.5 years): 50 HPR and 50 non HPR, the groups were similar for age and gender. All infants were visited between 1 to 18 months of life. We administered a revised headache questionnaire (2004), and χ^2 test was used. A Chi-square test revealed a significant relationship between HPR and headache disorders (Chi-square = 8.01; d.f.=2; $p<0,05$). A child who begins life "amplifying" internal and external stimuli will have the tendency of responding to the same stimuli in an "amplified" manner for the rest of his/her life. HPR may be an important risk factor for migraine development, stressing the role of early hyperexcitability in the pathophysiology of migraine.

Osmophobia and juvenile primary headaches in Italy

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Background In the ICHD-II, the accompanying symptoms nausea, vomiting, photophobia and phonophobia remain an essential part of the differential diagnosis between migraine (M) and tension-type headache (TTH) [1]. In the Appendix of this classification (point D), it was hypothesized that osmophobia (OSM) could be introduced among diagnostic criteria of migraine without aura (MO). Recently, this symptom has been found to be very specific for the diagnosis of adult migraine [2], but systematic studies in children are still lacking [3].

Objectives To investigate the prevalence of OSM in juvenile headache sufferers and to analyse the diagnostic utility of OSM in order to distinguish MO from episodic tension-type headache (ETTH).

Methods We examined 1020 consecutive patients (4–17 years, mean age: 11.1±2.8 SD, 484 males and 536 females) presenting at 10 Italian Juvenile Headache Centres from 2005 to 2007 by means of a semi-structured questionnaire. The diagnosis was M in 585 patients (57.4%), TTH in 254 (24.9%), "Probable formes" of M and TTH in 178 (17.4%) and Headaches not elsewhere classified in 3 (0.3%).

Results The prevalence of OSM during attacks in all patients was 28.5%, mainly in M (34.5%) versus TTH (14.6%) ($p<0.0001$), without correlation to age or gender ($p=0.42$). In particular, OSM was found in 35.6% of MO, in 21.4% of migraine with aura, in 38.5% of chronic migraine, in 16.0% of ETTH and in 7.1% of chronic TTH. In TTH patients, the subgroup with OSM presented a greater family history for M than those without OSM (73.0% vs. 63.1%).

OSM showed more specificity (85.4%) than photophobia (84.5%) or phonophobia (72.8%) in the differential diagnosis between both M and TTH, as well as MO and ETTH (respectively, 84.0%, 83.5% and 70.7%).

Conclusions The prevalence of OSM during M attacks in children was similar to the data of adults [2]. This confirms that OSM represents a poorly sensitive (35.6%), but a fairly specific symptom (84.0%), that could become a supportive diagnostic criterion for the differential diagnosis between MO and ETTH even in children.

The finding of OSM also in a subgroup of TTH patients represents a prognostic feature for an increased tendency of this cohort to become migrainous.

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Focal gray matter changes in the cerebral pain network of child and adolescent migraine patients

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Introduction Migraine is considered a frequent, primary headache disorder due to transient abnormal brain function. According to the current classification of the International Headache Society, structural brain lesions are absent in primary headaches. However, recent studies with voxel-based morphometry (VBM), a highly sensitive technique to detect focal gray and white brain matter abnormalities, demonstrated selective brain alterations in migraine (gray matter decrease in right superior temporal gyrus, right parietal operculum, right inferior frontal gyrus, left precentral gyrus and gray matter correlation in anterior cingulate cortex, left middle frontal gyrus, left parietal operculum, left amygdala and insula with the frequency of migraine attacks). The purpose of this study was to search for the presence of structural abnormalities in child and adolescent patients with migraine using the optimized voxel-based morphometry method.

Materials and methods A group of 9 right-handed migraine patients (7 females, 2 males; mean age ±SD: 12.33±3.04 years, range 8–17 years), diagnosed according to the ICHD-II criteria,

underwent high resolution structural magnetic resonance imaging (MRI). Data was analysed using MATLAB 7.1 and Statistical Parametric Mapping 2 (SPM2). A regression analysis was performed because a matched control group was unavailable to search for a relationship between local gray matter changes and the clinical characteristics of migraine.

Results We found a significant correlation between the frequency of migraine attacks and the reduction of gray matter concentration in Middle Cingulate Cortex, Medial Frontal Gyrus, Inferior and Superior Frontal Gyrus and the increase of gray matter concentration in Right Middle Frontal Gyrus of migraine patients.

Discussion and conclusions Our study shows significant gray matter changes in young migraine patients in several cortical areas involved in pain processing related to frequency of migraine attacks. Functional neuroimaging shows that several brain regions are activated by pain, including frontal and pre-frontal cortices, operculo-insular cortex, primary and secondary somatosensory cortices, cingulate cortex, thalamus and regions within the parietal and temporal cortices. Our data supports the hypothesis that migraine may be considered a progressive brain disorder involving the brain development of young patients and highlights the importance of prophylactic antimigraine therapy in order to avoid the progression of the disease.

Spatial attention in children with primary headache: a combined neurophysiological and neuropsychological approach

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Introduction Although attention capability has been investigated in patients with primary headache by using neuropsychological tools, the cerebral mechanisms underlying spatial attention, as expressed by somatosensory evoked potential (SEP) modifications following spatial discrimination, have never been explored.

Materials and methods We studied 36 children: 16 patients with migraine without aura, 10 children with tension-type headache (TTH), and 10 healthy subjects. Scalp SEPs were recorded by 4 electrodes, placed in the T3, T4, Cz, and Fz locations of the 10–20 International System, after stimulation of both right and left median nerve. Two different conditions were investigated: 1) neutral (NC) and 2) spatial attention (SAC). In the NC, subjects were invited to relax and to disregard the electrical stimuli. In the SAC, subjects counted silently mechanical targets (taps) delivered to the tip of the first and second finger of the hand ipsilateral to the median nerve stimulation. Spatial attention was assessed by the “deux barrages” test, in which children had to mark target symbols mixed with others as fast as they were able to.

Results SEP recording in the NC showed a N120 component in both temporal regions (N120c – contralateral N120 – and N120i – ipsilateral N120) and a central N140 potential, which reached its maximal amplitude at Cz vertex. There was a significant effect in the study group (migraineurs, TTH patients, and controls) on the N140 amplitude modification between the NC and the SAC (ANOVA test: $F=21.4$, $p<0.001$). The post-hoc analysis showed that the N140 amplitude increase in SAC, as compared to the NC,

was significantly higher in both migraine and TTH patients than in healthy subjects ($p=0.03$). Moreover, in migraineurs the N140 amplitude increase in SAC showed a significant positive correlation with the R2 index of the “deux barrages” test ($p=0.02$). Given that the R2 index is a marker of the subject’s ability in identifying the highest number of target signs, our results showed that migraine patients with a higher N140 amplitude increase in SAC had also a better neuropsychological performance.

Conclusions The higher N140 amplitude increase between NC and SAC in headache patients, as compared to healthy subjects, suggests that a larger amount of attentional resources have to be used in patients to accomplish the task. This strategy appears particularly effective in migraineurs in whom the neuropsychological performance showed a positive correlation with the neurophysiological result.

Sleep pressure score and neuropsychological impairment in childhood migraine

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Introduction Migraine is recognized as a primarily neural condition, with changes in neural physiology. Several reports suggest relationship and/or comorbidity between sleep disorders and headache, linked to common pathophysiological substrates. Moreover, sleep-disordered breathing (SDB) and excessive daytime sleepiness (EDS) are more frequent compared to children from a normative community sample. It is well known that in SDB, reciprocal changes in the frequency of spontaneous and respiratory-related arousals occur with increasing SDB severity in children and that a sleep pressure score (SPS) could be developed to potentially reflect mounting sleep pressure in children who breath abnormally during sleep and could explain their neuropsychological impairment.

Objectives The aims of this study were to assess the relationship between SPS and executive functions in childhood migraine.

Materials and methods A total of 19 children (10 males) aged between 7–11 years (mean 8.6 ± 1.9) with migraine were invited to the Sleep Laboratory of the Clinic of Child and Adolescent Neuropsychiatry of the Second University of Naples overnight to undergo complete polysomnography. The obstructive apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of total sleep time. Arousals were expressed per hour of total sleep time (the arousal index) and included respiratory related (occurring within 3 seconds following an apnea, hypopnea, or snore) and spontaneous arousals. In addition, the SPS was calculated as $SPS = (\text{respiratory arousal index}/\text{total arousal index}) \times (1 - \text{spontaneous arousal index}/\text{total arousal index})$, and the empirically derived score of 0.25 was used as the threshold for evidence of increased sleep pressure [1]. To examine planning and problem solving ability, the Tower of London Test (ToL) was used referred to Italian normative data and expressed as z-score.

Results Twelve children were in the group with a calculated $SPS \geq 0.25$ (SPS_{High}) and 7 children in the group with a $SPS < 0.25$ (SPS_{Low}). No statistical differences were found in the two groups regarding age ($p=0.958$). Children with High SPS had a lower ToL score with respect to the Low SPS group (0.98 ± 0.45 vs. 2.06 ± 0.96 ; $p=0.004$).

Discussion Research has shown that migraine could affect neuropsychological functions (i.e., verbal, visuo-spatial memory, and selective attention tasks) [2]. SPS is a measure of sleep fragmentation, associated with significant decrements in the neurocognitive

function in children. These deficits in neurocognitive performance persisted even after controlling for all potential confounding factors, such as AHI and SaO₂.

Conclusions The abnormal executive performance score in children with high SPSs is consistent with prefrontal cortex dysfunction in SDB, which could also explain the same impairment in headache children.

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Mitral valve prolapse and prothrombotic risk factors in children and adolescents with migraine with aura and other idiopathic headaches

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Introduction A complex bidirectional relation between migraine, mostly migraine with aura (MA), and ischaemic stroke (IS) is known [1]. The mechanism by which migraine predisposes to IS has not been clearly delineated yet, although the risk of IS in women with migraine seems to increase by means of oral contraceptive use and smoking [2]. Other potential factors increasing the risk of stroke in migraineurs include endothelial dysfunction, prothrombotic factors, vasospasm, hyperhomocysteinaemia and possible embolic mechanisms such as paradoxical embolus via a patent foramen ovale (PFO) or related to mitral valve prolapse (MVP) [3].

Objective The prevalence of cerebrovascular risk factors, i.e., mitral valve prolapse (MVP) and abnormalities of haemostasis, was investigated in children and adolescents affected by MA and compared with controls (i.e., other idiopathic headaches).

Materials and methods We recruited twenty MA patients (10 M and 10 F; range 8–17 years) and 20 sex- and age-matched controls. Both groups underwent M-mode, 2D and color-doppler transthoracic echocardiography to detect MVP and the following laboratory investigations: plasma Prothrombin Time, activated Partial Thromboplastin Time, Thrombin Time, Fibrinogen, Protein C, Protein S, Homocysteine, Lupus Anticoagulant, vWF Ristocetin Cofactor activity, Anticardiolipin antibodies IgG and IgM. Factor V Leiden, Factor II and MTHFR were investigated for genetic mutations.

Results The prevalence of MVP was significantly higher in MA subjects compared to controls (40% vs. 10%; $p < 0.05$). MA patients showed a higher rate of positive Anticardiolipin antibodies (aCL) IgM titres (45% vs. 10%; $p < 0.05$). Moreover, we found a higher prevalence of aCL in MA patients with MVP compared with control subjects with MVP.

Discussion If confirmed by larger studies, these findings should be considered in the clinical practice and suggest a possible difference in pathophysiology between MA and other idiopathic headaches.

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Sleep disorders in children with headache

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The relationship between headache and sleep has been documented in medical literature [1]. Headaches that occur at night or in the early morning sometimes reflect increased intracranial pressure, but many migraine episodes occur at night and awaken a child who went to bed without symptoms. Changes in sleep duration and sleep quality are capable of affecting headaches of different types [2]. The aim of the present study was to assess sleep disorders in a clinical sample of children attending our Paediatric Headache Centre in the year 2007. During this period, 327 children aged 4 to 17 years were evaluated for headache for the first time. They underwent a physical examination and structured interview. Sleep complaints occurred in 39 patients (11.9%), aged 7 to 13 years; 19 were males and 20 females. Six of them had migraine without aura; two migraine with aura. Twenty-six had tension-type headache and three chronic daily headache. Two girls had migraine only during the night (hypnic headache?) [3]. Different types of headache were diagnosed according to the ICHD-II criteria. The sleep complaints we observed were: insufficient total sleep (22 children); difficulty falling asleep (15); night wakings (32); daytime sleepiness (5); snoring (7); bruxism (2); child co-sleeping with parents (9); nightmares (3); breathing pauses (3); somnambulism (2); sleep talking (8); sweating during sleep (3). Many patients had more than one disorder. Our findings provide further support for an association between headache and sleep disorders among children and adolescents with primary headaches. In developing a treatment strategy, it is important to include appropriate sleep hygiene. Behavioural therapies, such as relaxation techniques, and interventions targeting sleep habits may improve headache symptoms and sleep patterns.

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Case reports

Case report: sporadic hemiplegic migraine or migraine with hemiplegic aura and liquor pleocytosis (Mollaret's)?

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We report the case of G.G., female, 9-year-old, positive familiarity for migraine without aura (maternal grandmother, mother and sister). She started suffering from a slight illness with nausea, sometimes vomit, stomach-ache, dizziness and fronto-temporal bilateral headache. She was hospitalized in a paediatric division 3 years ago and she was discharged with the diagnosis of “infantile jerks”. She arrived in our Emergency Room from school, because of sudden nausea, visual disorder with perception of “coloured spots”, with the sensation of “being in a dream”, followed by difficulty in walking and fronto-temporal pulsing headache. Neurological examination showed a pyramidal motor right hemisindrome with asymmetric ROT for right > left and Babinski on right side. Brain MRI with diffusion study and angio MRI were normal. The symptomatology completely cleared up after about 4 hours. Two days later a new similar clinical manifestation lasted about two hours. EEG revealed theta waves on the left side. Her parents refused the lumbar puncture to evaluate the possible presence of liquor pleocytosis to exclude a migraine with hemiplegic aura or “Mollaret’s”. What to do? After consultation with her parents, it was decided that a genetic investigation be performed to exclude hemiplegic isolated migraine; we also suggested that the patient be brought immediately to the Emergency Room, in case of a new attack similar to the previous ones, for the execution of rachicentesis during the acute phase, which her parents agreed to do. While waiting for the results of the genetic investigation, we decided to start a prophylactic therapy with valproic acid because of the great number of crisis described as migraine (3–4 each month). After about 40 days the patient was free of crisis at the control visit. Could an epileptic seizure be completely excluded? What other kinds of examinations could be useful? The case is presently unresolved and in discussion.

Status migrainosus and persistent aura without infarction as an atypical manifestation of CADASIL

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Introduction CADASIL is an autosomal dominant disease characterized by migraine with or without aura, psychiatric disturbances, stroke, and dementia. In patients with incomplete family history and an unusual clinical presentation the diagnosis of CADASIL may be challenging. We describe an atypical presentation of CADASIL.

Case report A 34-year-old woman was hospitalised for headache associated with visual disturbances. In the previous four years she had three recurrent typical attacks of migraine with visual aura that were treated with oral sumatriptan. Family history revealed that her father had an ischemic stroke at the age of 40 and her grandfather had cognitive impairment and psychiatric illness. On February 2008, after sporting, she had flashing lights in the visual field and left oral and arm paresthesias that lasted a few minutes and were followed by a severe migraine attack. The day after, despite having taken 4 pills of sumatriptan 50 mg she had no pain-relief and developed a visual field defect. She arrived to our attention 7 days after the onset of migraine. Due to persistent headache she had taken a total of 700 mg of oral sumatriptan. At the neurological examination she was confused, disoriented, with left hemianopsia, and

paresthesias on the left side of the face and of the upper limb. Brain magnetic resonance imaging (MRI) showed on FLAIR sequences, multiple lacunar infarcts and bilateral hyperintense lesions in the periventricular regions and in the temporal lobes without contrast enhancement. Diffusion weighted sequences did not reveal any acute ischaemic lesion. Shortly after brain MRI the patient had a generalized epileptic attack treated with midazolam and mannitol i.v.. After mannitol infusion her neurological deficits and the headache gradually vanished within 2 hours. Laboratory and cerebrospinal fluid examinations, echoduplex and transcranial duplex scans were normal. The Notch3 gene analysis revealed a heterozygous mutation in the exon 4 (R141C) and the skin biopsy showed deposits of granular osmiophilic material (GOM) within the vascular smooth muscle basal lamina, thus suggesting the diagnosis of CADASIL [1].

Discussion Our patient had a status migrainosus with persistent aura without infarction consistent with an atypical presentation of CADASIL [2]. We caution in prescribing triptans in the absence of a careful diagnosis even in young subjects and to consider the possible relief of some accompanying symptoms with osmotic agents.

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Bilateral blindness secondary to giant cell arteritis: a reappraisal

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An 84-year-old woman was referred to the Department of Surgery because of persistent abdominal pain in the right iliac region associated with vomiting and possible melena; the laboratory tests revealed an iron deficiency anemia. On the fifth day of hospitalization, she complained of a sudden and progressive loss of vision in her left eye, that resulted in complete blindness. Therefore, she underwent a cerebral CT scan, which showed the presence of several bilateral areas of tomographic hypodensity in the cerebellum and in both occipital lobes, with no enhancement after contrast medium injection. Within 12 hours, she also lost the vision in the right eye. Further data about her clinical history indicated that several months before she had had a transient visual loss in the left eye; shortly afterwards she had started complaining of a persistent, dull headache in the left fronto-temporal region, without any further neurological signs or symptoms. She took NSAIDs, with partial relief of the pain. The neurological examination was unremarkable, except for the bilateral blindness. Because of notably elevated erythrocyte sedimentation rate (100 mm/1 hour) and C reactive protein level (17.5 mg/dl), the diagnosis of giant cell arteritis became most likely, and a high-dose steroid therapy was started, even in absence of a temporal artery biopsy. The clinical course rapidly worsened, with the occurrence of an epileptic seizure, and later with the appearance of a right motor hemisindrome. A cerebral MRI with gadolinium revealed the presence of several

ischemic areas, most of them in the cerebellum and in the mesencephalon. The general conditions quickly aggravated, and the patient died, due to an acute heart failure. Irreversible blindness may complicate the course of giant cell arteritis especially if the diagnosis is delayed and/or the steroid therapy is started too late. Systemic symptoms can mask the diagnosis, in particular when headache is not pointed out by the patient as a major symptom and the temporal arteries are not swollen, tender and thickened to palpation. The presence of cerebrovascular accident, previous episodes of amaurosis fugax and anemia on admission represent a warning to the development of irreversible blindness. Moreover, blindness can be bilateral in up to 5% of the cases in some reports and, although rare, it may appear even simultaneously in both eyes. An early diagnosis of giant cell arteritis is therefore of paramount importance to prevent blindness.

Chronic migraine in atypical Cogan's syndrome

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Cogan's syndrome is a rare autoimmune disease with systemic involvement. It appears in young people and has two presentations: the typical form characterized by keratitis, sudden deafness with or without vestibular syndrome and the atypical form with different non keratitic ocular diseases (mainly uveitis and episcleritis) and a great variety of systemic symptoms related with the autoimmune etiology of the process [1]. Fever, cardiovascular, vasculitis, gastrointestinal and neurological symptoms are further manifestations of the syndrome whose aetiology remains unknown. For most patients either the eye or ear alone are first involved. In the typical form the mean interval between the involvement of the two organs is 3 months, but it can be as long as 11 years for the atypical one. Cogan's syndrome has a bad prognosis and deafness appears in 25% of treated cases and in 60% of untreated patients. No treatment has proven spectacularly effective. We report a case of atypical Cogan's syndrome in a 42-year-old woman with chronic migraine. At the age of 17 she developed a hearing loss. Audiometry revealed a bilateral high- and mid-frequency sensorineural hearing loss. At the moment the patient uses an acoustic prothesis. At the age of 18 the patient experienced an important visual failure in RE and a diagnosis of anisometropic amblyopia was done. In the following years frequent episodes of conjunctivitis, subconjunctival hemorrhage and episcleritis occurred. At the age of 20 polyarthralgias and myalgias appeared, followed by Raynaud phenomenon at 27 years of age. The clinical features evolved with the presence of upper arts and trunk livedo reticularis with ANA and APA positiveness and reduction of C4 at age 40. Mixed connectivitis was diagnosed and a therapy with hydroxychloroquine and acetyl salicylic acid was established. The patient comes to our observation for migraine without aura, dating since she was 20 years old; the critical frequency in the last months, results almost daily. Magnetic resonance images showed multifocal hyperintense lesions in the supratentorial white matter. Cerebral fluid protein levels were normal. No oligoclonal bands were detected in CSF. EEG highlights diffuse theta anomalies. Anomalous transmission along acoustic way was detected by BAEP. Retinic fluoroangiography results normal. We diagnosed atypical Cogan's syndrome. Therefore headache can be a part of Cogan's syndrome neurological onsets.

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Understanding headache associated with intracranial neoplasms in pre-verbal children: a case report

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Introduction Signs and symptoms of brain tumours are by no means pathognomonic in the paediatric age. For this reason, the diagnosis in the early course is often very difficult [1]. Abnormalities associated with raised intracranial pressure, motor and visual systems dysfunction, weight loss, macrocephaly, growth failure and precocious puberty are the commonest features [2]. Several studies report headache is one of the first symptoms in children with intracranial neoplasms. The approach in this age group is peculiar in several ways: first of all the verbal expression of pain is frequently wanting and other behavioural indicators should be considered. We relied upon them in suspecting diagnosis of intracranial tumour in a 3-year-old child with incomplete development of language.

Methods The patient was referred to us because of a behavioural change with crying and irritability, with frequent nocturnal awakenings. On neurological examination, she showed unsteadiness and walking disturbances. The EEG disclosed focal sharp and wave paroxysms in the left frontal-temporal (F-T) area. We hypothesized a secondary headache related to an intracranial neoplasm and decided to perform neuroradiological investigations.

Results The brain MRI confirmed the presence of a voluminous mass in the left F-T area nearest to the motor area of the right lower extremity. The patient was subjected to a neurosurgical treatment of ablation of the tumour with success. Microscopic examination showed neoplastic growth characterized by both spindle and enlarged cytoplasm cells, at times arranged in vortex patterns. Cancer cells were immunoreactive for EMA. There was the presence of brisk mitoses (>10/10 HPFs) and multiple necrotic foci. Proliferation index Ki67 was at times 15%-20% and it was documented focal infiltration of cortical nervous tissue. On the basis of these neuropathological findings, the diagnosis of atypical meningioma (WHO grade II) was considered.

Conclusions In young children the frequency of secondary headaches is extremely high, but our attempt to make a quick diagnosis is conditioned by the development of their language skills. The majority of studies have attested the importance of a quick diagnosis to improve the prognosis. For this reason, it is crucial to consider also non language-dependent indicators of headache, such as crying, irritability and neurological signs [3]. In case of doubt or to confirm a suspect, it is also recommended to perform neuroradiological investigations.

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Glossopharyngeal neuralgia, syncope and Collet-Sicard Syndrome: case report

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Introduction Glossopharyngeal neuralgia is an uncommon condition that has rarely been described in association with syncope identified by brief episodes of bradycardia, asystole and hypotension [1, 2].

Case report We report the case of a 47-year-old male who came to our observation for episodes of left parietal stabbing pain, irradiated to homolateral neck and tongue, followed by vomiting and brief loss of consciousness. During the last year he complained of progressive dysphonia and dysphagia. EEG during an attack showed diffuse, bilateral delta activity. During one of these episodes, personally observed, he had prolonged bradycardia with asystolia which required cardiopulmonary resuscitation and bicameral Pace Maker implantation. Neurological examination revealed left Collet-Sicard syndrome (deficit of IX, X, XI, XII cranial nerves). Neck TC showed a small lesion with mild contrast enhancement in the region of the left jugular foramen and C1 lateral mass. The lesion was surgically removed through extreme lateral transcondylar approach (histological examination: chondroma). Soon after surgery the patient experienced other similar episodes: gabapentin at the dosage of 900 mg/day was effective. Later the drug was stopped and the patient was asymptomatic.

Discussion Headache and loss of consciousness associated with EEG abnormalities could lead to a diagnosis of basilar migraine or epilepsy. In this case neuralgic headache was attributed to compression of the glossopharyngeal nerve by a benign tumor mass (13.2.2 of International Classification of Headache Disorders). Syncope was caused by the involvement of IX and X cranial nerves. Surgical removal of the lesion determined a complete resolution of the symptoms.

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A case of complex facial pain

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Introduction The case highlights a complex clinical situation of pain in the head which evolved over time and with overlapping forms of different pathogenesis effectively treated with hypo-stimulating loco-regional therapy [1].

Case report A 40-year-old woman, single, without major diseases and a regular lifestyle had been under estroprogestinic therapy for 3 years at the time of evaluation. Her father suffered from headache and Bruxism. Her headache began during adolescence with a continuous pain in the fronto-temporal bilateral lobe, of mild-medium intensity and constrictive type, lasting one day at a frequency of 3–4 attacks per month, perimemstrual, and sometimes induced by eating chocolate or fermented cheese. In 2005 she reported a herpetic neuralgia at left retroauricular (earlier branches of C2–C3) with remission of the pain in a week after antiviral therapy, and skin rash after about a month. From February 2007 the characteristics of the headache changed and the pain became button intensive alternating in time, and unilaterally. Furthermore, her crises

occurred twice a month and they were triptans-responsive. The headache was accompanied by nausea, vomiting, phono- and photophobia. During the same period paroxysmal attacks were "like an electric shock" lasting seconds on the left side of the face located in the area of the jaw trigeminal branch. The pain was sudden, spontaneous or triggered by chewing and brushing teeth. It appeared in combination with a continuous dull pain, and was reported similar to a "spasm". The antiepileptic therapy was partially effective but poorly tolerated (oxcarbazepina at 600 mg/die). The MRI brain detected "close near superior cerebellar left artery with the root of the fifth cranial nerve" with probable neurovascular conflict. The TC-scan was negative for sinusopathy. At about seven months of paroxysmal symptoms inadequately controlled, the patient came to our observation. She objectively presented tactile hyperesthesia of the left side of the face at the I and II trigeminal branch with strong hyperalgesia at pressure of the emergence points of the epicranial nerves: supraorbital, infraorbital, mental and great occipital nerve. The patient was repeatedly treated with local-regional anaesthetic blocks at epicranial nerves (8 days) [2]. The treatment was effective with complete crises remission and paroxysmal headache after 10 days from its onset allowing, moreover, a gradual reduction of medication until complete suspension within three weeks [1]. At 4-month follow-up, the patient referred complete remission of paroxysmal neuralgia and only one monthly migraine crisis readily controlled with triptans.

Conclusions The case is of interest due to the coexistence of various forms of clinical cranio-facial pain, because of somewhat different pathogenesis, or perhaps, changes that have occurred over time. The headache initially appeared to be predominantly of a tension-type form, evolving into a form of typical migraine in 2007. The tensive form presented some factors typical of migraine (familiarity and food). In our opinion, it is conceivable that, this clinical case could be generated by the presence of two nosographic and subsequent distinct forms namely tension-type headache and migraine without aura, or by the presence, from the beginning of symptomatology of a migraine clinically atypical. To complicate the picture, a herpetic neuralgia was superimposed later in time (2005), with the addition of an idiopathic trigeminal neuralgia (2007). These last two pain syndromes clinically showed their nosographic specificity. Treatment with anesthetic blocks had proven timely and extensively effective, as an alternative to drug therapies both in controlling the paroxysmal crisis from idiopathic trigeminal neuralgia as well as the headache crisis and confirming an extremely helpful therapy against pain cranio-facial diseases with different pathogenesis [1–3].

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Effectiveness of topiramate for hemifacial spasm but not for migraine in a patient with both conditions

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Introduction Hemifacial spasm (HFS) is a peripherally induced movement disorder characterized by intermittent involuntary, unilateral contractions involving the upper and the lower facial muscles. Primary HFS is commonly attributed to vascular loops compressing the facial nerve at its exit zone from brainstem. Secondary HFS frequently follows peripheral facial palsy or may arise from facial nerve damage produced by tumors, demyelinating disorders, traumatism, and infections.

Materials and methods We report the case of a 57-year-old man, who started suffering from migraine without aura at the age of 18. The pain was unilateral, with alternating sides, and responded completely to triptans, when they became available. When he was 45, he began having a right-sided HFS. The MRI performed 4 years later showed a direct compression of the facial nerve root by an aberrant loop of the basilar artery.

Results He underwent microvascular decompression in 2001, and after an initial 4-month relief, HFS relapsed. Since the age of 40, the migraine frequency had progressively been increasing up to 6–7 attacks per month. In 2003 topiramate was commenced at the dose of 100 mg/day for migraine prevention. The drug was only partially effective for migraine, reducing the attack frequency by less than 50%, but unexpectedly HFS completely resolved after 2 months and never recurred over a 5-year follow-up period. Topiramate withdrawal led to reappearance of HFS, which disappeared again after its reintroduction.

Discussion Microvascular decompression is considered the treatment of choice for HFS, although treatment failure, recurrences, and neurosurgical complications (hearing loss and permanent facial paresis) may occur. For patients who have no identifiable lesion, botulinum toxin injections of the affected muscles remain the mainstay of medical therapy. However, repeated botulinum toxin injections may have limitations, such as denervation of the injected muscles and high costs. Recently, neuromodulators such as pregabalin in association with botulinum toxin and levetiracetam and topiramate alone have proved to be effective.

Conclusions We describe the second case in the literature that achieved a complete and sustained cessation of HFS with topiramate. This drug should be considered as a possible therapy for those patients who cannot or do not want to undergo neurosurgical intervention or are intolerant to botulinum toxin injections. Similarly to other anticonvulsants agents used for the management of HFS, central mechanisms may govern the action of topiramate in HFS. Curiously, it failed to reduce the migraine frequency, that was the main indication for our patient.

Franco Michele Puca Award 2007

Modulation of visual evoked potentials by diffuse noxious inhibitory control (DNIC) in migraine patients between attacks

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Background A common interictal feature of the migraineurs brain is represented by deficient sensory habituation. It has been hypothesized that reduced cortical preactivation from the brainstem monoaminergic nuclei could be the culprit of this phenomenon. Cold pressor test (CPT) is a widely employed method to induce a reproducible pain stimulation in humans and activate diffuse noxious inhibitory controls (DNIC). There is evidence which supports a decisive role for brainstem nuclei in mediating DNIC activity. In

fact, they are central effectors of the endogenous antinociceptive system as well as playing a crucial role in central processing of sensory, for example visual, stimuli by controlling the signal-to-noise ratio in cortical and thalamocortical neurons. It would be of interest to study the effect of DNIC activation on visual evoked potentials (VEPs) habituation in migraineurs patients (MO) compared with healthy subjects (HS).

Materials and methods Seventeen subjects (7 MO and 10 age-similar HS) were enrolled. VEPs habituation was assessed during 3 recording sessions: baseline, non painful (dipping the hand in water at 25° C), and 1 min after the start of pain (hand in water at 3–4° C). Habituation was defined as the N1-P1 amplitude change (%) between the 1st and 6th block of 100 sequential averaged responses.

Results At baseline a reduced response (habituation) in HS (-11.6%) and an augmented response (deficient habituation) in MO (+6.1%) was observed ($p=0.01$). Similar results were obtained during the non painful session. During the painful session the 1st block amplitude in both HS and MO groups decreased (respectively -9.9% in HS, and -4.6% in MO). Lack of habituation in HS (+9.6%, $p=0.007$ vs. baseline) and in MO patients (+11.1%, $p>0.05$ vs. baseline) was observed.

Discussion It is well known that DNIC activation inhibits cortical activity. In fact during CPT we observed a reduction of VEP 1st block amplitude in both the groups (HS and MO). We hypothesize that in HS the DNIC activation of the brainstem monoaminergic nuclei could be the culprit of the lack of habituation, because it induced a lowering of the cortical preactivation level. Since in MO patients the DNIC activation did not produce any further significant variation of the already present lack of habituation this can be related to the presence of a basically reduced cortical preactivation level.

Interdisciplinary Session with the Italian Society for Hypertension: Headache, hypertension and cerebrovascular disease

Migraine, between heart and brain

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Much evidence supports an association between migraine and cardiac diseases including congenital heart disease such as patent foramen ovale (PFO) and coronary heart disease (CHD) [1]. The association of migraine, and particularly of migraine with aura, with PFO has been well recognised. Patients with migraine with aura present a higher proportion of PFO with respect to the general population (50% vs. 27%). So far, several observations reported a marked improvement or the resolution of migraine attacks in migrainous patients who underwent closure of the PFO. Such observations have led to the hypothesis that PFO might have a causal role in the pathogenesis of migraine and led some physician to suggest PFO closure as a therapeutic option in patients with migraine with aura. However, the MIST trial recently reported that patients with PFO and migraine with aura (with frequent migraine attacks and previous treatment failure with 2 or more classes of prophylactic agents) who were randomized to PFO closure with the STARFlex implant did not show any significant benefit in cessation or reduction of migraine attacks with respect to patients treated with a sham procedure. Those results might indicate that PFO represents only a comorbidity in migraineurs, possibly due to a common underlying disorder, rather than a causal factor acting on migraine pathogenesis and

deserve caution in suggesting PFO closure in migrainous patients. More recently, migraine has been associated also to an increased risk of CHD, including myocardial infarction, angina, and coronary revascularization both in men and in women. The mechanism leading to the increased risk of CHD in migraineurs is still unclear. One possible explanation relies on embolization in the coronary arteries of venous emboli passing through the PFO. However, this hypothesis seems unlikely and might be responsible only for a minority of cases. Another possible explanation is the worst cardiovascular profile, in terms of risk factors, in migraineurs with respect to non migraineurs. In fact, according to the GEM study, migraineurs were more likely to smoke, less likely to drink alcoholic beverages, and more likely to report a parental history of early myocardial infarction; migraineurs with aura were more likely to have an unfavourable cholesterol profile, to have elevated blood pressure, and to report a history of early onset CHD or stroke. The last possible explanation is that a common endothelial dysfunction might contribute to the pathogenesis of the migraine attacks and to the increased risk of CHD as well as of stroke [2]. A better understanding of the complex relations between migraine and cardiovascular diseases should represent a primary aim of future research in order to clarify unsolved questions and to improve the management of migrainous patients.

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Headache, hypertension and vascular diseases

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The identification of individuals unaware of being hypertensive or hypertensive control by patients with hypertension persists as a challenge to policies about cardiovascular disease prevention. The characterization that a symptom is associated with elevated blood pressure (BP) before the development of signs of target organ damage would be useful in recognising individuals with undiagnosed or uncontrolled hypertension. Migraine is a common symptom, affecting up to 25%–28% of adults during their lifetime and 10%–12% yearly. Women are more likely to report migraine episodes than men, at a 3:1 ratio, and the peak prevalence occurs during mid-life in both sexes. Migraine has been associated with elevated blood pressure, stroke, epilepsy and psychiatric disorders. The association between the complaint of headache, high blood pressure levels and hypertension is widely accepted despite the absence of corroboration by well designed studies. Different sampling criteria, variable definition of cases, inadequate control for confounding factors, absence of characterization of the diverse types of headache, among others, are limitations unresolved by most investigations. Some prospective studies, using ambulatory blood pressure monitoring, showed no association between blood pressure and headache. In some cases the symptom seemed to be associated with hypertension after its diagnosis, reinforcing the prevailing view that there is no link with headache or that, if there is, the headaches are attributable to anxiety and tension induced by being told one has “hypertension”. Recently, an editorial asked, “Why does the hypertension headache myth persist?” [1]. Headache has been associated to the action of some antihypertensive drugs, such as calci-

um antagonists and alfa blockers. Against this negative observational data, it is striking that published intervention studies have suggested that blood pressure-lowering drugs prevent headache. Data from 7 randomized double-blind trials of blood pressure-lowering drugs angiotensin II receptor antagonists, showed that they prevented headache; a large randomized controlled trial (not double blind) of doctors using any drug to lower blood pressure showed fewer headaches in treated patients; and 2 nonrandomized intervention studies showed that when patients diagnosed as hypertensive received treatment, headache became less prevalent [2]. The randomized double-blind trial data, however, relate to only 1 drug, and the other results are susceptible to bias.

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Headache and hypertension in outpatients from a tertiary headache centre

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Introduction The variability of literature data concerning the comorbidity of primary headache with hypertension might be due not only to different methods used when diagnosing headache but also to different techniques in measuring and classifying blood pressure. Hypertension prevalence was found to be 33.8% after a single evaluation of blood pressure in a sample of 240 primary headache sufferers [1]. In the same study a higher occurrence of hypertension was observed in tension-type headache sufferers than in migraineurs. Hypertension was defined as blood pressure (BP) higher than 140/80 mmHg after a single measurement [1]. This study was designed to evaluate the distribution of hypertension, measured and classified according to the European Guidelines [2] in a sample of headache patients from a tertiary headache centre and its possible correlation with headache type, attack frequency and concomitant therapy.

Methods A sample of 197 adult headache patients consecutively referred to the Headache Disorders Centre of Bari was enrolled. A detailed personal and familial medical history particularly, concerning cardiovascular risk factors and therapies, was collected. Patients underwent a physical and neurological examination. Appropriate investigations were made when suggested by clinical suspicion. BP level was obtained as the mean value of three consecutive evaluations. Patients were classified as hypertensive when BP was equal or higher than 140/90, and/or they were under antihypertensive therapy. Headache diagnosis was obtained according to diagnostic criteria of the International Classification of Headache Disorders [3]. Data were analysed by means of SPSS 11.0 for Windows.

Results The prevalence of hypertension in the whole sample was 27.40%. The hypertension occurrence was significantly higher in tension-type headache sufferers (TTH) than in migraineurs (M). Patients suffering from a chronic form of headache showed a higher prevalence of hypertension than those suffering from an episodic headache.

Discussion and conclusions The results of this study showed a hypertension prevalence lower than that observed in a previous study [1]. Probably a single measurement of blood pressure may cause an overestimation of comorbidity. Hypertension prevalence appeared to be more elevated in headache sufferers than in the general population. The higher prevalence of hypertension in TTH than in M was confirmed. Thus, the application of a method in defining blood pressure after three consecutive measurements reduces the problem of hypertension in headache patients, but does not resolve it. Further studies are needed to better define the weight of this problem.

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Patent foramen ovale (PFO) and migraine: quantitative assessment of PFO and its relation with clinical phenotype

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Background and objective A potential relation between patent foramen ovale (PFO) and migraine, mostly migraine with aura (MA), has been recently suggested, based on the results of sparse epidemiological studies which demonstrated higher prevalence of PFO in patients with MA than in controls. These observations support the hypothesis that PFO closure might be an alternative and effective treatment option for patients with migraine and, actually, in several studies, a decrease in attacks of migraine was observed. However, these data must be interpreted with caution because of several methodological shortcomings and potential biases (recall bias, use of anti-platelet drugs, and the placebo effect of any treatment for migraine, particularly invasive ones). A large double-blind randomised trial on PFO closure in MA prophylaxis was conducted in the UK (MIST). At present it seems that the association is a mere comorbidity and there is no evidence of a cause effect relation. Thus, the possibility that the PFO related MA might be another example of symptomatic migraine having little to do with migraine as a primary disorder (i.e., migraine without aura) seems unlikely. Based on the available evidence, as well as on the results of the MIST trial, PFO closure as a treatment for migraine seems a too simplistic generalization.

Patients and methods Contrast 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-, 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%), subdivided into 86 (53.4%) small, 45 (27.9%) medium, and 30 (18.7%) large; 12 MA- (16.2%), subdivided into 8 small, 3 medium, and 1 large.

There was no significant association among clinical variables (prevalence of autonomic symptoms, frequency, intensity of pain, and the clinical features of aura) and PFO prevalence and size in each subgroup.

Conclusions Because of the reported pathogenic link between PFO size and thromboembolism in ischemic stroke, we analysed our

population to try to find a correlation between the presence or the size of PFO and the clinical phenotype of migraine. Our findings do not allow to extend the same assumption to the PFO migraine relationship and, indirectly, further strengthen the hypothesis that PFO and migraine might be a phenotypic expression of a common underlying genetic disorder without any pathogenic link.

Hyperhomocysteinemia in patients with migraine with aura genetic – epidemiology study of 4 families

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Objective Migraine is an independent risk factor for stroke. Hyperhomocysteinemia has been proposed as a risk factor for stroke [1]. The reasons for this association are unknown but it is believed that one, or several, shared factors may cause both disorders and/or increase risk for stroke in migraine patients. The aim of the study was to investigate homocysteine serum levels in migraine patients to characterize the genetic and epidemiology study.

Materials and methods A sample of 26 familial cases of patients with migraine (14 women, 12 men; mean age: 28 years) and 26 healthy controls (18 women, 8 men; mean age: 32 years) were studied. The mean values of homocysteine serum levels were 14.21 ± 1.4 in patients with migraine with aura, and 8.56 ± 1.9 in controls. Statistical analysis values were significant in migraine with aura versus controls ($p < 0.05$). Furthermore, the proportion of subjects with hyperhomocysteine (defined as homocysteine levels > 10 in women, and > 15 in men) was significant in migraine patients with aura versus controls ($p < 0.04$). Our results showed that familial cases of young adults with migraine with aura tend to show higher homocysteine levels than normal subjects. These findings suggest that hyperhomocysteinemia may be involved in predisposing migraine with aura patients to ischemic stroke.

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Interdisciplinary Session with the Italian Society of Psychopathology: Neuropsychological and psychopathological features in headache

Psychopathological aspects of headache

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Headache is a quite common referred symptom in psychiatric patients. General population studies suggest a non-casual association between migraine, major depression and anxiety disorders (panic attack disorder, obsessive-compulsive disorder, generalised anxiety disorder). The risk of developing affective and anxiety disorders is not increased uniformly in the different migraine subtypes, but it is more elevated in migraine with aura patients. The relationship between migraine and depression is “bi-directional” and specific [1]. There is evidence that psychiatric comorbidity is higher in transformed migraine than in episodic migraine.

However, research into the possible mechanisms underlying these associations remains limited. Comorbidity with psychiatric disorders has also been described for chronic tension-type headache and for chronic daily headache, although these findings are based only on clinical population data. Subjects with migraine should be carefully screened for depression, which should be managed to prevent transformation of migraine, to increase quality of life and to gain more successful migraine therapies [2]. Moreover, community-based studies showed high comorbidity of psychiatric disorders and suicidal risk in adolescents with chronic daily headache. The presence of migraine attacks, especially migraine with aura, was the major predictor for these associations [3].

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Quality of life, temperament, depression and suicide risk in patients affected by daily chronic headache

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Objective To assess depression, hopelessness and suicidal ideation in daily chronic headache and overuse of therapeutic drugs.

Methods One hundred and sixteen patients (102 women [87.9%], age range 16–78 years, mean 48.11, SD=12.03) with daily chronic headache and drug overuse underwent assessment in a Day Hospital setting (Sant’Andrea Hospital, Rome) with the following: Mini International Neuropsychiatric Interview, Hamilton Rating Scale for Depression (HAM-D), Quality of Life Index (QL-Index),

Beck Hopelessness Scale (BHS), TEMPS-A, Illness Perception Questionnaire (IPQ-R), Drug Abuse Screening Test (DAST), and Suicide Score Scale (SSS).

Results Patients with depression (37% who scored at least 15 on the HAM-D) scored lower on the QL-index (4.70±3.00 vs. 8.43±1.88) and higher on irritability (6.70±3.60 vs. 4.85±3.08), Dysthymia/Cyclothymia/Anxiety (Dys/Cyc/Anx) (37.33±9.93 vs. 29.24±11.05) of the TEMPS-A, and on the last-12-months (0.25±0.31 vs. 0.09±0.22), lifetime (0.35±0.33 vs. 0.11±0.23) and total SSS (0.29±0.28 vs. 0.10±0.19) and on the emotional representation subscale of the IPQ-R (0.44±0.17 vs. 0.36±0.14); furthermore, they scored higher than the cut-off on the BHS more often than the “non-depressed” sample (patients scoring less than 15 on the HAM-D) [1]. However, by dichotomising the sample in at least 15 vs. <15 HAM-D score basis and introducing this as a dependent variable for performing logistic regression, only the BHS >9 variable (OR=21.88; $p<0.05$), QL-index (OR=0.31; $p<0.01$), and last-12-months (OR=0.00; $p<0.05$) and lifetime (OR=152.41; $p<0.05$) SSS were found to be significant. Patients with elevated hopelessness were most frequently women (100% vs. 0%), had elevated depression (65.4% vs. 34.6%), scored lower on the QLindex (6.00±3.23 vs. 7.98±2.33) and on the Hyperthymia scale of the TEMPS-A (7.57±4.20 vs. 10.28±4.01), and higher on Irritability (7.94±2.84 vs. 3.79±2.64), Dys/Cyc/Anx (41.03±11.28 vs. 26.44±9.71) scales of the TEMPS-A, on the DAST (6.42±6.56 vs. 3.45±3.95), on the last-12-months (0.28±0.31 vs. 0.5±0.16), lifetime (0.33±0.35 vs. 0.10±0.21) and total SSS (0.29±0.29 vs. 0.07±0.16), and on Chronicity (0.51±0.19 vs. 0.43±0.16), Consequences (0.47±0.14 vs. 0.40±0.15) and Emotional Representation (0.47±0.16 vs. 0.35±0.15) scales of the IPQ. However, logistic regression using the BHS score ≥ 9 as a dichotomous dependent variable found only the Dys/Cyc/Anx (OR=1.35; $p<0.05$) to be significantly associated with it [2, 3].

Conclusions Patients with daily chronic headache show poor quality of life associated with depression, mood temperament traits and constructs underlying higher risk for suicide.

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Biochemical, neurophysiology and neuroimaging features in headache

Thalamo-cortical activity and lack of habituation are related phenomena in migraine

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Background Between attacks, migraineurs lack habituation in visual (VEPs) and somatosensory (SSEPs) evoked potentials. It was hypothesized that cortical habituation deficits are determined by a reduced cortical pre-activation level, setted by thalamo-cortical loops. We have studied in migraine patients the high-frequency oscillations embedded in SSEPs and found indications of a reduced activity of thalamo-cortical afferents which would rather support the hypothesis that a decreased cortical pre-activation level is the cause of the habituation deficit in migraine. To better investigate the relationship between deficit of habituation and cortical pre-activation level we studied VEPs habituation and SSEPs HFOs in the same group of migraine patients and compared them with a group of healthy subjects.

Material and methods We recorded VEPs (600 sweeps, 15 min of arc checkerboard, 3.1 reversal rate, 80% contrast) and SSEPs (500 sweeps, galvanic stimulation of the median nerve at the wrist, 1.5 motor threshold, 4.4 Hz) in 20 healthy subjects and in 16 migraine patients between attacks. Habituation of the visual EPs was defined as the percentage change of the N1-P1 amplitude between the 1st and 6th block of 100 averaged responses. The early and late high-frequency components superimposed on the N20 SSEP cortical response were extrapolated from broad-band activity by off-line digital filtering.

Results We found a significant interictal N1-P1 VEP habituation deficit ($p=0.001$) together with a reduced early somatosensory HFOs amplitude maximum ($p=0.037$) in migraineurs compared to healthy subjects. There was a significant positive correlation between early HFO amplitude maximum and each of the 6 N1-P1 VEP amplitude blocks of 100 averaged sweeps in migraineurs ($p<0.05$), but not in controls ($p>0.05$). Moreover, when both subject groups were combined, VEP habituation slope was inversely related with early HFOs amplitude maximum ($r=-0.425$, $p=0.005$), suggesting that loss of habituation increases when thalamo-cortical activity decreases.

Discussion Taken together, these data suggest that VEP habituation and somatosensory thalamo-cortical activation vary in parallel, especially in migraine, and that they may be modulated by similar neuronal networks. An inadequate monoaminergic control might be a plausible explanation for both lack of habituation and low thalamo-cortical activity.

A laser evoked potential study in patients with medication-overuse headache

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Introduction Medication-overuse headache (MOH) is a medical condition associated with considerable long-term morbidity and disability. Patients with MOH are usually managed in specialist centres by withdrawal of the overused drugs and treatment of withdrawal symptoms (in an in-patient or outpatient basis), in order to begin the prophylactic treatment and to limit use of acute medication. The physiopathology of medication-overuse headache (MOH) is complex and includes central sensitization from repetitive activation of nociceptive pathways. CO₂ laser evoked potential (LEP) habituation to repetitive stimuli has been proven to be reduced in episodic migraine. Our aim was to assess the LEP habituation to experimental pain in patients with MOH, before and after a detoxification scheme.

Methods We studied 14 patients affected by 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 perioral region. The habituation of both the N1 and the vertex N2/P2 components was assessed by measuring the LEP amplitude changes across three consecutive repetitions of 30 trials each.

Results In the 8 patients with clinical improvement, the N2/P2 amplitude habituation, lacking before the treatment, was recovered after MOH had resolved. In particular, the N2/P2 amplitude habituation was significantly higher after treatment than before treatment following both hand ($F=43.1$, $p<0.001$) and face stimulation ($F=6.9$, $p=0.009$). Conversely, in the patients who still had chronic daily headache and were still overusing acute medication at follow-up the N2/P2 amplitude still showed reduced habituation after both hand ($F=3.1$, $p=0.08$) and face ($F=0.7$, $p=0.4$) stimulation.

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 a normalization in the pain-processing mechanisms and of a "desensitization" of central nociceptive pathways.

Plasma adiponectin levels are decreased in chronic migraine and medication-overuse headache

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Introduction Adiponectin, an adipocytokine secreted by adipose tissue, has been demonstrated to exert a protective role against the development of insulin resistance, dyslipidaemia and atherosclerosis, and exhibits anti-inflammatory properties. An alteration of this

adipocytokine has been suggested to be involved in migraine, in particular in its chronic form, with and without symptomatic medication-overuse [1].

Materials and methods We measured plasma levels of adiponectin in 20 patients with MOH, with a previous history of episodic migraine without aura (MwA) and 15 patients with chronic migraine (CM) without medication overuse, comparing them with those of 20 episodic MwA patients and 20 age- and sex-matched controls. The plasma concentration of total adiponectin was evaluated by a sandwich ELISA system (adiponectin ELISA kit; Otsuka Pharmaceutical Co Ltd, Tokyo, Japan).

Results Plasma adiponectin concentrations were significantly decreased in both MOH and CM compared with episodic MwA patients ($p<0.04$ and $p<0.03$) and controls ($p<0.01$ for both). In CM patients as an entire group they were inversely correlated with body mass index (BMI) ($r=-0.54$, $p<0.01$), waist-hip ratio ($r=-0.48$, $p<0.02$), glucose ($r=-0.34$, $p<0.05$), and fasting insulin ($r=-0.41$, $p<0.04$).

Discussion and conclusions Large population-based studies suggest that obesity is a risk factor for CM after adjusting for other comorbidities. Reduced plasma adiponectin concentrations may, at least in part, account for this association. They could also be involved in altered insulin sensitivity and, potentially, a proinflammatory state, which may contribute, together with obesity, to the transformation from episodic to CM [2]. These aspects should be investigated in future research.

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Altered ghrelin levels during oral glucose tolerance test in chronic migraine and medication-overuse headache

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Introduction Previous research showed that both corticotropic and somatotrophic functions are significantly impaired in chronic migraine (CM) and medication-overuse headache (MOH) patients and suggested a role for hormonal dysfunction, in particular growth hormone (GH), in the development of CM [1]. In the present study the attention was focused in both chronic headache conditions on the plasma levels of ghrelin, which has been reported to be the natural ligand of the GH secretagogue receptor and strongly stimulates GH release if exogenously administered.

Materials and methods Circulating acylated ghrelin concentrations were measured during oral glucose tolerance (OGTT) and insulin tolerance testing (ITT) in 10 patients with MOH, 10 patients with CM and 10 age/sex/BMI-matched controls. Plasma serum GH, insulin and glucose levels were also measured during each test.

Results Fasting plasma ghrelin levels correlated negatively with serum insulin levels in controls ($r=-0.51$; $p<0.03$) but not in patients with MOH and CM. During OGTT, circulating ghrelin levels decreased significantly with a nadir at 30 min in controls ($p<0.05$) but not in chronic patient groups in which there was no rapid fall in plasma levels of acylated ghrelin after OGTT at 30 min, but a paradoxical increase at 60 and 120 minutes was observed

($p<0.01$ and $p<0.02$). Also, ITT was followed by a significant decrease in circulating ghrelin levels with a nadir at 30 min in controls ($p<0.05$) but not in patient groups. Baseline acylated ghrelin levels did not differ with respect to GH levels, and furthermore, the variation of acylated ghrelin levels during OGTT or ITT was independent of GH levels during the tests.

Discussion and conclusions In MOH and CM the dynamic of the response to OGTT is slower with a delayed upregulation of active ghrelin in the second half of OGTT, which is independent of GH levels. This can reflect an altered insulin sensitivity that has already been demonstrated in episodic migraine and is more accentuated in both chronic headache disorders [2].

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Oral nitric oxide donor induces sensitization in spinal cord pain processing in migraineurs: a double-blind, placebo-controlled, cross-over study

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Background and objectives Nitric oxide (NO) plays an important role in the pathophysiology of migraine as well as in the sensitization of the extracephalic pain pathways. In migraineurs, NO-donors (NOD) cause more headaches than in healthy subjects and are used as a provocative test to induce migraine attacks. The aim of the present study was to investigate if such differences may also reflect a different effect of the NOD on the pain processing at spinal level between migraineurs and healthy subjects. We used the temporal summation threshold (TST) of the nociceptive withdrawal reflex (NWR) as an objective method to explore the spinal cord pain processing before and after NOD administration.

Methods In a double-blind, placebo-controlled, crossover study, 28 migraine patients (21 females and 7 males, mean 34.5±8.2, aged 18–55 years) and 15 healthy subjects (9 females and 6 males, age 23–49 years, mean 34.5±8.2) were selected. Each subject underwent a first neurophysiological examination (baseline), followed by a random administration of NOD (nitro-glycerine 0.9 mg sublingual) or placebo during two different session. NWR-TST and the subjective painful sensation were measured before and 30, 60, 120 and 240 min after drug/placebo administration.

Results Sixteen out of twenty-eight migraine patients and none of healthy subjects developed a typical migraine attack. All the subjects who had taken NOD showed a reduction of the TST between 30' and 180' compared to the baseline. These differences reached statistical significance at 60' and 120' in both the whole group of migraine patients ($p=.028$ and $p=.002$ respectively) and in the group of migraine patients with positive response to provocative test ($p=.007$ and $p=.002$ respectively).

Conclusions The NWR-TST facilitation induced by NOD reflects an extracephalic generalized hypersensitivity of pain pathways that

provide the susceptibility for triggering migraine attack and probably its persistence in migraineurs.

Patients with headache and irritable bowel syndrome present a meal-induced hypersensitivity of the colon

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Background and objective Headache is a frequent symptom in patients suffering from functional gastrointestinal disorders. We have already shown that patients with functional dyspepsia present an alteration of gastric sensitivity thresholds induced by meal ingestion. However, no data are yet available on the pathophysiological mechanism responsible for this association in patients with irritable bowel syndrome (IBS). The aim of this study was to analyse visceral sensitivity of the colon in patients with IBS suffering from headache.

Patients and methods Twenty-six patients (12 females, mean age: 31±6 years) affected by IBS with (16 patients) and without (10 patients) migraine without aura, depending on IHS criteria, took part in the study. As a control group, ten age- and sex-matched healthy volunteers were also enrolled. All subjects underwent an evaluation of sensitivity thresholds at recto-sigmoid level in fasting condition and after the administration of a liquid meal, by barostat. The device consists in a computer-controlled system connected to a double-lumen extrusion and a non elastic balloon placed at its distal end, which is introduced through the anus and positioned at the recto-sigmoid junction. At fasting and after the administration of a 200 ml, 200 Kcal liquid meal, an evaluation of perception and discomfort thresholds was performed by sequential ramp distentions in stepwise increments starting from MDP (2 mmHg, 2 min duration). At the end of each distention, the subject was asked to score the sensation on a semi-quantitative scale.

Results As expected, IBS patients showed fasting perception and discomfort thresholds significantly lower than healthy volunteers, but patients with migraine showed sensitivity threshold values not different than patients without migraine. Conversely, discomfort threshold after meal was significantly lower in IBS-migraine patients (fasting 12.6±5.1 mmHg vs. post-meal 9.3±4.5 mmHg) than in IBS patients without migraine (fasting 10.1±5.1 mmHg vs. post-meal 9.2±4.1 mmHg).

Conclusions In IBS patients, the presence of migraine is associated with a reduction of postprandial threshold for discomfort. Further studies are needed to define the pathophysiological role of this alteration.

Implementation and evaluation of existing guidelines and optimisation of recommendation on the use of neurophysiological tests in non-acute migraine patients. A Eurohead Project

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Objectives The main goals of this study were: a) to evaluate the diffusion, use and perception of usefulness of 2004 EFNS guidelines on neurophysiological tests and imaging procedures in non-acute headache patients, in a cohort of headache specialists, neurologists, and general practitioners (GPs); b) to survey the frequency of recommendation of the different neurophysiological tests in non-acute migraine patients by guideline conscious and unconscious headache specialists, neurologists, and general practitioners; c) to evaluate the motivation for recommending a neurophysiological testing and to verify their appropriateness and concordance with EFNS guidelines; and d) to survey the perception of usefulness of neurophysiological testing in the differential diagnosis of migraine.

Methods One hundred and fifty physicians selected from the membership list of the Italian Federation of GPs (FNOMCEO), Italian Neurological Society (SIN) and Italian Society for the Study of the Headaches (SISC) were contacted via e-mail and requested to fill in a questionnaire created for the aims of the study.

Results Of the targeted sample of 150 physicians, 136 (40 GPs, 48 neurologists and 48 headache specialists) returned the questionnaire (participation rate 90.6%). Almost 92% of the headache specialists, 8.6% of the neurologists and 0% of the GPs reported to know the EFNS guidelines (Table 2, $p<0.001$ headache specialists vs. neurologists and vs. GPs). The vast majority of the physicians (93.4%) declared to follow EFNS guidelines and recommendations in their practice. A significantly higher proportion of headache specialists did not recommend any neurophysiological test (EEG, EP, blink reflex, EMG, TCD) to their migraine patients visited in the last three months, whereas these tests were frequently prescribed by GPs and neurologists. Overall, 80%, 42% and 42.6% of the motivations reported by headache specialists, neurologists and GPs, respectively, for recommending a neurophysiological testing to migraine patients were appropriate ($p<0.01$ headache specialists vs. GPs and neurologists).

Conclusions The EFNS guidelines and recommendations on neurophysiological tests and neuroimaging procedures had an optimal diffusion among headache specialists and a very limited diffusion among neurologists and GPs. The great majority of guideline conscious physicians expressed positive comments about the EFNS guidelines and declared to use them in their everyday clinical practice. Coherently, guideline conscious physicians (headache specialists) recommended neurophysiological tests to migraine patients less frequently and more appropriately than guideline unconscious physicians. The most frequent misconceptions regarding neurophysiological tests were their usefulness in discriminating between migraine and secondary headaches, and between migraine and primary headaches, their usefulness in orienting toward an appropriate recommendation of a neuroimaging procedure and their ability to confirm the diagnosis of migraine. EFNS guidelines should be more explicit in establishing that it is false.

Sensory evaluation in fibromyalgia and headache

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Introduction Different forms of primary headache (H) are significantly more frequent in fibromyalgia patients than in the general population, suggesting a possible common underlying mechanism for pain in the two conditions [1]. Fibromyalgia (FMS) is characterized by a generalized increase in sensitivity to painful stimuli at somatic level [2]; on this basis, the aim of the present study was to verify if the association of FMS with headache involves different levels of hypersensitivity with respect to one condition only.

Methods Three groups of 30 patients each who were affected by: 1) headache (migraine or tension-type); 2) fibromyalgia; and 3) headache plus fibromyalgia (H+FMS) were examined. The groups were age- and sex-matched. Headache patients of Groups 1 and 3 did not differ significantly regarding the number of years they had been suffering from headache and mean number of monthly attacks. Fibromyalgia patients of Groups 2 and 3 did not differ significantly regarding the number of years they had been suffering from diffuse chronic musculoskeletal pain. In all groups pain thresholds to electrical stimulation in skin, subcutis and muscle were measured in multiple body sites (deltoid, trapezius and quadriceps) not coinciding with the areas of spontaneous pain and muscle pain thresholds to pressure stimulation were evaluated in the same locations as well as in the typical 18 Tender Point Sites. Measurement was made in the pain-free interval and with a wash-out of at least 72 hours from any drug potentially interfering with pain sensitivity.

Results The lowest electrical thresholds at all body sites and all tissues and lowest muscle pressure pain thresholds were found in group 3 (H+FMS), followed by group 2 (FMS) and group 1 (H). The trend for variation among groups was significant ($p < 0.01$).

Conclusions The results indicate that the association of headache with fibromyalgia involves a higher state of generalized hypersensitivity towards painful electrical and pressure stimuli applied at somatic level with respect to one condition only. They suggest different levels of central sensitization in patients with headache only, fibromyalgia only and headache plus fibromyalgia, which are expressed clinically with higher/wider manifestations of spontaneous pain complaints in the three groups.

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Clinical aspects and therapeutic strategies in headache

Electronic vs. paper headache diary for in-patient monitoring: a pilot study

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Background The use of monitoring charts is crucial in the diagnosis and management of headache disorders [1]. These diaries, usually booklets, to record prospectively the characteristics of every attack, to increase the accuracy of the description, and to distinguish between coexisting headaches types are filled in at home by the patients and returned at follow-up. Moreover, headache diaries provide the physician with information concerning other important features, such as the frequency and the temporal pattern of attacks, the drug intake, the trigger factor, and the monitoring of the treatment response.

Objective To compare an electronic handheld version of the headache diary with the traditional diary chart in a group of headache in-patients with medication-overuse headache.

Methods In this pilot phase, an extensive electronic headache diary (Palm device) developed in accordance with ICHD-II criteria [2]

with included detailed but simple instructions, was given to 30 hospitalized patients suffering from medication-overuse headache (Female:Male = 2:1; mean age: 45.5±8.8 years; education level: 13.1±3.2 years). Patients were asked to fill in the diary on a daily basis. The electronic headache diary included 14 items that provided the characteristics necessary to diagnose and distinguish between migraine with and without aura and tension-type headache. When discharged, patients were asked to evaluate the comprehension of both the diary and the instructions, the screen, the layout, the facility to fill in the electronic diary and the easiness of it compared with the traditional paper version.

Results The electronic handheld diaries were completely filled in by all the patients. The diary was considered easy to understand and easy to use. Finally, when we compared the electronic version versus the diary chart, one patient preferred the last one for its easiness and for its practicality and patients did not show any preference between the two versions.

Conclusions In our small cohort, preliminary data show a highly satisfactory degree for the handheld version diary. Most of the patients considered it easier and handier than the traditional paper version. Moreover, all of them accepted to receive the forthcoming software of this diary for monitoring headache in palm/smartphone or laptop version.

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3D kinematic analysis of neck movements in control 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. Neck ROM was assessed using an optoelectronic system equipped with 6 CCD cameras, which allows the real time recognition of passive markers locations and their 3D co-ordinates reconstruction (SMART system - BTS - Milan). The kinematic model designed requires the positioning of 6 markers, allowing the reconstruction of space motion of head and trunk. The acquired anatomical 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 performed at usual velocity as follows: 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 20 control subjects during flexion-extension, rotation and lateral bending movements. The test was repeated on two separate occasions.

Results The test showed good reliability, with an intra-class correlation coefficient of 0.936 in flexion and extension; 0.892 in axial rotation and 0.756 in lateral bending. The flexion ROM was 38±12.9, the extension ROM 56.9±8.8, the lateral bending ROM 38.6±14.8 and the axial rotation ROM 34.5±19.4.

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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Therapeutic use of nabilone in medication-overuse headache: a preliminary report

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Introduction The endocannabinoid system modulates the perception of pain in presence of allodynia and inflammatory neuropathic pain. Activated CB1 receptors inhibit pre-synaptic release of GABA and glutamate and facilitate 5-HT₂ mediated post-synaptic release of serotonin. Activated CB2 receptors inhibit the release of CGRP, bradykinin, nerve growth factor, the synthesis of prostaglandins E₂, the PPAR γ proliferation and platelet aggregation [1]. CB1 and TRPV1 receptors antagonists may increase glutamatergic activity in several cerebral areas involved in processing pain. Aberrant hyperactivity of enzymes that inactivate anandamide could justify the low systemic levels of anandamide in patients with chronic headache [2]. Preclinical and clinical studies confirm that nabilone has a potent analgesic, anti-inflammatory and anti-allodynic effect, without psychoactive property [3].

Objective The aim of our study was to evaluate the efficacy and tolerability of nabilone (0.5–1 mg/die) for the treatment of chronic pain in daily chronic headache associated with analgesic overuse (ICHD-II, 2004, Medication-Overuse Headache, (MOH)) and resistant to common pharmacological treatments.

Material and methods Ten patients, randomized after a period of wash-out of 2 weeks executed in the Day Hospital at our Headache Clinic, were assigned to treatment A (nabilone 0.5–1 mg/die) or treatment B (ibuprofene 600 mg/die) for a period of eight weeks. At a 2-week follow-up the patients exchanged treatment for another eight weeks. Headache Index, rescue medication and pain intensity were recorded before taking the drug and, subsequently, at 12–24–48 hours after taking the drug and also at the 14th, 28th, 56th day from the beginning of therapy and the days/month with headache. The headache pain was measured by a four scoring scale (absent, mild, moderate, severe). A SF36 scale evaluation was also performed.

Results Seven of ten patients, treated with nabilone, showed a reduction of intensity of headache pain vs. 3 cases which improved during ibuprofen treatment ($p < 0.05$). At the end of the second period of treatment, nine patients, and also the three patients who complained of a persistent daily headache, declared to prefer nabilone. The SF36 scale showed a significant improvement of QoL during the nabilone treatment. Adverse events were somnolence and sense of dysphoria in the nabilone group vs. gastric discomfort in the ibuprofen group.

Conclusions Nabilone (0.5–1 mg/die) seems to be an effective and safe alternative treatment in patients with MOH resistant to usual treatments. A double blind larger study is now in progress to confirm these preliminary results.

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Migraine and haemochromatosis

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Introduction Genetic mutation in the *HFE* gene is quite frequent in the general population, that is 1 case every 227 people in the Caucasian population [1]. Recently, the prevalence of *HFE* mutation in migraineurs seems to be the same as in the general population, and homozygote mutation in H63D gene correlates with more severe headache at a later age onset [2].

Objectives To evaluate the prevalence of iron metabolism alteration and, where present, the presence of *HFE* gene mutations, in migraineurs. A secondary aim was to evaluate how therapy for haemochromatosis modified patient’s headache.

Patients and methods We examined all the consecutive patients suffering from migraine, according to the ICHD-II International Classification, in a 2-year period. All patients underwent a general and neurologic examination and hematologic evaluation. Personal, general and headache anamnesis were recorded. Women with ferritin >25 and men with high iron plasma levels were studied for *HFE* mutations. Those patients with abnormal iron parameter and genetic mutation were treated when needed and followed-up by a specialist in haematology (RI).

Results In 2 years we visited 328 migraineurs (68 men and 260 women), mean age 40 years, mean headache lasting 46 years, and headache severity index of 31. Among these, 58 patients presented altered iron metabolism (19 men, 39 women; mean age: 38 years; headache severity 33). Among these, 21 patients had a *HFE* mutation. They are 11 women and 10 men, mean age: 39 years, mean lasting headache history 20 years, and headache severity index 39. Homozygote mutation H63D resulted in 1 case, heterozygote mutation H63D in 14 cases, heterozygote C282Y in 5 cases, and heterozygote S65C in 1 case. One patient was advised to become a blood donor; 7 patients were threatened with bleeding.

These patients showed an important improvement in their headache severity index that decreased from 24 to 6. Treatment was well tolerated and the patients expressed clinical satisfaction.

Discussion Depending on known prevalence data, that is 1 case every 227 people, the expected number of patients with *HFE* mutation should be 1.5 patients in our study population. Our record of 21 patients, affected mainly from heterozygote mutation without clinical systemic or haematological signs, suggest the possibility of a higher prevalence of haemochromatosis in migraineurs. Our data are in accordance with data referring to a possible iron pathogenetic role in brainstem alteration in migraineurs [3] and the improvement of headache after iron displacement.

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Relationship between headache and exercise in professional rugby players

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Objectives Rugby is an old team sport, developed in United Kingdom in 1823, contributing to promote friendship, courage, life-long commitment to physical fitness, and team spirit. In contact sports such as rugby, head trauma may cause concussion syndrome. Concussion is common in rugby players and is triggered by a mild brain injury determining loss of consciousness, amnesia, dizziness, attention and memory deficits, nausea, postural instability and headache. The International Classification of Headache Disorders, 2nd Edition, identifies a secondary headache attributed to head and/or neck trauma characterized by a cluster of pain patterns such as migraine and more often tension-type headache, and a primary exertional headache precipitated by any form of exercise occurring only during or after physical exertion. The aim of the study was to evaluate the prevalence of primary headaches (migraine, tension-type headache, and exertional headache) and of secondary headache (headache attributed to head and/or neck trauma) in professional rugby players.

Methods Anamnestic data collection and neurological examination were performed in forwards and in backs players of Easy Living L'Aquila Rugby (Italian First Division League 2007/8). The exercise strength of physical training was measured by the Borg CR 10 scale.

Results We enrolled 36 professional rugby players (18 forwards and 18 backs) (mean age: 28±7 years). The Borg CR 10 scale mean score was 7.8. No history of headache was found in 24 (66.6%) players. Primary headaches were checked in 12 (33.4%) players: a diagnosis of migraine without aura was reached in 3 (8.4%), episodic tension-type headache in 4 (11.1%), and exertional headache in 5 (13.9%). The migraine without aura and tension-type headache diagnosis was reached in rugby players who reported the attacks outside of their physical activity. No headache was attributed to head and/or neck trauma. Exertional headache was diagnosed in 4 (22.3%) backs and in 1 (5.6%) forward player.

Conclusions Rugby is characterized by players' continuous and hard physical effort both during the match and the training sessions as proved by the high Borg CR 10 scale score reported. The overall prevalence of headache and also the specific prevalence of migraine and tension-type headache in rugby players are lower than in the general population. Controlled and regular exercise training promoting physical and psychological well-being may reduce primary headaches, and especially exertional headache, in rugby players. The higher prevalence of exertional headache in backs with respect to forwards might be explained by the strenuous physical effort that backs, slim and quick physical types, stand in opposing the forwards, which are strong physical types, during the match. A complete and tailored individual physical and technical conditioning programme may improve players' performance and sustain prevention of contact injuries decreasing headache prevalence in rugby players.

Peri-ictal headache: prevalence in a population with epilepsy

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Consecutive adult patients with epilepsy, referring to our Epilepsy Centre, were recruited to investigate the prevalence of peri-ictal headache. All patients had had a definite diagnosis of epilepsy for more than one year. Patients with learning disability were excluded. Epilepsy was classified according to the criteria of The International League Against Epilepsy (ILAE). The headaches were classified according to the ICHD-II based on the clinical interview, and were further divided in interictal, preictal, ictal, postictal. Interictal headache was defined as headache starting not earlier than three hours after a seizure, or headache never proceeding directly into an epileptic fit; preictal headache as headache starting not more than 24 h prior to the seizure and lasting until the onset of a seizure; ictal headache as headache occurring during a simple partial epileptic seizure; and postictal headache as a headache starting within three hours after a seizure and ceasing within 72 h after the attack. We recruited 194 patients (96 females, 98 males; age 47±15, range 16–85 years) with diagnosis of epilepsy. Of them, we have found 110 (57%) patients with cryptogenetic focal epilepsy, 45 (23%) with symptomatic focal epilepsy, 34 (17%) with idiopathic generalized epilepsy, 3 undetermined whether focal or generalized, 2 with epilepsies characterized by specific mode of seizure precipitation. In this population, we identified 82 (42%) patients with primary headaches (interictal headache): 31 (16%) with migraine (M), 29 without aura (MO), 2 with aura (MA), 3 of whom with migraine-triggered seizures (in the past referred to as “migralsepsy”); 49 (25%) with tension-type headache (TTH); 2 primary stabbing headache (one of whom with also migraine); and 1 new daily-persistent headache. Preictal headache was found in 7 patients (4%), 2 of whom with interictal MO, 2 with interictal TTH. Postictal headache was found in 42 patients (22%), 13 of whom with interictal MO, 10 with interictal TTH. Postictal headache was present in 28% (23/82) of patients with interictal headache and in 17% (19/112) of epileptic patients without interictal headache. No case of “pure” ictal headache was found; in 3 cases the headache was present preictal and also after the seizure. In this epileptic population we found that interictal and postictal headaches are common, preictal headaches occur only in some patients, whereas ictal headaches are very rare; we also found an association between interictal and postictal headaches.

Dopamine and migraine: use of haloperidol in medication-overuse headache treatment

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Introduction Medication-overuse headache (MOH) in migraine patients is a medical condition associated with long-term morbidity and disability. Subjects affected by MOH represent a large proportion of patients referring to headache centres. Discontinuation of overused medication is the treatment of choice, but this may be difficult due to increased headache severity observed immediately

after withdrawal. Dopamine has been considered as playing a role in the pathogenesis of migraine and some polymorphisms of dopaminergic genes are associated to migraine [1]. Different dopamine receptor antagonists show a good clinical efficacy in migraine therapy [2]. A recent randomized, double-blind, placebo-controlled study demonstrated the efficacy of intravenously (IV) haloperidol in treatment-resistant migraine attacks [3].

Objective The aim of this retrospective study is to evaluate the efficacy and safety of IV haloperidol treatment in patients with migraine and MOH diagnosis (IHS criteria 2004).

Methods A total of 35 migraine patients (3 men, 32 women) with probable MOH were recruited into the study. The subjects had been consecutively admitted, from February 2005 to April 2008, to the Day Hospital of our Headache Centre. All patients received haloperidol infusion for at least 10 days. Haloperidol response for each patient was estimated evaluating the number of days of headache/month, and the number of days of acute medication intake/month, before and after infusion treatment.

Results The mean age of patients was 44.3 years, mean age at onset 17.31 years; mean years of illness 27 years. The number of days of headache/month before treatment was 22.31 and number of days of acute medication intake/month was 20. The mean length of the treatment was 15.86 days; the mean haloperidol dosage was 1.01 mg/die. After infusion treatment there was a significant reduction in the number of days of headache (22.31 vs. 6.31; $p < 0.0001$) and in the mean number of days of acute medication intake/month (20.00 vs. 4.31; $p < 0.0001$). The majority of patients ($n = 20$; 57%) had mild and temporary side effects, mainly consisting in agitation (16; 45%).

Conclusions This study shows a significant efficacy of haloperidol IV in the treatment of migraine patients with MOH. Our data confirm the efficacy of dopaminergic antagonists in chronic headache and support the dopamine role in migraine pathogenesis, although more studies are necessary to confirm our findings.

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Iron deficiency, with or without anemia, as a systemic pathogenetic co-factor in chronic migraine

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Clinical practice indicates that migraineurs with anemic disorders have a high frequency of attacks. Iron deficiency is the most common cause of anemia. This study was carried out on 71 patients affected by both iron deficiency and severe chronic migraine (daily headache and frequent acute attacks). Forty-eight patients (45 females, mean age: 31.02±4.11 and 3 males, mean age: 49.33±4.33 years) had low iron and hemoglobin (tolerated levels). Twenty-three (all females, mean age: 24.56±4.32 years) showed only low iron. The only causes of the alterations found were abundant menstrual cycles in women. No history of analgesic misuse. All patients were treated with iron sulfate (120 mg/day) for 3 months. No headache therapy was prescribed, except acute medication. The

headache and accompanying symptoms were evaluated before, during and after treatment with a daily questionnaire. Iron treatment produced a normalization of the hematologic parameters in both iron and hemoglobin. A concomitant improvement of headache was found in 40 patients with low iron and low hemoglobin and in 19 with only low iron. The daily occurrences of the headaches were discontinued (amelioration from 40% to 70%) and the number of exacerbations was reduced (average of 40%). The present results indicate that an iron deficiency could be a pathogenetic co-factor in chronic migraine. The mechanism could be related either to anemia, (decreasing oxygenation?), or to a consequence of the insufficient non-hemoglobin iron on various substrates, including the nervous tissue. Systemic disruptions should be taken into consideration as possible factors affecting migraine clinical course.

Migraine as possible alteration of visceral nociception: clinical and experimental evidence

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Objective Migraine could be related to an alteration of visceral sensitivity. This study has been designed to verify this hypothesis.

Materials and methods First, a retrospective investigation was carried out on electronic archives (collected during the last two years) of the Pain and Headache Centre at the University Campus Bio-Medico of Rome, verifying the co-existence of migraine and irritable bowel, as a model of visceral sensitivity disorders. A second part of the study concerned an experimental evaluation of the visceral pain thresholds through two tests: the rectal distension test, performed by means of barostat inflated with a manometer (from 0 to 2.8 mmHg) and the cold pressure test which consisted in measuring the latency between the onset of the stimulation (immersion of one hand in 1.5° water) and the occurrence of pain. The two tests were also repeated at the same time to verify their influence on each other. The study was carried out on 9 subjects (6 females and 3 males, mean age: 42.21 5±32 years) suffering from both migraine and irritable bowel and 12 (8 females and 4 males, mean age: 39.86±4.91 years) only affected by migraine. A group of 16 healthy subjects (comparable for sex and age) were also tested.

Results The retrospective study showed that 154 out of the 325 examined subjects were affected by migraine and irritable bowel. The experimental study showed that no statistical difference between patients and controls was present in the cold pressure tests. The pain threshold of the rectal distension test was significantly lower in migraine patients (both with and without irritable bowel and with no difference amongst themselves) compared to controls: mmHg, mean ± ES: 1.86±4.33 vs. 2.31±5.14, $p < 0.05$, manova test. When both tests were contemporaneously administered also the cold pressure test was more sensitive in migraineurs (again in both groups) compared with controls (mean latency in seconds: 64 vs. 99, $p < 0.05$, χ^2 square test).

Conclusions This study demonstrates that an elevated percentage of migraineurs (significantly greater than the general population) suffer also from irritable bowel, indicating an alteration of the visceral sensitivity as a possible common pathogenetic factor. Also the major sensitivity to the visceral pain tests in migraine patients either with or without irritable bowel strongly support this hypothesis. Finally, the difference in the sensitivity of the cold pressure test only when both tests are administered suggests that the alteration could be localized at the central level of nociceptive pathways.

Evolution and classification of probable medication-overuse headache (p-MOH): two-year follow-up in 140 subjects (CARE I Protocol)

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Background Since 2005, the CARE I protocol has been in use at the Mondino Headache Centre (Pavia), for the management of MOH [1]. The ICHD-II (2004) and later revision [2] underlined/questioned the need for "two months" observation of p-MOH in order to confirm the MOH diagnosis. The risk of relapsing is higher in the first year after detoxification [3].

Objective To monitor p-MOH two years after detoxification, looking for confirmation (or otherwise) of MOH diagnoses two months after in-patient detoxification.

Methods One hundred and forty patients (28 males, 112 females; mean age: 44.5±11.4 years) diagnosed with p-MOH underwent infusion-detoxification therapy and were followed up, through scheduled visits, for two years. The Statistical Package for the Social Sciences was used for the statistical analysis. Chi-Square test (SPSS, version 14.0) was carried out with the level of significance at 5%.

Results Follow-up data were available for 130 patients (93%) two months after withdrawal, for 114 patients (81%) one year later, and for 102 (73%) after two years. At two months, MOH diagnosis was confirmed in 92 patients (71%) (group 1). Chronic headache was still shown by 38 patients (29%): in 29 (22%) despite discontinuation of the overused drug (group 2), while the remaining 9 (7%) had never stopped their overuse (group 3). At one-year follow-up, 14.6% (n=12) in group 1 and 24.1% (n=7) in group 2 had relapsed; 89% (n=7) of group 3 still showed overuse. Interestingly, the patients classified as persistent abusers or relapsers at one year were more likely to belong to the groups not responding to detoxification after two months than to the group of responders ($p<.001$). During the second year of follow-up, three patients of group 1 and five of group 2 patients relapsed. The seven patients of group 3 with persistent overuse two months after detoxification continued to overuse. At two-year follow-up, 34 patients (33%) were overusing. Again, at this stage, patients with overuse were more likely to belong to the groups that had not responded to detoxification than to the group of responders ($p<.0001$). It is worth noting that 70% (19/27) of patients relapsed in the first year.

Conclusions Our data indicate that headache pattern two months after detoxification predicts the subsequent evolution and strongly confirm the diagnostic importance of the ICHD-II two-month criterion. According to the literature, it is important to stress that the risk of relapsing is greater in the first year after detoxification.

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Not otherwise specified headache in the Emergency Department: a one-year follow-up study

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Background Patients attending the Emergency Department (ED) because of non-traumatic headache have frequent diagnoses of "not otherwise specified" (NOS) headache (32%–59%). These patients are not specifically treated in the ED, and are rarely referred to the Headache Centre by the ED physicians. Aim of the study was to follow-up and evaluate patients with ED diagnosis of NOS-headache.

Methods We evaluated patients presenting to the ED because of non-traumatic headache and discharged with a ED diagnosis of NOS headache referred to the Acute Headache Centre (AHC) of the Clinical Neurology Unit of the University of Trieste. A one-year prospective analysis of all consecutive patients attending the AHC was performed. Causes for referring to the ED, diagnostic tests, consulting visits, ED diagnosis, treatment, MIDAS scores, and the final diagnosis and therapy administered in the AHC were analysed using SPSS 13.0.

Results Ninety-four patients, 75 females (79.8%) and 19 males (20.2%), mean age 44±15 years were evaluated. Twenty-four patients (25.5%) presented more than once to the ED because of headache in the previous six months. Unresponsiveness to treatment (46.8%) was the most frequent cause of presentation to the ED. Twenty-seven patients (28.7%) underwent a CT scan of the skull. Consulting visits were required in 57 patients (60.6%). The most administered ED therapy were NSAIDs (74.1%), whilst triptans were used only in 3.2% of cases. Only 5.3% of patients initiated a prophylactic treatment. Headache was still severe at ED discharge in 21 patients (22.3%). The diagnosis in the AHC was primary headache in 69 patients (73.4%), secondary headache in 19 patients (20.2%), not classified headache in 6 patients (6.4%). In the AHC, the most used attack treatment was triptans (50%). Mean MIDAS score was 48±46, and 42.6% of patients met the criteria for prophylactic treatment.

Conclusions AHC evaluation allowed correct classification of NOS headache according to the International Classification of Headache Disorders 2nd Edition in the majority of patients. The more interesting finding is the classification of headache as secondary in a significant percentage of patients which were not identified and properly treated in the ED setting. In addition, patients with NOS-headache had high disability and often needed a specific prophylactic treatment.

Migraine, oral contraception and stroke in young women

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Background and objective We investigated the influence of migraine with and without aura on the incidence of ischemic and hemorrhagic stroke; how migraine interacts with oral contraception, hypertension, and smoking in determining stroke, and whether the development of aura with migraine is a predictor of stroke in oral contraceptive users.

Methods At the time of abstract submission, a migraine questionnaire was administered to 35 stroke patients and 48 matched con-

trols, mean age 43±2.5 years participating in this 24-month prospective study.

Results A personal history of migraine was present in 25% of stroke cases, and in 8% of controls, leading to odds ratios (OR) adjustment of 1.78 (1.14–2.77) (95% C.I.) for all stroke cases; 3.54 (1.30–9.61) for ischemic stroke; and 1.10 (0.63–1.949) for hemorrhagic stroke. The odds ratio for ischemic stroke was similar to the ratio for migraine with aura 3.81 (1.26–11.5). A family history of migraine was present in 26% of all stroke cases, and 12% of controls, irrespective of a personal history of migraine. In migraineurs, coincidental oral contraceptive usage and a history of hypertension or smoking, had greater multiplicative effects on the OR for ischemic stroke associated with migraine.

Conclusions Migraine in women of childbearing age is a significant risk factor for ischemic stroke, but not hemorrhagic stroke, and the risk is disproportionately increased by coincidental smoking or oral contraceptive consumption.

Clinical characteristics of 5940 attacks of “without and with aura migraine” in 297 patients

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Introduction Unilateral pain in migraineurs is still not sufficiently studied [1]. Many questions have still not been answered: why do some patients have unilateral pain more frequently? Why do some patients always have pain on one side of the head [2], while in others it alternates side? Is there a relationship between type of migraine and the side of pain? and what is the role of handedness [3]?

Objective To evaluate clinical characteristics of migraine patients and migraine attacks in order to acquire useful data to better understand the pathophysiology of migraine.

Methods We evaluated 297 migraine with (MA) and without aura (MwoA) patients (ICHD-II criteria) and 20 migraine attacks for each patient (total: 5 940), during a 1-year observation period.

Results Two hundred and forty (80.81%) women, 57 men (19.19%), mean age: 38.26 years were administered the Edinburgh Handedness Inventory Questionnaire: 79.80% were right-handed, and 20.20% were left-handed. According to the types of attacks, we identified 3 groups: 1) patients with MwoA attacks (84.18%); 2) patients with MA attacks (7.41%); and 3) patients with MwoA and MA attacks (8.42%). MwoA attacks were 90.07% (n=5 350): 88.25% in men, and 92.53% in women, while MA attacks were 9.93% (n=590): 11.75% in men, and 7.47% in women. Unilateral pain was present in 69.90% of all attacks and bilateral pain in 30.10%. Unilateral pain was present in 69.46% of MwoA attacks and in 73.90% of MA attacks. The bilateral pain was found in 30.54% of MwoA attacks and in 26.10% of MA attacks. The unilateral pain increased in MA attacks, while the bilateral pain decreased. The “pulsating pain” was recognized in about 67% of attacks, the “pressing/tightening” pain in 28% and the “throbbing, like-a-knife and not-specified” pain in 5%. The pulsating pain was, generally, unilateral in about 70% of cases and bilateral in 30%; the contrary was noticed for the pressing/tightening pain. According to the side of the pain, we found 3 groups: 1) patients who experienced only unilateral pain attacks (54.9%); 2) patients who experienced unilateral pain attacks or bilateral pain attacks (26.6%); and 3) patients who experienced only bilateral pain attacks (18.5%). One hundred and six patients (35.69% of all patients) referred constant pain to the same side of the head (right or left) in all their unilateral attacks, which was not what was expected (50% of attacks on the right side and 50% on the left side): the right-handed-

patients (72.64%) referred pain, constantly to the right side in 68.83% of attacks and to the left side only in 31.17% of attacks; the left-handed-patients (27.36%) referred pain, constantly to the right side, in 51.72% of attacks and to the left side in 42.28% of attacks.

Discussion This study contributes to better evaluate the main characteristics of migraine attacks and migraine patients and to clarify the influence of sex, type of migraine and of pain, handedness, on clinical presentation of migraine.

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Hormonal preparations intake and headache

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Introduction The possible influence of hormonal preparations intake either on headache onset or course is an old but not fully resolved question. The percentage of headache worsening after exogenous hormones intake reported in previous studies varies between a range of 18%-50% [1]. This variability might be due to several reasons: in older studies the IHS criteria were not used for headache diagnosis and women were using preparations containing a higher dose of ethinylestradiol than in more recent ones. Granella et al. showed the development of about 11.4% of migraine with aura (MA) and 1.2% of migraine without aura (MO) after the intake of oral contraceptives (OC) [2]. The same authors also described a worsening of headache in 56.4% of migraine with aura women and in 25.3% of those with migraine without aura. In a study by Cupini et al., 22.2% of MA and 16.2% of MO women reported headache onset related to OC intake [3]. This study was aimed at evaluating possible differences in onset and course of headache in women with migraine and/or tension-type headache using different formulations of hormonal preparations for several indications.

Patients and methods Three hundred and eighty-seven women, referring to the Headache Disorders Centre of Bari were included. Inclusion criteria were: diagnosis of migraine and/or tension-type headache according to the diagnostic criteria of the International Classification of Headache Disorders (2004) and a history of intake of hormonal preparations. Data concerning patient’s age at headache onset, course of headache, family history of headache, menarche, pregnancy, menopause, type of hormonal preparation and aim of administration were collected. The patient sample was subdivided into age matched groups according to their headache diagnosis. Data were analysed by means of SPSS 11.0 for Windows.

Results When considering the whole sample, the headache onset after OC intake was found in 4.9% of patients with a prevalence significantly higher in tension-type headache sufferers than in the migraine ones. The percentage of worsening in headache course was about 55% with no differences either among monophasic or biphasic or triphasic pills. No differences were found in headache onset and worsening between MA and MO patients.

Discussion The results confirm the main role of hormonal preparations as possible headache triggers for both migraineurs with and

without aura with similar effects. These findings are not fully in agreement with previous data suggesting a more frequent worsening in MA [2, 3]. The most surprising result was the importance of the hormonal worsening effect for tension-type headache. This finding should be taken into account when managing this type of headache.

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Neuromodulation in chronic migraine and in medication-overuse headache: a protocol of prospective, randomized, cross-over study

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Patients affected by chronic headache present a reduced work performance and a significant alteration in quality of life. According to the International Classification of Headache Disorders (ICHD-II), primary episodic headaches become chronic or are defined primary chronic when pain attacks are more frequent than 15 days a month, for at least three months. Chronic migraine (CM) is a condition fulfilling IHS criteria for migraine without aura, temporarily characterized by more than 15 episodes per month persisting for more than 3 months. In population-based surveys, CM occurs in 1.3%–2.4% of the population. Medication-overuse headache (MOH) is a new entrant condition in ICHD-II characterized by drug overuse. Headache is present on more than 15 days per month for more than 3 months with triptan, ergotamine, opioid or combination medication consumption for more than 10 days, more than 15 days consumption for analgesics. The prevalence reaches approximately 1% of the world's population [1] and shows an increasing trend. Several large population-based longitudinal studies clearly demonstrated that overuse of any kind of acute headache medication is the main risk factor leading to the development of chronic headache. Management of MOH remains difficult; the only effective treatment concept is consequent to withdrawal therapy. Recurrence rate is high at 1-year follow-up. A recent prospective study of 240 patients with MOH treated with drug withdrawal and prophylactic medications demonstrated that at 1-year follow-up, 137 (57.1%) patients were without chronic headache and without medication-overuse, 8 (3.3%) patients did not improve after withdrawal and 95 (39.6%) relapsed developing recurrent overuse. Electrical stimulation of primary sensory afferents is known to have an antinociceptive effect [2]. We describe a prospective, randomized cross-sectional study evaluating safety and efficacy of bilateral suboccipital neurostimulation in patients with CM and MOH. Secondary endpoint is to evaluate the improvement in the quality of life and the reduction in drug intake. In this preliminary phase 13 headache patients, who registered drug intake frequency in a standardised diary for 3 months, were studied. After informed consent, two leads were implanted subcutaneously on both occipital nerves (temporary implant). After 30 days, if attack frequency or intensity reduced more than 50%, definitive implant was performed. Patients were randomized to ON or OFF stimulator arm. At week 4, cross-over was performed and follow-ups are in progress.

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Final results of a withdrawal and detoxification therapeutic regimen in patients with medication-overuse headache

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Introduction The overuse of symptomatic headache drugs in patients with primary headache disorders is often associated with the development of a new type of headache, called Medication-Overuse Headache (MOH) following the Second Edition of the International Classification of Headache Disorders (ICHD-II). Criteria for MOH were subsequently revised. Controlled trials and guidelines for the treatment of MOH are currently unavailable. We studied the efficacy of a therapeutic regimen for the withdrawal of the overused drug and detoxification in a sample of patients suffering from MOH during admission to eight hospitals of the Regions Piemonte – Liguria – Valle d’Aosta.

Materials and methods Seventy patients, 58 females (83%) and 12 males (17%), mean age at observation 51.04±12.59 years, affected by MOH following IHS diagnostic revised criteria were treated as in-patients or in Day Hospital. Headache Index (HI) and Daily Drug Intake (DDI) were used for evaluating the severity of headache and medication-overuse. The patients were treated by abrupt discontinuation of the overused drug and by a therapeutic protocol including i.v. hydration, dexamethasone, metoclopramide and benzodiazepines for 7–10 days. Prophylactic medication was started immediately after admission. Analgesics or triptans were used under medical control only in case of severe rebound headache. Diagnostic protocol included routine blood tests (at admission and at discharge), dosage of B12 and folic acid. Patients underwent follow-up controls one, three and six months after discharge.

Results The initial diagnosis was MOH in all patients included in the study. The overused medications were simple analgesics in 18 cases (25.7%), combination analgesics in 26 cases (37.1%), triptans alone in 9 cases (12.9%) or in combination with analgesics in 13 cases (18.6%) and ergot derivatives (alone or in combination) in 4 cases (5.7%). We collected data from 59 patients at first follow-up (1 month), 56 after 3 months, and 42 after 6 months.

Discussion Mean HI was 0.92 at admission, 0.19 at discharge, 0.35 after 30 days, 0.39 after 3 months, and 0.42 after 6 months. Mean DDI was 2.72 at admission, 0.22 at discharge, 0.31 after 1 month, 0.38 after 3 months, and 0.47 after 6 months.

Conclusions These results are on average positive and tend to remain stable with time. They seem to be encouraging regarding long-term use of this therapeutic protocol on a larger number of patients suffering from MOH.

Prevalence of illicit drug use in cluster headache

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Objective The aim of this study was to examine the prevalence of illicit drug use in a clinical population of cluster headache (CH) patients compared with that of the general population.

Methods Seventy CH patients (59 males, 11 females; 56 episodic CH, 14 chronic CH) attending two headache clinics were asked to fill in a questionnaire designed to gather information about the lifetime use (once or more in their life, LTU), the recent use (once or more in the last year, LYU) and current use (once or more in the last 30 days, CU) of cannabis, cocaine, heroin, hallucinogen, amphetamine, and ecstasy. The results were compared with the data regarding drug use in the Italian general population (IPSAD@Italia2005).

Results In CH men the LTU of cannabis (42% vs. 28.5%, $p < 0.05$), cocaine (20.3% vs. 6.2%, $p < 0.001$), and heroin (6.8% vs. 1.6%, $p < 0.01$), the LYU of cannabis (25.4% vs. 9.2%, $p < 0.001$) and the CU of cannabis (18.6% vs. 6.2%, $p < 0.001$) was significantly higher than in the general population. In CH women the LTU (45.4% vs. 17.4%, $p < 0.05$), LYU (27.2% vs. 5.3%, $p < 0.01$) and CU (18.1% vs. 3.4%, $p < 0.05$) of cannabis was significantly higher than in the general population. No difference was found between chronic and episodic CH.

Conclusions Our study indicates that CH patients use of illicit drug, especially cannabis, cocaine and heroin, is higher than in the Italian population suggesting a biological susceptibility to addictive behaviour.

Negative prognostic factors in medication-overuse headache: one year of follow-up in 215 patients (CARE I Protocol)

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Background The identification of prognostic factors in medication-overuse headache (MOH) is crucial to furthering study of its etiological and pathophysiological mechanisms and to optimizing therapeutic approaches, starting from drug withdrawal.

Objective We prospectively monitored probable MOH patients enrolled in our in-patient CARE protocol [1] over a 12-month follow-up, looking for factors related to the one-year prognosis; we compared subgroups with and without resolution of drug overuse after in-patient detoxification.

Methods This prospective, non randomized study considered all patients (n=215) enrolled for the first time in CARE between May 2004 and October 2006. MOH was diagnosed according to the revision of the ICHD-II criteria. We analysed the likely predictor factors for headache resolution after drug withdrawal and detoxification, such as sex, age, type of primary headache, psychiatric comorbidity, duration of chronic headache, type of overused drug, and period of overuse (days and doses/month, months of overuse). First, we described singular risk factors using Mann-Whitney U-test for quantitative variables and Chi-Square test for binary data. Significance was set at 5%. Second, logistic regression analyses were carried out to estimate the strength of associations between

the likely risk factors and abuse at one-year follow-up. We ran a logistic regression model using the forward likelihood ratio method. The Statistical Package for the Social Sciences (SPSS, version 14.0; Chicago, IL, USA) was used for statistical analysis.

Results Complete data sets were available for 172 patients (80%) 12 months after withdrawal: 38 patients (22%) showed overuse vs. 134 (78%) who did not. According to the results of the logistic regression analyses, negative prognostic factors for relapsing were: intake of more than 30 doses/month ($p = 0.004$) at baseline, smoking ($p = 0.012$) and alcohol consumption ($p = 0.037$), non confirmation of diagnosis two months after detoxification ($p = 0.000$), and return to overused drug(s) after detoxification ($p = 0.000$).

Conclusions Many factors are involved in MOH and may influence the path from drug use to abuse, from headache to rebound headache. In our study, the one-year relapse rate was 22%. Other studies reported relapse rates between 22% and 44% during the first-year follow-up [2]. Patients with higher numbers of doses per months (>30), no headache improvement/resolution two months after detoxification and re-intake of overused drug(s) after withdrawal showed a higher rate of relapsing than patients without overuse. Interestingly, patients with significant consumption of alcohol/cigarettes showed the same risk, suggesting that medication over-users have a tendency towards dependent behaviors [3]. We suggest that subgroups of MOH patients exist, with likely consequences on the treatment strategies.

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Postmenopausal migraine: an item to predict its evolution

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Background Throughout the reproductive life cycle, as hormonal levels fluctuate, many women suffering from migraine experience significant modifications in the illness' pattern [1]. Although migraine prevalence decreases with advancing age, after menopause migraine attacks can decline or flare up or their frequency and clinical characteristics remain unchanged [2]. Up to now, no data exist, predicting the outcome of the illness after the onset of menopause. In a previous study we observed that in the majority of cases the outcome of migraine after menopause tended to follow the course of the patients' mothers.

Objective In order to find some predictive factors regarding the development of the illness, we studied the course of pre- and postmenopausal migraine in a number of postmenopausal patients focalising the attention on the existence of a possible link between a correlation of migraine attacks with menstruation and the evolution of migraine after menopause.

Methods Two hundred and fifteen postmenopausal women (age 35-78 years) suffering from migraine according to ICHD-II criteria, referring for the first time to the Turin University Headache

Centre, in the years 2003–2005, were studied. We asked these women if and how the characteristics of their migraine had changed after menopause and if their migraine attacks had been in some way correlated to the menstrual cycles, during the fertile age. The data were statistically analyzed using the χ^2 test.

Results In 34 (15.08%) patients migraine improved after menopause, in 129 (60%) it worsened, while in the remaining 52 (24.2%) of them migraine remained unchanged. Thirty-two (94.1%) of the 34 patients whose migraine improved after menopause had migraine attacks correlated to menstruation, while only 95 (73.6%) of the patients whose migraine worsened after menopause and 40 (76.9%) of the patients whose migraine remained unchanged had this correlation ($p<0.02$).

Conclusions On the basis of these data, it seems that if migraine attacks are correlated to menstruation during the reproductive life, it is more probable that migraine improves after the onset of menopause. Since at present there are little or no data on this particular aspect of the illness more studies are needed to assess this tendency. If these data will be confirmed this will be a very useful indication for many women approaching the menopausal period.

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Interaction between chronic analgesic-overuse in migraine and tension headache

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Background and objective Chronicity may be regarded as a complication of both migraine and tension headache. Chronic migraine starts more often as an episodic migraine, while tension headache may start as a more/less chronic form in many cases. Chronicity is also a factor that contributes to significant changes of headache characteristics among migraine patients. High frequency of analgesic overuse may be considered as a further complication of primary headache, mostly for the episodic and chronic forms. Aim of the present study was to detect interaction between chronicity symptomatic drug-overuse in migraine and tension headache.

Methods We observed patients with primary chronic headache, with a history of headache for more than 15 days per month for at least 6 months; and without significant comorbidity. We analysed the patients' characteristics (age, gender, time of headache onset, family history of headache), type and duration of headache symptoms (migraine with and without aura, tension-type headache and combination of migraine and tension-type headache), pattern of medication-overuse. Statistical analysis was performed using χ^2 test, ANOVA and Kaplan-Meier.

Results Sixty patients were evaluated (M/F 12/48; mean age: 46.2±12.07 years; mean age of headache onset: 19.5±11 years). Thirty-nine patients (65%) with chronic migraine recognized previous episodic migraine. Sixteen patients (26.7%) had combination of migraine and tension-type headache, while 5 patients (8.3%) had tension-type headache alone. Overuse of medications was reported in 39 patients (65%) and in this group the use of analgesics was experienced in 35 patients (89.7%). Medication-overuse development was prevalent in patients with chronic migraine (40%). A positive association was observed between headache type and gender ($p<0.001$). Gender (female) and medication-overuse were statisti-

cally associated ($p<0.05$) and a positive correlation was observed between the variables "prophylaxis with antiepileptic drugs" and drug-abuser ($p<0.05$). Analgesics overuse and chronic daily headache were statistically associated ($p<0.01$). The lowest age of headache onset was found in patients having migraine and tension-type headache in combination vs. the other groups (ANOVA; $p<0.01$). Patients with chronic history of primary headache had a higher risk for medication-overuse ($p<0.05$; HR 0.38, 95% CI: 0.21–0.83).

Conclusions Chronic daily headaches without drug-overuse are almost rare. A previous prophylactic treatment, of adequate duration, may reduce the risk of medication-overuse, i.e., on the other hand, statistically correlated with a higher lasting history of chronicity.

Case Reports

Painful ophthalmoplegia: orbital pseudotumor secondary to Crohn's disease?

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Clinical case A 54-year-old woman came to our observation with a symptomatology that began 1 month prior to her admission, characterised by a retrobulbar headache of severe intensity and stabbing pressure in her right eye, aggravated by ocular movements, associated with oedema of the upper and lower eyelids with ipsilateral ptosis and binocular diplopia with upward and downward gaze. The patient referred a similar episode of retrobulbar pain of the right eye 1 year before, which spontaneously regressed. The patient's history revealed systemic arterial hypertension, Crohn's disease for 15 years treated with ileo-cecal resection, and migraine with and without aura. About 2 months before admission the patient underwent control blood tests which revealed reactivation of Crohn's disease. Brain MRI with contrast revealed an increase in volume and gadolinium enhancement of the right medial rectus muscle. The lumbar puncture showed a modest increase in CSF proteins with other parameters in the norm. Blood tests showed mild neutrophilic leukocytosis and increase in the indicators of inflammation. With suspicion of an orbital pseudotumor, probably correlated to exacerbation of Crohn's disease, therapy was begun with prednisone 50 mg/day with regression of the symptomatology. Clinical and neuroradiologic follow-up at one month and at one and three years after discharge are in the norm.

Discussion The development of a painful unilateral ophthalmoplegia can be caused by an aneurysm, a tumour, or an inflammatory-granulomatous process of the cavernous sinus or orbit. The orbital pseudotumor determines an inflammatory swelling of one or more extraocular muscles; thus, it can be accompanied by conjunctival injection, palpebral oedema and ptosis. Treatment in the majority of cases is based, initially, on corticosteroid therapy. The extraintestinal manifestations of Crohn's disease occur in 20%–40% of cases. Ocular complications of Crohn's disease are infrequent (less than 10% of cases); of these the most frequent are iritis, uveitis, episcleritis, scleritis, and conjunctivitis [1]. Few cases of orbital pseudotumor in the course of Crohn's disease have been reported in the literature. Clinical cases have been described in which orbital pain, diplopia, ptosis and hyperlacrimation are the sentinel symptoms and precede the diagnosis of Crohn [2]. Obviously, the definitive diagnosis requires an orbital biopsy, even though such a histopathologic

procedure has not been completely accepted as a diagnostic criterion. In our case this procedure, in agreement with the patient, was postponed due to the regression of the symptomatology.

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Successful preventive therapy of bromazepam in a patient suffering from hypnic headache: case report

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Background and objective Hypnic headache is a rare and recurrent primary headache disorder. Multiple medications with different mechanisms of action have been used with variable success rates. Although lithium and indomethacin seem to be the most effective, their frequent side effects and the old age of the patients limit their use.

Case We report a case of a 64-year-old woman with a history of strictly nocturnal headache since 5 years that used to awaken her almost every night around 2 or 3 a.m.. The headache was described as diffuse, non pulsating, of severe intensity, and it was not associated with any autonomic features like nausea, vomiting, photophobia or tearing. The headache continued for up to 5 hours (average 3 hours) and, therefore, this woman was not able to go back to sleep without taking medication. She found that the only analgesic that resulted effective was indomethacin 100 mg, that she took every time with pain-relief after 1 hour. MRI, angioMRI, EEG, and carotid ultrasound Doppler failed to reveal any structural pathology. We performed a continuous EEG during the night together with the recording of cardiac frequency, blood pressure and oxygen saturation to exclude a nocturnal apnea syndrome or a desaturation episode. Because of the presence of a comorbidity of anxiety, in an attempt to prevent nocturnal attacks, we chose bromazepam at the dosage of 3 mg 3 times a day (at 8 a.m., 4 p.m. and 10 p.m.). She has been taking this medication for the past 2 months and the headaches have completely disappeared. With the exception of ezopiclone (an atypical hypnotics) any other hypnotic or benzodiazepine has not been previously reported to be effective for this disorder.

Conclusions The mechanism of its efficacy remains speculative at this time, but a possible explanation could be a regularization of the sleep structure (REM-non REM time or REM density) or a stabilization effect (gaba-mediated) of a speculated impairment of the suprachiasmatic nucleus that could cyclically activate a nociceptive mechanism leading to both a sudden awakening and headache.

Acute glaucoma during treatment with topiramate with spontaneous resolution

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Topiramate is a new antiepileptic drug used also for migraine prophylaxis; its action is based on reduction of voltage-gated sodium channels currents in cerebellar granule cells, limitation of activa-

tion of AMPA-kainate subtype of glutamate receptor and enhancement of postsynaptic GABA_A-receptor currents. The principal possible side effects reported using topiramate are paraesthesias and renal calculosis; acute glaucoma is also reported, but in very few patients. Renal and ocular side effects are due to the inhibition of carbonic anhydrase. We report the case of a woman, 36-year-old, black, 57 kg, 155 cm; in the clinical history we only found an autoimmune thyroiditis, which was not treated. From the age of 18 she refers 4–5 attacks/month of migraine without aura (mild-severe pain, bilateral, throbbing quality, worsened by movement, with nausea, phono- and photophobia, lasting from 1 to 2 days), only treated with nimesulide with poor reduction of pain duration and intensity. Topiramate was prescribed starting with 25 mg a day; after 5 days of therapy, she presented progressive loss of visus. The eye exam showed myopisation (-4, bilateral) and increased ocular tone (35 mmHg bilateral), thus acetazolamide 250 mg three times a day was prescribed, but the patient spontaneously refused therapy. Topiramate was interrupted and a subsequent eye examination, performed after 15 days from the first one, showed a bilateral ocular tone of 16 mmHg with complete recovery of visus. We conclude that topiramate is, according to the literature, a useful drug for migraine prophylaxis, but contraindications (especially renal calculosis and glaucoma) must be investigated and the patient must be instructed to refer any changes in visus, as well as onset of other symptoms after beginning the therapy.

Acute myocardial infarction after sumatriptan injection in a woman with normal coronary disease

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Sumatriptan is a specific agonist of the serotonergic 5-HT_{1B/1D} receptors that have increasingly been used in the treatment of migraine and cluster headaches. The mechanism of action is reverse abnormal cerebral vasodilation through their activity as 5-HT_{1B} receptor agonists. Triptan-induced vasoconstriction is attributed to its activity on peripheral 5-HT_{1B} receptors and a modest vasoconstrictor effect of sumatriptan has been demonstrated during coronary angiography. Although it is generally considered safe, there have been few reports of myocardial infarction, stroke, ischemic colitis and splenic infarction. We report a case of a 54-year-old woman with family history for vasculitis and without personal history of coronary artery disease who was admitted to our coronary care unit for acute myocardial infarction half an hour after injection of sumatriptan 6 mg sc. Coronary angiography, performed a few days later, revealed a normal coronary arterial system. The patient was taking amitriptyline and perphenazine for depression as well. She was treated with standard therapies, discharged after a few days and advised to permanently avoid triptans. Our case suggests that normal cardiac evaluation does not guarantee safety for the use of triptans.

Cytomegalovirus responsible for rare types of headache

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Cytomegalovirus is an ubiquitous double stranded DNA herpes virus. It infects only humans and causes a variety of clinical mani-

festations, ranging from unapparent to fatal infections. We report two patients who developed, during a cytomegalovirus infection, HaNDL syndrome and low cerebrospinal fluid pressure headache. Headache associated with neurologic deficits and cerebrospinal fluid lymphocytosis is a self-limited syndrome that is characterized by a sudden onset of headache with temporary neurologic deficit and cerebrospinal fluid lymphocytosis. It is a syndrome of unknown cause. A viral etiology is supported by the monophasic and self-limited course of HaNDL, viral prodromes, and cerebrospinal fluid mononuclear cells. A 33-year-old man with no previous medical history and personal history of migraine with aura was admitted to our department, because he complained of an episode of left-sided sensory and motor symptoms which lasted 1 hour, and bifrontal headache. During hospitalization (1 month) he experienced several episodes of dysphasia, right- or left-sided sensory and motor symptoms and headache. Brain MRI and CT scan were normal. A lumbar puncture showed pleocytosis (132 WBC/mm³; 97% lymphocytes), and elevated protein. The patient was positive for CMV DNA in CSF. During a 5-year follow-up he did not develop any further neurologic symptoms. Headache is the most common manifestation of intracranial hypotension. The headache in classic cases is an orthostatic headache. It is likely that, in some of the patients with spontaneous CSF leaks, an otherwise minor and trivial trauma may lead to CSF leakage. MRI has revolutionized the diagnosis of patients with intracranial hypotension. It highlights diffuse pachymeningeal gadolinium enhancement. We report the case of an acute primary infection with cytomegalovirus in a 42-year-old immunocompetent and healthy man. The course of the disease was characterized by febrile state, nausea, and myalgias. Indicators leading to diagnosis were reactive lymphocytosis, as well as elevated transaminases interpreted as concomitant hepatitis and increase of anti-CMV antibodies. The evolution of hepatitis was benign under symptomatic treatment. However, the patient, during hospitalization, manifested an orthostatic headache. A gadolinium-enhanced head MRI demonstrated diffuse pachymeningeal gadolinium enhancement. The patient recovered, after 6 months, with steroids therapy. Our case suggests that rare forms of headache, included in the seventh chapter of the ICHD-II classification, are due to cytomegalovirus infection.

Efficacy of PFO closure in a case of hemiplegic migraine: pathophysiological and therapeutical considerations

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Although rare, the presentation of migraine aura, like hemiplegic migraine (familial or sporadic) or basilar type migraine could present with a dramatic clinical picture, mimicking other severe neurological disorders. This could be particularly puzzling when complications of migraine such as "persistent aura without infarction" occur. Patent foramen ovale (PFO) has been reported to have an elevated prevalence in patients suffering with migraine with aura (MA) [1], and the possibility that right-to-left shunt may be a "trigger" in the genesis of aura has also been suggested, even if the causal relationship between migraine and PFO remains controversial [2]. Here we describe the case of a young (35-year-old) male patient with an unusual presentation of hemiplegic migraine (prolonged hemiplegia and basilar symptoms) in which transesophageal-echocardiography (TEE) showed a large PFO (with right-left shunt) and MRA evidenced a stenosis of basilar artery.

After PFO closure the patient experienced a consistent and prolonged improvement of the clinical picture that lasted for five years. Then hemiplegic migraine reappeared and re-opening of PFO was demonstrated with TEE. In this case, hemiplegia was associated to basilar symptoms (dizziness). Anticoagulant therapy with warfarin was started with benefit.

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Headache attributed to Paget's Disease of cranial bones: report of two cases

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Introduction Paget's Disease (PD) is an idiopathic metabolic bone disorder of the middle-aged and elderly, and is characterized by excessive bone resorption and formation due to activated osteoclasts. Most commonly PD involves the axial skeleton, but can affect any area. In the majority of patients, PD affects at least two bones, but in one third of patients only one bone is involved. Complications from PD include deformity, fracture, and pain. Among the headaches attributed to a disorder of cranial bone, placed at point 11.1 of the second edition of the International Headache Society Classification, PD is stated to be one of the few conditions, along with osteomyelitis and multiple myeloma, that can cause this kind of secondary headache.

Materials and methods We report two patients, a 73-year-old woman and a 52-year-old man, who were referred to our Headache Centre for a new-onset headache and were diagnosed with headache attributed to PD.

Results The female patient had suffered from migraine without aura until menopause. When she was 71, she started complaining of a continuous, dull, pressing, mild headache, located mainly in the forehead. The laboratory tests revealed an elevated serum alkaline phosphatase level and the skull X-rays showed a typical area of osteoporosis circumscripta in the frontal bone. The bone scan detected another active area in the pelvis. She was treated with risendronate, 30 mg daily for 2 months and the headache almost completely abated. The male patient at the age of 51 started suffering from a new-onset unilateral headache, that was of moderate intensity, continuous with exacerbations of severe pain, without autonomic signs and symptoms. The MRI showed typical features of osteolysis and osteosclerosis in the left greater wing of sphenoid bone, that were confirmed by the bone scan. No other skeletal involvement was found, and the serum alkaline phosphatase level was normal. He was treated with pamidronate 30 mg intravenously on 3 consecutive days. The headache was greatly relieved, the exacerbations ceased and the headache intensity became mild.

Discussion Headache attributed to PD of the skull does not seem to be such a rare condition, even if specific studies are lacking in the literature.

Conclusions Diagnosis of PD of the skull may be suspected when a new-onset continuous headache occurs in subjects older than 50 years. X-rays and bone scans can ascertain the diagnosis in most cases. Biphosphonates, usually given cyclically, are the treatment of choice for PD.

Migraine with aura and cerebral arteriovenous malformation: coincidence or pathogenetic link?

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A 36-year-old woman complained of a worsening of her usual headache pattern. She suffered from the age of 12 from recurrent episodes of severe, disabling throbbing pain in the right fronto-orbital region with a strictly unilaterality, associated with nausea, vomiting and photophobia; the pain was exacerbated by routine physical activity. The painful phase was constantly preceded by transient hemianoptic aura in her right visual field, consisting in fortification spectra which developed in 10 min and lasted 30 min. She referred an average frequency of 1 attack every other month until 40 days before our clinical observation. Since then, the crises presented with a daily incidence and her usual attack therapy with triptans partially lost its efficacy, allowing for recurrence within 2 hours. A month later the attacks returned to the previous frequency, and oral triptan therapy was not flawed by headache recurrence. In spite of the fact that the ICHD-II diagnostic criteria of migraine with aura were fulfilled and that the general and neurological examination were unremarkable, the recent modification of the temporal pattern of the attacks suggested to perform a cerebral MRI and an AngioMRI. Neuroimaging documented the presence of a high-flow cerebral arteriovenous malformation in the left parieto-occipital region. The patient underwent a thorough angiographic study, which evidenced hypertrophic arterious afferences from the left posterior cerebral artery and external carotid artery; the efferences drained directly into the superior sagittal sinus. Moreover, a bilobate aneurismatic formation in the left P1 tract was detected. Because of the dimension of the malformation and the high possibility of bleeding, a three-step neuroradiological intervention was proposed; two months after the first intervention, the frequency of the attacks do not show any modifications. The existence of a correlation between migraine with aura attacks and the arteriovenous cerebral malformation should be hypothesized considering the concordance between the vascular malformation and the constant right side of the aura. Nevertheless, only the disappearance of the attacks after the complete removal of the arteriovenous malformation will prove this case to be symptomatic.

Atrial fibrillation as an unusual complication of migraine

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Introduction Vegetative manifestations are a chief complaint of migraine. Furthermore, subclinical autonomic nervous system (ANV) abnormalities are widely found in the migraine population, particularly in those individuals with frequent or disabling attacks [1]. On the other hand, the ANV is known to play an important role in the pathogenesis of atrial fibrillation. We report the case of a patient who experienced a sustained episode of atrial fibrillation in close temporal relation with a migraine attack, which required intensive treatment.

Case report A 30-year-old, right-handed man was admitted for persistent and severe headache associated with vomiting and tachy-

cardia. Since the age of twenty the patient had been suffering from migraine without aura with weekly episodes rapidly alleviated with ibuprofen. During the last three months the pain became increasingly frequent and, in the four weeks prior to presentation, recurred on a daily basis. The day of admission the patient awoke with a severe, throbbing headache localised over the frontal region of both hemispheres, associated with photophobia, phonophobia, and profuse vomiting. A few hours later the patient experienced palpitations and mild respiratory distress. The neurological examination performed soon after his arrival to the hospital was unremarkable. The heart auscultation revealed a frequency of about 140 per minute. A EKG evidenced an atrial fibrillation with a high ventricular response. A CT scan of the brain was obtained which did not show parenchymal or skull abnormality. Indomethacin, metoclopramide and verapamil were administered intravenously, with a partial reduction of the pain and vomiting, but without effect on the heart frequency. IV propafenone infusion over two hours resulted in a slight reduction of frequency, but no return of sinus rhythm. Finally, the patient underwent electrical cardioversion about twelve hours after the onset of the symptoms. Two days later he was discharged in sinus rhythm and pain-free. Transthoracic and transesophageal echocardiography were unremarkable.

Discussion Atrial fibrillation as a complication of migraine has been rarely described [2]. In our case, as well as in previously reported cases, the atrial fibrillation was strictly associated with vomiting and other autonomic manifestations. The presumed pathophysiologic mechanism underlying cardiac arrhythmia in migraine patients is an increase in vagal tone resulting from vomiting, with subsequent bradycardia, and dispersion of the atrial refractory period. The intensive treatment of vomiting is crucial in preventing cardiac arrhythmia in patients with migraine and migrainous state.

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Unusual cluster headache: a case report

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We describe the case of a 20-year-old male, who suffered for many years of a recurrent but sporadic headache not better classified. In the following years the pain attacks became more severe in intensity, persistent between 30 to 180 minutes, with piercing pain, occurring 10–15 times per month, thus compromising quality of life and scholastic performance, occurring randomly with the same presentation and localized in the frontal or orbital region especially on the right side. No concomitant neurovegetative symptoms were indicated. In his history some affective problems and the continuous use of videogames were also reported. One-year from the onset of the disturbances, the headache attacks were more frequent but shorter: from 30 to 120 minutes. The patient underwent complete diagnostic screening: neurological and ophthalmic evaluation, brain MR, blood examinations, EEG and EEG in sleep deprivation were all normal. A prophylactic treatment (amitriptyline, 10 to 40 mg/die and propranolol, 40 mg/die) was not effective, while a successive treatment with topiramate (75 mg/die) improved the headache (at 16 years of age). During the last 3 years, without prophylaxis treatment, the headache became less severe but more frequent, with the

continuous use of unspecific symptomatic treatment. In May 2007, abrupt episodes of severe right ocular pain, pulsation, that last between 30 to 120 minutes, associated with ipsilateral conjunctiva injection, weeping, rhinorrhoea and ptosis, which always occurred only in the evening and at the same time. The pain attacks had features fulfilling the criteria for cluster headache according to the ICDH-II classification, which disappeared immediately after starting treatment with lithium carbonate at 600 mg/die. The interest of this case may be found in many considerations: first of all, a possible role of the use of a symptomatic drug for headache that exposed the patient to medication-overuse and to an unsuccessful therapy causing social and working problems. In these years, headache had shown a modification of presentation with a more clarifying picture of a recurrent cluster headache. Some considerations may be made about its evolution: the onset of headache was not clear and it is probable that some attacks were misunderstood at the beginning, otherwise the two entities could coexist. Also, the consequent psychopathological substrates might link the two forms?

Vascular compression of the oculomotor nerve in a young woman with transient unilateral mydriasis during migraine attacks: a case report

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Episodic unilateral mydriasis has been described as a benign sign, not usually requiring neurodiagnostic evaluation [1]. Moreover, isolated anisocoria can occur in migraine as a transient mydriasis [2]. We describe the case of a 34-year-old woman, who presented at our clinic with transient unilateral mydriasis during a severe migraine attack. Her headache history had started in adolescence, with sporadic migraine attacks increasing over the years and becoming daily in the previous five months. Her husband had recently noticed that throughout a severe headache attack she had shown asymmetry of pupil size (right > left), the right pupil being bigger than the left. During hospitalization a similar episode was observed. Neurological examination was normal. Visual capacity and eye tonometry were normal. Pupils were both reactive to light, near response was preserved, and there was no ptosis or limitation of movements. Pupillary diameter was measured, using a digital 5 Mpixel camera, at baseline and after administration of a directly acting sympathicomimetic (phenylephrine 1%) and parasymphaticomimetic (pilocarpine 1%) [3]. The anisocoria index (symptomatic pupil/symptomatic pupil+non symptomatic pupil ratio) showed no statistically significant difference among the different recordings. Initial diagnostic evaluation at another institution had shown a normal CT scan of the brain, but magnetic resonance imaging (MRI) and MRangiography (MRA), performed in our clinic, revealed a neurovascular conflict between the right posterior cerebral artery (PCA) and the adjacent ipsilateral third cranial nerve. The study showed a "foetal" variant of the circle of Willis with a large lumen posterior communicating artery (PCoA) continuing with a normal sized P2 segment of the PCA. The PCA P1 segment was depicted as a thin and very tortuous vessel "pushing" the 3rd cranial nerve from lateral to medial. The presence of neurological signs is a criterion for the diagnosis of secondary headache. To our knowledge, this picture is the first case of transient, unilateral mydriasis (occurring during some migraine attacks) explained by a neurovascular

conflict demonstrated by MRA. It could not be classified as a secondary headache because of the frequent association of the unilateral mydriasis with the migraine attacks, even though this was not a constant sign. We may best explain this variability by considering that the vasodilatation present during migraine attacks could also involve the PCA causing "irritation" of the 3rd cranial nerve and giving rise to the unilateral mydriasis.

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Migraine with aura and patent foramen ovale in patient with somatoform disorders: a case report

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Introduction Migraine is a common neurological disorder, the aetiological mechanisms of which remain complex. Patent foramen ovale (PFO) is considered to have a role in migraine. Many studies indicate an increased prevalence of patent foramen ovale in patients suffering from migraine with aura compared to patients with common migraine, and an increased prevalence of migraine and migraine with aura in persons with PFO. Moreover, there is a lack of data in the literature on the extent of psychiatric comorbidity such as anxiety disorders, major depressive disorder and dysthymic disorder in patients with different subtypes of headache, but not so common are descriptions of patients with migraine with aura, patent foramen ovale and psychological disorders.

Case Report We report the case of a 13-year-old girl that at the age of 12 began to suffer with sporadic episodes of migraine with aura characterized by right frontotemporal pain associated with scotoma, paresthesia on the left hemibody, which lasted one hour, followed by drowsiness. General blood exams, screening for coagulation disorders, echo-doppler of neck arteries, EEG and MRI were negative. Trans-thoracic echocardiography showed an interatrial septum aneurysm with patent foremen ovale and moderate right-to-left shunt. Treatment with cardioaspirin and flunarizine was given with very important reduction of migraine attacks. The patient subsequently developed tension headache with scalp diffuse pain and movements at right hand mimicking seizures associated with hypotonia or drop attack without lost of consciousness. Video EEG did not show any epileptiform discharges during the segmental myoclonias so it was possible to exclude the diagnosis of epilepsy. A psychological evaluation revealed the presence of depressive and anxiety traits associated with parents conflictual relationship. Psychotherapy reduced headache attacks and somatoform symptoms.

Discussion and conclusions Patients with tension headache had significantly more symptoms of anxiety, depression, and somatization disorders and medication-overuse was a significant occurrence, but the presence of psychological disorders also in patients with migraine and recognized organic disease suggests the need to evaluate possible common risks. In our patient the medical treatment for migraine permitted only a partial resolution of symptoms

because of the presence of a psychiatric comorbidity. We confirm the necessity of a multidisciplinary treatment approach for therapeutic success.

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Migraine with aura and vertigo triggered by photostimulation: case report

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Migraineurs report excessive sensitivity to light, sound, motion, smells and other sensory stimuli in between migraine acute attacks and among triggers of migraine attack, photic stimuli, is frequently referred to.

Case report (videotape): Male, 4-year-old, premature infant and suffering from cerebral palsy (right hemiplegia). In the clinical history: TTH in mother. Parossistic torticollis in the first year and cyclic vomiting in the first and second year. MR brain: cortical atrophy. EEG: frequent theta rhythm. Aged 4 years the child complained of attacks of headache characterized by frontal right pain, after vertigo lasting 10–20 seconds and accompanied by several vomiting episodes. These attacks were triggered frequently by photic stimuli such as sunlight. In the video the child showed the chronological events of 2 attacks, one triggered by sunlight and one by the TV monitor.

Conclusions This case underlines the importance of differential diagnosis between migraine with aura and epilepsy. It is very important to observe that banal events, such as sunlight from the window, can cause severe migraine attacks.

Diagnosis of Ehlers-Danlos type IV after a migraine with aura attack: a case report

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Headache is a common manifestation of genetically determined large and small vessels diseases. Migraine is the first symptom in 38% patients with CADASIL (migraine with aura representing 87% of the cases) and is part of the phenotypic spectrum of pseudoxanthoma elasticum and Fabry disease in which there is involvement of both small and large vessels. Migraine and secondary headache due to carotid or vertebral dissection may also be present in Ehlers-Danlos type IV, Marfan disease and Moya-Moya between the group of large vessel disorders. We present the case of a 21-year-old woman who came to our observation after a migraine attack preceded by visual and sensory aura accompanied by transient motor disturbance of the left leg. The patient had an uneventful familial and personal remote history except for migraine with aura by the age of 17 years. Due to the presence of slight neurological signs at the resolution of the crisis and of a motor component of the aura, a cranial MRI was performed with the evidence of an ischemic subcortical lesion near the head of the left caudate nucleus and a small ischemic frontal cortical

lesion. An angiogram was then obtained and a left carotid dissection, a small aneurysm of the left vertebral and dolichoectasia of the vessels were detected. Since the picture suggested a vessel disease, a skin biopsy with fibroblast culture was performed. The presence of anomalous synthesis of collagen type 3A1 led to the diagnosis of Ehlers-Danlos type IV. Ehlers-Danlos type IV is sustained by mutations in Col3A1 gene leading to the synthesis of anomalous 1 chain in the fibrillar collagen type III which is a component of skin, muscle and blood vessels. The disease is inherited as an autosomal dominant trait, however new mutations account for almost 50% of cases. Furthermore, the pathognomonic features such as cutis laxa may not be present and the involvement of joints may be limited to the hands. We suggest that these diseases be considered not only in young patients with stroke but also in patients with migraine with aura, if atypical features are present.

Headache and children

Sociality and migraine in childhood

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Introduction Migraine is a common primary headache which has a negative influence on the well-being and quality of life, as well as the professional life, of affected individuals in all ages of life. Primary headaches (PH), which are highly prevalent pathologies, are linked to high morbidity and disability rates and high costs for the health care system. Moreover, migraine contributes to missed school days, affects children's peer and family relationships, and significantly impacts children's quality of life, often carrying over into adulthood [1].

Objective The aim of this study was to verify prevalence of social impairment in children with migraine.

Materials and methods Mothers of 91 (mean age: 9.45 ± 0.96 years) children consecutively referring for migraine to the Clinic of Child and Adolescent Neuropsychiatry of the Second University of Naples were assessed with the Child Behavior Checklist/4–18 (CBCL) [2]. The Child Behavior Checklist/4–18 is a multi-axial empirically based set of measures for assessing children from parent-, teacher-, and self-reports. All three instruments include measurements of the following eight constructs or syndromes: Social Withdrawal, Somatic Complaints, Anxiety/Depression, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, and Aggressive Behavior [2]. The three corollary instruments also contain sections addressing the area of social competence in order to determine which reported competencies discriminate between those children who are adapting successfully and those who are not. The CBCL/4–18 contains 20 competence items grouped into 3 scales (Activities, Social, and School) [2]. Results were compared with a matched control group of 163 children (mean age: 9.32 ± 1.25 years; $p=0.077$).

Results When compared with the control group, migraine children presented a significant lower score in all items of social competence of CBCL 4/18. Specifically in Activities items mean values were 36.11 ± 6.68 vs. 30.55 ± 6.60 ; $p < 0.001$, in Social items 43.73 ± 6.73 vs. 41.55 ± 7.61 ; $p=0.01$ and in School items 48.30 ± 5.33 vs. 43.44 ± 7.41 ; $p < 0.001$), and in Competence category 38.98 ± 6.65 vs. 33.84 ± 7.56 ; $p < 0.001$.

Discussion In childhood disabilities, due to a physical illness, preserving quality of life is very important. All non medical aspects of migraineous children can worsen or improve therapeutic compliance.

Conclusions The CBCL is one of the most commonly used measures of child psychopathology and could contribute to improve medical diagnostic ability in migraine children.

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Migraine and enuresis: a casual relationship?

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Introduction The American Psychiatric Association has defined bed-wetters as children older than age five who are incontinent of urine at night. The prevalence of nocturnal enuresis (NE) has been difficult to estimate because of variations in its definition and in social standards, even if it is now generally accepted that 15 to 20 percent of children will have some degree of nighttime wetting at five years of age, with a spontaneous resolution rate of approximately 15% per year. Therefore, at 15 years of age only 1% to 2% of teenagers will still wet their bed. Presently, prevalence studies of NE in the migraine population have not been reported in clinical literature.

Objective Aim of study was to verify the differences in prevalence between migraine children and a control matched group.

Materials and methods To verify NE prevalence in the headache population, a retrospective investigation was performed on 223 children (114 females, mean age: 8.94±1.65 years) referred for migraine without aura diseases to the Clinic of Child and Adolescent Neuropsychiatry of the Second University of Naples between January 2005 and February 2007. Results were compared with a school aged population sample of healthy children (348 children, 197 females). Exclusion criteria were bladder instability and metabolic diseases for both populations.

Results NE prevalence in migraine children was 26.0% (58 subjects, 34 males) and 6.3% in the control group (22 subjects, 13 males) with a relevant statistical difference (Chi-square=42.105; $p<0.001$). Logistic regression showed an Odd Ratio=5.2 (95%, CI 0.06–0.26).

Discussion Primary nocturnal enuresis is a disease with no clarified causes. Many children with primary headache present sleep troubles with or without sleep disordered breathing, very common in enuretical children. We suggest that there is no casual relationship between these two different symptoms.

Conclusions A better clinical definition of migraine disorder and relationship with other symptoms would make it easier to identify in younger affected children and consequently to plan more specific therapeutic interventions, taking into account environmental and psychological factors.

The child with headache in a paediatric Emergency Department

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Introduction In previous literature, there are few data regarding the evaluation of headache in the paediatric Emergency Department (ED). The aim of our study was to investigate clinical features of a paediatric population presenting with headache to our ED and to identify headache characteristics which may lead to suspect serious life-threatening diseases.

Materials and methods A retrospective chart review of all consecutive patients who presented with a chief complaint of headache at the ED over a one-year period was conducted. Aetiologies were classified according to the International Headache Society (IHS) diagnostic criteria 2nd edition.

Results Four hundred and thirty-two children (0.8% of the total number of visits) aged from 2 to 8 years (mean age 8.9 years) were enrolled in our study. There were 228 boys (53%) and 204 girls (47%). The school-age group was the most represented (66%). The most common cause of headache was upper respiratory tract infections (30.8%). The remaining majority of non-dangerous headaches included migraine (28.1%), post-traumatic headache (8.6%), and tension-type headache (7%). Serious life-threatening intracranial disorders (6%) included meningitis (1.9%), acute hydrocephalus (1.4%), and tumors (1.3%). We found several clinical clues which demonstrated a statistically significant correlation with dangerous conditions: pre-school age, recent onset of pain, occipital location and child’s inability to describe the quality of pain, and neurological objective signs.

Conclusions Differential diagnosis between primary and secondary headaches is very difficult, especially in an ED setting. The majority of headaches are secondary to respiratory infectious diseases and minor head trauma. Our data allowed us to identify clinical features useful in recognizing intracranial life-threatening conditions.

Tolosa-Hunt syndrome or ophthalmoplegic migraine: a case of differenzial diagnosis

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In children with painful ophthalmoplegia, the diagnosis of Tolosa-Hunt syndrome or of ophthalmoplegic migraine should only be considered when tumoral, infectious, inflammatory or vascular causes have been excluded by appropriate investigations. Both entities are classified as “neuralgia” by the International Headache Society, and seem to share a similar pathogenic mechanism. Both diseases have many clinical similarities with slight differences concerning pain characteristics or ocular associated symptoms. High resolution CT scan or contrast enhanced MRI can be necessary to exclude other causes of painful ophthalmoplegia. They can sometimes objectify an inflammatory process of the cavernous sinus in Tolosa-Hunt syndrome or a reversible enhancement and thickening of the cisternal segment of the oculomotor nerve during an ophthalmoplegic migraine. Pain and ophthalmoplegia quickly resolve with corticosteroids.

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How children-adolescents with primary headache and their parents evaluate the Headache Centre's intervention

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Background and objective Headache is one of the most common disorders that affects children and adolescents and its prevalence seems to have increased in the last 50 years [1]. Paediatricians often send children and adolescents suffering from headache to the various headache specialists for a diagnostic and therapeutic assessment of the disorder. Nevertheless, while adult headache patients' satisfaction with the treatments has been widely investigated, less attention has been paid to children and adolescent headache patients' opinions and their parents' views. The aim of our follow-up study was to analyse the outcomes of the Headache Centre's interventions and the evolution of headache according to patients, until the age of 16, and their parents.

Methods We enrolled 84 patients (females: 45%, males: 55%; mean age: 12.9±2.9 years) with primary headache (migraine without aura: 66%, tension-type headache: 23%, migraine with aura: 11%) according to ICHD-II criteria [2], seen for the first time in 2005–2006, and at least one of their parents. The duration of the follow-up ranged from 1 to 3 years. For the purpose of our study, a specific questionnaire was created and administered by a telephone interview, which was carried out according to Narrative Medicine's approach [3].

Results Seventy percent of the patients thought that their headache had improved; in particular, 63% said that the frequency of headache had decreased, while intensity had only diminished in 37% of the sample. More than half the subjects interviewed ascribed the improvement to the fact of feeling better when at school. The majority (60%) of the patients declared to have followed the Centre's advice to minimize the factors causing headache; 87% had followed the prescriptions for acute attacks and these medications had been effective according to 77% of the patients. Only 16% of the parents still reported feeling anxious about their child's health, while 84% declared feeling calmer after attending the Headache Centre; 72% of the subjects interviewed and of their parents reported that attending the Headache Centre had been useful to better understand and manage headache.

Conclusions Children's and adolescents' headache has in most cases a favourable prognosis; the Headache Centre's intervention is considered as effective by most patients and parents. Narrative Medicine's approach is particularly fit to study headache from children's, adolescents', and families' point of view.

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Headache in childhood and adolescence in clinical practice: from parents' interview to clinical evaluation

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Introduction The request for a neuropsychiatric consultation in our clinical practice always comes from parents. The aim of the present study was to evaluate the reliability of headache description obtained from parents at first contact and to explore the evolution of headache characteristics at first clinical evaluation and over a one-month follow-up period.

Methods One hundred and nine consecutive first consultation requests for headache over a one-year period were examined. An ICHD-II based questionnaire was administered to the parents at the moment of the request for consultation (T0). The same questionnaire was administered to the patient at the moment of the first consultation (T1) and at a one-month follow-up (T2). ICHD-II diagnosis was performed at T0 and T1. Sociodemographic variables as well as headache characteristics at T0, T1 and T2 were recorded.

Results The ICHD-II diagnosis at T0 was confirmed at T1 in 68.8% of cases (sensitivity = 0.8, specificity = 0.6). When a family history of headache is present, an ICHD-II 1.1, 1.2 or 1.6.1 diagnosis is more probable at T0 but not at T1. Headache showed a significant clinical improvement in about 50% of patients between T0 and T2.

Conclusions Information gathered from parents regarding their children's headache is not completely reliable. Headache may show a marked improvement at follow-up over a short time after first consultation. The interaction of sociodemographical, clinical and family variables play a role in determining the clinical characteristics of headache, and this interaction should be explored in neuropsychiatric consultations.

Migraine and tension-type headache: quality of life expressed by children and their parents. A controlled study

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Introduction Quality of Life (QoL) is a multidimensional construct that reflects the interplay between disease and patient's subjective evaluation of his or her physical, social, and emotional functioning [1]. Recent studies showed that QoL of patients with migraine was lower than that reported by patients with other chronic diseases [2]. Moreover, patients' and parents' reports concerning the impact of the ailment on QoL often differ [3].

Objective The aim of this study was to determine the impact of headache on QoL in children and adolescents by comparing a clinical population with a control group of healthy peers, with regard to the difference between children's and their parents' perception.

Methods A specific questionnaire, "Inventory Life Quality" (ILQ), was administered to 89 patients (m/f ratio=0.78; mean age: 12.27±3.03 years, range 6–18 years) suffering from migraine (with or without aura) and tension-type headache (TTH) consecutively referred to our Headache Centres, and to 321 sex- and age-matched control subjects from local schools (m/f ratio=0.58; mean age:

12.53±3.51 years, range 6–20 years). ILQ was also administered to all parents. Clinical data about headache were collected and ICHD-II diagnoses were performed for both cases and controls. Two multivariate statistical models were implemented. Age, sex, school, headache diagnosis and case-control conditions were considered independent variables, parents' and children's global ILQ score were considered dependent variables.

Results Logistic regression showed that cases had a lower global QoL than controls according to their parents ($p<0.05$, CI 95%=2.13–13.4) but not according to patients themselves. Conversely, children and adolescents affected by migraine showed a lower QoL compared to peers affected by TTH or free from headache ($p<0.05$, CI 95%=1.08–2.02).

Conclusions Our study showed that QoL is estimated differently by children and adolescents compared to their parents. Different QoL between cases and controls is described by parents but not by children themselves. Moreover, migraine headache affects children's QoL more than TTH or no-headache condition.

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“Airplane headache” may occur in paediatric age: description of the first case

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Airplane headache is a condition characterised by severe head pain whose onset is strictly related to the different phases of a flight (take-off, flying, landing). Considering the fairly stereotyped features of the attacks [1–4], we have recently suggested provisional diagnostic criteria for this headache [3], with the intention of better understanding its underlying mechanisms. Headache attributed to airplane travel seems to be more frequent in young people, but to our knowledge, no paediatric case has ever been described so far. An 8-year-old boy experienced the occurrence of very intense prolonged jabs located over the top of the head, lasting up to 15 minutes after take-off, associated with a sensation of ear stuffiness, but without local or general autonomic symptoms. This occurred on his first flight. He currently flies on average twice a year and the pain occurs in more than 50% of the flights; the chances of developing headache become higher in long-duration travels, lasting more than 2 hours. He neither performed any specific maneuver to reduce or abort the pain, nor took any analgesics with the exception of a homeopathic remedy (Tissue salt no. 8). No previous history of allergy or asthma was reported; furthermore, no signs or symptoms attributable to upper respiratory tract or sinus inflammations were documented in association with the attacks. Anxiety and fear of the possible occurrence of headache have negatively influenced his attitude towards flying. This aspect is frequently noted in patients with headache attributed to airplane travel, indicating the severe

intensity of the attacks, even if their duration is rather short and self-limited. The quick change of barometric pressure in the cabin during the rapid ascending and landing of the aircraft is a possible pathophysiologic mechanism, along with a potential malformation of the sinus foramina that could increase the risk of having a “barotraumatic” pain. The variety of the possible underlying mechanisms suggests that airplane headache should be considered to be a multifactorial condition.

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Childhood migraine and malocclusion: what relationship is between the two?

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Among the causes for secondary migraine, an important role is ascribed to orthodontic anomalies and alterations of the ATM, and how such anomalies are often present among joint causes for tension headache [1]. In young headache sufferers a high percentage of malocclusion is often found, which plays a role in the origin and worsening of the migraine pathology. Among the subjects who underwent a Day Hospital in our Centre in March 2007, 42 young patients were selected at random (38 MwoA, 4 MwA; 24 females, 18 males; range 7/17 years), of these 60% showed malocclusion (25% I°, 75% II°, 60% also Bruxism); all of them were prescribed orthodontic treatment. Of these, 20 (11 females, 9 males) underwent only an orthodontic therapy, whilst for the other 22 (13 females, 9 males) the orthodontic treatment was associated with different types of prophylaxis (calcium antagonists, antidepressants, mild tranquilizers). At TO, T6 months and 1-year, controls were made with Total Pain Index (FxDxI). The group that underwent only an orthodontic therapy experienced a certain improvement, even though it was not significant (52.4>41.3>39.5), whilst in the other group an improvement was evident (61.8>31.4>32.9; $p<0.05$). The high presence of malocclusion in children is certainly connected to modifications in food habits in recent years; we no longer chew hard fibers that require a third molar, and the wisdom teeth extend to atrophy [2]. We believe that even just treating malocclusion is important for young headache sufferers, since malocclusion has *per se* a certain relevance in triggering the headache because the forces that are generated in a bad mastication amplified by the habit of grinding teeth during the day (gnasching) and at night (Bruxism) [3], increase the muscular tension of the head, which can then amplify the characteristics of headache.

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Contribution to the identification of a valid technique within a Pet Therapy Protocol

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No standard treatment method exists within Pet Therapy, and no studies have been conducted aimed at ascertaining the effectiveness of the methods applied, which currently derive their origin more from personal experience acquired in the field by individual therapists, than from well articulated theoretical constructions supported by targeted empirical studies [1]. Even though within the scope of the empiricist pioneer sector where Pet Therapy is applied, thanks also to the easy acceptance by the patients of the treatment assisted by animals, Pet Therapy represents a choice intervention practice, above all in those pathologies where a difficult compliance exists with the therapeutic treatment, both pharmacological and/or psycho-therapeutic. This is often the case with headache suffering patients in developmental age [2]. We wish to draw attention to a series of peculiar "duties" and "instructions" (which have now become standard in the framework of the Pet Therapy Protocol applied by the team "PET Rehabilitation S. Carlo Nancy IDI" in Rome) given to the young patient, thanks to which we found that his/her relationship with the animal was made easier, to such a point as to obtain a shorter treatment time, simultaneously with an equal stability of the results achieved. We compared two samples of young patients suffering from MwoA: the first group of patients (n=22; 13 females, 9 males; age range 7–18 years) followed a standard Pet Therapy course with 20 sessions per week; and the second group (n=20; 11 females, 9 males; age range 7–16 years) focused on peculiar "duties" and specific instructions, but with 12 sessions per week. The duration (D) and the number of days of headache per month (M) were compared at T.0 and T.24 weeks: Group 1 (D 6.2>3.7 M 7.3>4.3; $p<0.05$), Group 2 (D 8.2<4.9 M 9.8<4.7 $p<0.05$). Pet Therapy, including the shorter programme, is confirmed to be an effective intervention in the therapy of childhood migraine. Its success derives both from the fact that the patient learns to cope with migraine, but and above all, from the patient's ability to cope with the events triggering the headache crisis.

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Paediatric headaches: when to use neuroimaging. Preliminary results

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Introduction Most causes of headaches are benign, however there is a small percentage of headaches that require urgent diagnostic evaluation because the headache could be the initial symptom of life-threatening disorders such as meningitis, brain tumor, cerebral vas-

cular diseases or another dangerous illness. Help to develop a decision rule when to use neuroimaging investigations can come from the use of "red flags". Several "red flags" in the patient's clinical history and general or neurological examinations may provoke more attention and induce to undergo several important diagnostic tests.

Objective Aims, of this study were: 1) to evaluate if the use of red flags in paediatric headaches may help as screening tools to undergo neuroimaging examination; 2) to establish what are the "red flags" that are more helpful in the decision rule.

Methods Every child between 2 and 18 years who, from April 1st 2006 to February 29th 2008, was admitted complaining of a headache and had one or more of the 39 defined "red flags" was included in the study [1]. Every child received one or more neuroimaging investigation (CT, MRI, AngioMRI) chosen by defined clinical criteria. The outcomes were defined in 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 coincidental.

Results A total of 79 children (34 males and 45 females) met inclusion criteria. The mean age was 9.4±4.8 years (range 3 to 16 years). The most reported "red flag" was: daily headache <3 months. Neuroimaging was positive in 30 cases (37.9%). In 11 (13.87%) cases the abnormal finding helped to change therapy or diagnosis (10 sinusitis, 1 Arnold-Chiari type 1).

Discussion Our preliminary results show that the paediatric headaches are usually benign and that by using the "red flags" as screening tools the significant abnormal radiological findings in paediatric headaches are few and rarely help to modify therapy. However, it is interesting to underline that the literature has reported a prevalence of "positive" (coincidental or causal) radiological findings, about half of those found in our study [2]. Perhaps the use of "red flags" in paediatric headaches can help to point out more positive radiological findings. It is mandatory to carry out further studies in a larger population to better understand the utility of "red flags".

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Cluster headache in adolescents: case report

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Introduction The prevalence of cluster headache (CH) in young age (9–18 years) is extremely low: around 0.03% [1]. At present, specific guidelines for therapy in patients of this age group are lacking [2]. We describe a clinical case of CH in developmental age and the outcome of the adopted therapy.

Case report An 11-year-old boy was referred to our Centre from the Emergency Department, because of headache persisting for 15 days, which caused absence from school and notable limitation of daily activities. The patient was born from dystocic twin delivery and had a negative clinical history of any pathologic condition, including previous headache episodes. His father was affected with CH. The boy described his current headache as an extremely intense, lancinating pain in the left eye, periorbital and temporal area, associated with ipsilateral lacrimation, sweating and nasal

obstruction, occurring in repeated crises (2–4/day) of 20–25 min each, which had first manifested 15 days previously. Pain disappeared after assumption of ketoprofen (10 drops/40 mg). Though the neurological examination revealed no abnormalities, due to the recent headache onset, an urgent brain CT scan was performed, the results of which were negative. During medical examination, the patient presented a typical crisis; ketoprofen (40 mg) was administered, with pain cessation after 2–3 min. A diagnosis of CH was made and treatment prescribed: prophylaxis with prednisone (30 mg/day, reduced by 5 mg/day every 5 days) and ketoprofen (40 mg) on demand. Magnetic resonance imaging (MRI) plus Angiographic MRI of the brain were also prescribed. At re-examination seven days later, the patient reported that crises had ceased 48 hours after starting the prophylaxis. After 20 days (still under prednisone) again no crises were reported; MRI revealed no abnormality except for alteration of the left maxillary sinus (inflammatory sinusopathy). Re-examinations at 2, 3, 4 and 5 months (patient no longer under prophylaxis) evidenced no new crises. Regular monthly examinations are now scheduled, to monitor possible re-occurrences and re-start prophylaxis if necessary.

Conclusions This paradigmatic case of CH in developmental age shows the importance of a positive family history of this condition as a predisposing factor. Since the patient has a twin, it will be interesting to also monitor the so far unaffected brother, to verify if he develops CH in the future. This case also shows how ketoprofen, normally ineffective in adults, is instead a valid symptomatic therapy in young people with CH.

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Prevalence of migraine equivalents and allergies in patients attending a Paediatric Headache Centre

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Introduction It is known that in paediatric age some clinical conditions different from headache may share a common physiopathology with migraine. These, including recurrent abdominal pain (RAP), cyclic vomiting (CV), lower limb pain (LLP), periodic torticollis (PT), motion sickness (MS), and benign paroxysmal vertigo (BPV), are currently named as migraine equivalents. Among the diseases which are often searched for in children referred to a medical visit for headache, are allergies, although their relationship with headache has not been demonstrated.

Objectives The aims of the present study were: 1) to calculate the prevalence of migraine equivalents in patients referred to our Headache Centre in a time interval of around 2 years, and 2) to investigate the presence of allergies in patients with definite diagnosis of headache.

Materials and methods Three hundred and sixty-two consecutive patients with primary headache, referred to our Headache Centre from April 2006 to February 2008, were considered. Their age ranged from 4 to 18 years.

Results Migraine equivalents were present in 164 patients (45.3%). Among them, 137 patients had migraine without aura, 11 patients

had migraine with aura, 7 patients had tension-type headache, and 9 children had chronic headache. The most prevalent migraine equivalents were RAP (84 children, 51.2%) and LLP (70 patients, 42.7%). A defined diagnosis of allergy was made in 31 patients (8.5%).

Conclusions Our results show that migraine equivalents, in particular RAP and LLP, are much more frequent in children with primary headache than in the general population [1], thus suggesting common physiopathological mechanisms with primary headache. Conversely, since the prevalence of allergies in patients with primary headache is not different from that of the general population [2], the headache physiopathology is likely independent of the immunological mechanisms of allergies.

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A combination of magnesium, L-hydroxytryptophan and niacina as a preventive treatment for paediatric tension-type headache

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Introduction Migraine and tension-type headaches are two of the most common types of primary headache disorders in children. Management of tension-type headache is difficult because it requires comprehensive medical and psychological evaluation and an individualized approach for a successful outcome. For this reason headache management includes not only pharmacological agents but also a complete assessment of the patient’s life-style and stressor factor. There are no controlled studies on the pharmacological prophylaxis of tension-type headache in children and often the behavioural treatment is better accepted than medication.

Objectives The aim of this study was to evaluate the effectiveness of preventive treatment in paediatric tension-type headache in a group of patients examined at the Paediatric Neurology Department of the G. Salesi Children’s Hospital of Ancona.

Materials and methods A combination of magnesium (90 mg/die), L-Hydroxytryptophan (350 mg/die) and niacina (25 mg/die) was given once a day for 3 months, twice in a year. No other medication was administered during the year at follow-up. Forty-four patients were treated: 24 males, 20 females, age range 7–17 years, mean age 10.8 years. Twenty-five were affected by episodic tension-type headache (ETTH), 10 by ETTH + migraine without aura (MO), and 9 by chronic tension-type headache (CTTH). Positive effect was considered the reduction of frequency and intensity of headache attacks at 6 and 12-month follow-up.

Results The treatment was well tolerated and no relevant side effects were reported. Patients with ETTH had symptoms decrease by 85% (frequency and intensity); patients with ETTH + MO had migraine attack reduction and tension-type symptoms decrease by 80%; patients with CTTH had symptoms decrease by 40%.

Conclusions In paediatric patients a combination of “magnesium, L-Hydroxytryptophan and niacina” is well tolerated and it is an effective therapy in the treatment of ETTH. The approach to chronic tension-type headache is complicated because it is often associated with depressive and anxiety disorders in paediatric patients and it requires both pharmacological and psychological treatment. Although uncontrolled, these data are encouraging but controlled

trials are necessary to confirm the efficacy of this pharmacological treatment in paediatric episodic tension-type headache.

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Children headache in the Emergency Department

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Introduction The medical information and the collaboration between the hospital specialist physician and family physician represent the first approach to headache in children.

Objective To investigate the rate and the diagnosis of acute headache in children presenting to the Emergency Department of a general hospital.

Material and methods The period of observation was 4 years (January 2003 to January 2007). Among 178 359 admissions, 6 893 consultations were for children. Headache was diagnosed in 168 children. The causes of hospital consultation were: fever, vomiting, epistaxis, abdominal pain, upper respiratory infections, loss of consciousness, blurred vision, dizziness, and head injury. CT scan was performed in 2% of children, MR brain in 2.8% of children, head Rx in 8% of children, ECG and EEG in 6% of children.

Results The causes of headache were: upper viral infections in 42% of the cases, meningitis in 0.6%, epileptic seizures in 2%, posttraumatic headache in 20%, ventriculoperitoneal shunt infection in 0.6%, brain tumours in 1.8%, allergy in 0.6%, migraine in 18%, tension-type headache in 7%, undetermined causes in 11%. Consequently, neurological cases represent 6% of patients. Seventeen children with the diagnosis of undetermined headache were observed after 2 months: 14 children had migraine, 2 cases were diagnosed as sinusitis, and 1 case which was diagnosed at the first examination as sinusitis was, after second observation, Arnold Chiari Type 1 disease.

Conclusions The abrupt onset of headache represents 2% of all consultations in the Emergency Department of a general hospital, 12.8% of all headaches observed in the Neuropaediatrics Department, and 0.2% of hospitalisations.

Memory evaluation by T.E.M.A test in children affected by headaches

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Introduction The correlation between headaches and neuropsychological abnormalities is studied more in adults than in children. The negative consequences of headache in childhood and adolescence are often underestimated. Increased absences from school, a greater amount of school problems, and more time needed to finish homework are referred frequently.

Objective The aim of this study was to evaluate memory and learning in children affected by headache and to compare behaviour in different headache types.

Materials and methods Forty children, aged 5–17 years, 8 males and 32 females, were the sample. Diagnosis of headache was made according to ICHD-II 2004 criteria. T.E.M.A test (1995) was administered to the children. Four subtests could be utilized to make a learning profile. Sixteen children did not complete the test, thus, 24 children, 5 males and 19 females composed the sample of study. All the children underwent brain MR and EEG.

Results Eleven children (3 males and 8 females) suffered from migraine without aura (MwoA), 3 females migraine with aura (MwA), 7 children (1 male and 6 females) from tension-type headache (TTH), and 4 females from headache migraine like and lesional anomalies. The brain injuries were: cortical dysplasia in the left occipital lobe in a female aged 17 years; arachnoid cyst of left temporal lobe in a female aged 15 years, and arachnoid cyst of right temporal lobe in a female aged 11 years. Six children suffered from epilepsy. Ten children suffered from MwoA (90%), 6 children (85%) among TTH, 2 children (66%) among MwA and 3 (75%) among children with lesional anomalies showed deficit on recall of words. Eighteen children (75%) had learning profile deficit. All the children also suffering from epilepsy had learning profile deficit. The recall of selective words was the more achrestic item. This item is very important in recall of brief and long-term memory.

Conclusions Several studies show memory deficit in migraineurs. Controversial data are on cognitive defects in children suffering from headache [1, 2]. The learning profile of migraineurs and TTH is the same with the one for children with brain injury. Also, all the patients suffering from headache and migraine showed the same deficit of profile.

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Somatosensory system excitability in alternating hemiplegia of childhood

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Introduction Alternating hemiplegia of childhood (AHC) is a rare neurological disease of unknown aetiology characterized by recurrent paroxysmal attacks of hemiplegia affecting either side of the body, oculomotor and autonomic disturbances, movement disorders, and progressive cognitive impairment. Tests performed on patients and their family, including magnetic resonance imaging and magnetic resonance angiography of the brain as well as metabolic evaluation, were usually normal. Aim of the study was to assess the recovery cycle of the somatosensory evoked potentials (SEPs), a marker of somatosensory system excitability, in a group of children with AHC during both the ictal and the interictal phase and to compare these results with a control group.

Materials and methods Seven children (mean age 14.9 years, range 4–34 years; 4 females, 3 males) with AHC were recruited. Right and left median nerves were stimulated at the wrist by surface electrodes. SEPs were recorded from four electrodes placed: at Erb's point ipsilateral to the stimulation (Erb_i), over the 6th cervical vertebra (C6), over the parietal area contralateral to the stimulation (P3/P4), and over the frontal midline (Fz). The somatosensory system excitability was assessed by calculating the SEP changes after paired electrical stimuli at 5 ms, 20 ms and 40 ms interstimu-

lus intervals (ISIs), as compared with a single stimulus condition assumed as the baseline. All patients were studied during the interictal phase, while SEPs were recorded also during the ictal phase in 4 patients. We also studied 10 control age-matched subjects (CS).

Results In patients with AHC during the interictal phase, the amplitudes of the cervical N13 and of the cortical N20, P24 and N30 responses showed a faster recovery at 20 and 40 ms ISIs than in CS (two-way ANOVA, $p < 0.05$). In AHC patients during the ictal phase, the recovery cycles of the cervical N13 and cortical N20 potentials were prolonged (two-way ANOVA, $p < 0.05$), when compared with the interictal phase.

Conclusions The main finding of our study is represented by a shortened SEP recovery cycle in patients affected by AHC during interictal phase, suggesting a multilevel somatosensory cortex hyperexcitability in AHC. A short-lasting reversion of this phenomenon during the ictal phase possibly reflects a functional reset of the somatosensory system, which may be linked to the pathophysiological mechanisms of the disease.

Epidemiology and social impact of headaches

Self-help groups in patients with chronic daily headache

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Self-help groups, born with Alcoholic Anonymous, is a valid intervention model also for people with other ailments; it is recognised by the World Health Organisation (WHO) as an interesting tool for endowing people with responsibility and leadership, to humanise health care and improve well-being in the community. The aim of a self-help group is to provide people living in similar conditions the opportunity to share their experience and help them show each other how to face everyday problems. It is a valid means to ensure group participants emotional support. Within the group, each individual effort tends to resolve one's own problem, which simultaneously becomes the effort to resolve a common problem. Each person simultaneously receives and provides help. Hence, specific skills are acquired regarding practical solutions appraised by direct experience, which usually cannot be obtained through publications, professional workers or healthcare institutions. Despite self-help groups cannot substitute adequate individual or group psychotherapy, they constitute a valid support tool, allowing its members to insert themselves in some kind of miniature social milieu, where they stop being carriers of an ailment, but become instead members of a small social network. Specifically, in our clinical experience, forming self-help groups composed of patients with chronic daily headache is framed within drug disintoxication treatment which is carried out at the Day Hospital of the Sant'Andrea Hospital. The primary objective is to reduce relapses/recurrences, which are the main obstacles in treating patients with headache. The impact on the group is monitored by measures of clinical course assessing treatment efficacy, allowing to optimise therapeutic strategy. Measures are assessed at baseline and after three, six, and nine months. With this aim in mind we used assessment scales, both self- and clinician-rated, and diagnostic interviews, such as Mini International Neuropsychiatric Interview, Hamilton Rating Scale for Depression, Quality of Life Index, Beck Hopelessness Scale, Temps, Illness Perception Questionnaire, and Drug Abuse Screening Test (DAST). The project aims to recruit 90 patients; currently, 20 patients have been involved, and have been subdivid-

ed into four groups meeting for about one hour weekly under the supervision of three clinical psychologists.

Acute headache centre reduces migraine disability

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Background Migraine is a common, major cause of disability in daily living activities, at work, in scholastic performance, household work and participation in social and leisure activities. Migraine in the Emergency Department (ED) is underestimated, not specifically treated and rarely referred to a Headache Centre for proper evaluation.

Objective Aim of this study was to evaluate the role of an Acute Headache Centre (AHC) in reducing the disability of patients discharged from the ED with diagnosis of migraine.

Methods One-year prospective analysis of all consecutive patients discharged from the ED with diagnosis of migraine and referred to the AHC of the Clinical Neurology Unit of the University of Trieste was performed. The validated Italian version of the migraine disability assessment questionnaire (MIDAS) was used to assess the impact of migraine. Demographic and clinical information, ED treatment, the diagnosis issued and the therapy administered in the AHC, and the MIDAS scores were analysed using SPSS 13.0.

Results We studied 57 patients, 47 F (82.5%) and 10 M (17.5%), mean age: 37 ± 10 years. In the ED, NSAIDs (71.9%) were the most frequent therapy, triptans were used in only 5.3% of cases. Only 7% of patients initiated a prophylactic treatment in the ED. In the AHC the diagnosis was migraine without aura in 52.6% of patients, migraine with aura in 7%, migraine with and without aura in 24.6%, migraine plus tension-type headache in 15.8%. In AHC, 44 patients (77.2%) were treated with triptans and 29 patients (50.9%) started a proper prophylactic therapy. The mean MIDAS total score was 43.1 (SD 38.5, median 36). Mean subgroups MIDAS scores were: days with work/school missed 5.5; days with workplace productivity severely reduced 11.9; days with housework missed 8.3; days with housework reduced 9.9; days with family/social activities missed 8.3. The mean MIDAS total score in the three-month AHC follow-up visit was significantly reduced (27 (SD 24), median 22.5; $p < 0.01$).

Conclusions Patients with the ED diagnosis of migraine bear a marked personal and social burden. The AHC evaluation allowed a prompt specific acute and prophylactic treatment, starting with a significant reduction of disability. Our data confirm the high efficacy of a dedicated AHC for the management of migraine in the ED.

The optimal management strategy for migraine care in the Calabria Region

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Background and objective In current clinical practice, usually about half of all migraine sufferers do not consult a physician for care. Therefore, many sufferers do not receive care from a physician and their management is likely not optimal. Given that migraine is heterogeneous in frequency duration and intensity of symptoms, management should ideally be tailored to each patient's needs. The use of a formalized care strategy enables physicians to

select appropriate management for their patients. The most common approach in acute migraine management has been to move patients through a sequence of medications, ordered by a combination of perceived safety, cost and efficacy, until they either find an effective therapy or lapse from care. Following consultation and diagnosis, migraine patients are often routinely given simple analgesics as first-line acute treatment. Specific migraine therapies are frequently restricted to third- or fourth-line therapy when all other treatments have failed.

Operative proposal Effective communication between the physician and the patient is the key to the development of personalized, effective management strategies for migraine headache, according to the Headache Management Programmes of the Health Care System in the Calabria Regione. While patients are interested in hearing their doctor's explanation of their condition, they also want a doctor who is amenable to working with them. The paternalistic, authoritarian model of medicine is increasingly being challenged by patients. Physicians often fail to ask their headache patients about their preferences for treatment. Patients make treatment decisions based on these preferences. Physicians should make sure to ask patients to quantify, if at all possible, their disability levels. Other important information to elicit during the headache consultation include: whether the patient has sought treatment in an Emergency Department, whether the patient was taking herbal or over-the-counter medication, what treatment the patient has tried, the patient's beliefs about what is causing the headaches, and what the patient's family would say about the headache problem.

Conclusions A co-ordinated policy involving specialist and primary care physicians, pharmacists, and other health care professionals and patients will help to spread information, encourage consultation, and aid diagnosis and the provision of appropriate care at the time of the initial consultation. Education of primary care physicians by neurologists on the importance of headache, and related disability will help with the provision of migraine care and ensure appropriate referrals.

Effective management of primary headache through a care group model in the Calabria Region

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Background Primary provider visits are time restricted, prohibiting adequate headache evaluation and management. The group model offers an educational forum that empowers patients to participate in the management of their headaches. The model creates a treatment plan for each individual patient that allows for long-term follow-up in primary care.

Objectives To evaluate a care group model for primary headache disorders by assessing patients' responses, measured by quality, subjective improvement, and use of fans and triptans. To assess the satisfaction of the primary care provider with the headache management programme. To implement individualized headache guidelines to better manage headaches and reduce excessive analgesic use.

Patients and methods Primary care provider referrals are seen in a group model consisting of a headache class taught by a neurologist with a subsequent general practitioner consultation followed by a two-month control visit. The GP optimizes headache treatment for each patient utilizing existing headache guidelines and by consulting a neurologist. Thereafter, the primary care provider manages the

patient. Outcome measures are by means of patient and primary care provider surveys. The migraine specific questionnaire and MIDAS and patient subjective improvement questionnaires were completed at baseline, and at return visits 4 months after entry into the programme. In addition, we compared patients' use of fans and triptans at 4 months pre-enrolment with that at 4 months post-treatment.

Results At the time of abstract submission, the first 32 patients who completed the programme were analysed. The migraine specific questionnaire and MIDAS results showed significant improvement at 2 months and 6 months compared to baseline measurements. At 2 months, improvement surveys (91%) showed that patients subjectively improved. In the 24 patients whose use of fans/triptans was assessed, use of fans decreased by a statistically significant 40% and use of triptans increased, but not significantly.

Conclusions These data support the concept that a care group model with a headache specialist GP is a cost-effective method in providing care to patients with primary headache disorder. Headache guidelines are implemented with high levels of patient and primary care provider satisfaction. The model also facilitates a reduction in the patient's use of fans and more appropriate use of triptans.

Disability in menstrual migraine

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Introduction Menstrual Migraine (MM) attacks are reported to be more severe, of longer duration, and more resistant to treatment than attacks occurring at other times in the menstrual cycles. These data were obtained from two population-based studies and by sporadic clinic-based studies conducted in tertiary care centres.

Materials and methods We performed a study using the 6-item paper-based Headache Impact Test (HIT-6) to measure the impact of Menstrually-Related Migraine (MRM) and Pure Menstrual Migraine (PMM), compared to Non-Menstrual Migraine (NMM), according to the definition placed in the Appendix of the second edition of the International Headache Society Classification (ICHD-II). We screened in our database all the females aged 18 to 50 years who were referred to our Headache Centre from 2005 to 2007. The inclusion criteria were: ICHD-II diagnosis of migraine without aura for at least one year, frequency of 1 to 3 attacks per month for the previous 6 months, regular menstrual cycles, and properly recorded prospective diary cards. Out of the 211 screened women, 96 were eligible for the study. In this latter group, 44 had NMM, 4 suffered from PMM and the remaining 48 had MRM. They were examined and were asked to complete the HIT-6 questionnaires. The data were evaluated using ANOVA (analysis of variance).

Results Women with PMM and MRM appeared to be slightly older than those with NMM ($p=0.05$). The average HIT-6 scores were higher in PMM and in MRM than in NMM, the difference being statistically significant ($p=0.02$).

Discussion We confirmed that MM attacks are associated with greater disability when compared to other attacks occurring outside of the menstrual window. We also found out that women with combined PMM and MRM seem to be older than those with NMM, even to a low extent of significance. As a matter of fact in the daily clinical practice, most women who present with MM are in their late 30s or 40s. It is not uncommon, in fact, for women to have had migraine for many years but without the link with menstruation, becoming apparent until the years leading up to menopause.

Conclusions On the basis of the greater impairment due to MM attacks, an effective treatment for this disabling condition is paramount in order to improve the quality of life of individual sufferers, their families, and their employers. Fortunately, the predictable nature of MM lends itself to short-term prevention strategies.

Education in headache medicine. La Sapienza University's Master's Degree within WHO's Global Campaign *Lifting the burden**

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In recent years, headache disorders have migrated from a hidden area of clinical medicine, a process due to increased awareness of headache disorders and their widespread adverse consequences. As it continues, a much larger body of specialized physicians will be needed if the medical profession is to be adequately prepared for a health problem of global dimensions. The recent publication of "Aids for the management of common headache disorders in primary care", with approval from WHO, contributes strongly to GPs' education in headache medicine worldwide. Beyond this, the educational demands of headache medicine as a postgraduate specialty are increasingly evident. On each side of the Atlantic, the American Headache Society (AHS) and European Headache Federation (EHF) have responded in different ways, both aimed at training a new class of experts in this field. AHS in 2006 instituted a Headache Medicine Diploma accredited by the United Council for Neurological Subspecialties (UCNS) while EHF has operated its Headache School in most years since 1992.

A new academic initiative - the Master's Degree in Headache Medicine <http://w3.uniroma1.it/headache> - came to life in Europe in 2003, and was subsequently incorporated within *Lifting the Burden* [1], WHO's Global Campaign to Reduce the Burden of Headache Worldwide, as the first endeavour of the Campaign to meet the requirements of specialist education. Thus, was created a positive cultural chain in headache medicine [2, 3] which will make it possible to activate *Lifting the Burden's* second teaching step - at a national level and aimed towards primary care physicians - through regional trainers who have achieved academic excellence by means of obtaining the Master's Degree [4]. In this second step, the ready availability of diagnostic and therapeutic aids for primary care is crucial. The key to a better future is inclusion of headache disorders in undergraduate medical education.

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Prevalence and burden of primary headache in Akaki textile mill workers, Ethiopia

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Headache disorders are the most common complaints worldwide. Migraine, tension-type and cluster headaches account for the majority of primary headaches and impose a substantial burden on the individual, family or society at large. The burden is immense on workers, women and children in terms of missing work and school days. There are few studies that show relatively lower prevalence of primary headaches in Africa as compared to Europe and America. There might be many reasons for this lower prevalence. The objective of this study is to determine the prevalence and burden of primary headaches among the Akaki textile factory workers, which may provide data for the local and international level toward the campaign of lifting the burden of headache worldwide. The overall 1-year prevalence of all types of primary headaches was found to be 16.4%, and that of migraine was 6.2%. The prevalence of migraine in females was 10.1% while it was 3.7% in males. The prevalence of tension-type headaches was found to be 9.8%. This was 16.3% in females as compared to 5.7% in males. The burden of the primary headaches in terms of lost work days, gross under recognition and absence of effective treatment is tremendous. In conclusion, the prevalence of primary headaches in the Akaki textile mills is significant, particularly in females, and the burden is massive, in a place of poverty and ignorance. We recommend the availability and administration of specific therapy to the factory workers with primary headaches, and community based well-designed study representing the whole nation's rural and urban population.

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Prevalence of primary headache related to work activity in a group of temporomandibular disorder patients

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Introduction Since headache is one of the most frequent complaints in temporomandibular disorder (TMD) patients, its burden in terms of the both social cost and individual suffering is considerable. Headache is a frequent cause of absence from work and decreased productivity. This study was aimed at identifying specific occupational factors able to modify the prevalence of headache in a group of TMD patients.

Materials and methods Out of 320 TMD patients, 30 employed female patients suffering from headache were randomly selected. Mean age: 44 years. They answered two telephone-administered questionnaires about the characteristics of headache and work.

Results According to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD), 5 patients presented muscle disorders (axis I group I), 3 patients disc displacements

(axis I group II), and 6 arthralgia, osteoarthritis, osteoarthrosis (axis I group III) and 16 muscular and articular diagnosis. In the Axis II assessment, 17 patients had moderate/severe depression scores, 18 had moderate/severe somatization scores and based on graded chronic pain scores, 6 had psychosocial dysfunction (grade III and IV). Most of the patients described the headache as a bilateral, temporal-frontal pain that lasted from 20 minutes to 3 hours, and moderate in intensity. In 13 patients, the headache was sometimes accompanied by nausea. Patients typically self-treated their headaches with analgesics and staying in a safe place. Many patients identified stress and working position as precipitating factors. Mood change was one of the commonest prodromal symptoms. All the interviewed patients had a diurnal work of 8 hours daily. The group was composed of 15 employees, 6 labourers, 4 traders, 2 teachers, 2 maids, 1 physiotherapist.

Conclusions The results obtained suggest that specific occupational conditions such as employee job, sedentary work and PC use may play an important role in headache development, even in the presence of a wide number of professional risk factors. It was indeed suspected that poor posture could be a predisposing factor for headache pain in TMD patients.

Prevalence and clinic characteristics of migraine among medical students of “Federico II” University of Naples

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Introduction Migraine is a significant health problem. Studies in well-defined populations are useful in identifying factors that influence frequency and severity of headache and in understanding its impact on people.

Objectives The aims of this study were to determine the frequency of migraine in medical students of “Federico II” University of Naples; to examine migraine impact on the quality of life; to evaluate the presence of anxiety and depression; and to describe the self-medication level.

Subjects and methods The study was carried out in two stages. The first stage aimed to identify medical students with migraine by using a standardized International Headache Society (IHS) questionnaire. Students were also asked about medical consultations and medicines used during attacks. The standard questionnaire was applied to 570 medical students (250 men and 320 women), with mean age 22 years (DS: 1.2), from January to June 2006. At the second stage, students who presented higher frequency and higher intensity of migraine underwent a neurological examination, then we evaluated the impact of disease on daily life by administering the Specific Questionnaire I version (MSQ V1), depression and anxiety level by Hamilton Anxiety Scale (HAMA) and Hamilton Rating Scale for Depression (HRSD), and the presence of major psychiatric symptoms by Symptom Check-List-90 Revised (SCL-90).

Results Migraine was found in 81 students (14.2%); of these headache sufferers, 45 students (8%) presented an important migraine form (intensity ≥ 8 on a scale from 0 to 10 and/or frequency ≥ 4 attacks per month). MSQ V1 showed that the degrees of disability were important in 30 students (66.7%) and migraine is associated with a considerable degree of handicap in activities of daily living. HAMA demonstrated that the degree of anxiety was minimal or absent in 10 students (22.2%), moderate in 16 students (35.5%), and severe in 19 students (42.2%). HRSD showed that

severe depression levels were present in 3 students (6.6%) and 12 students had a moderate degree of depression. SCL-90 confirmed these results. Despite the high rate of disability, only 5 (11%) of these students with migraine had sought medical treatment. Twenty-nine students (64.4%) continue to treat their migraine with simple analgesics.

Discussion and conclusions In conclusion this study shows that a great part of medical students with migraine has moderate to severe disability leading to educational failure. Headache sufferers have higher scores on the Hamilton’s scale of anxiety and depression. Many students do not consult a physician. Global educational programmes may be required for patients to recognize the importance of effective migraine treatment. Informing students about the disease through informative programmes is not only an important step in treatment of migraine attacks, but also reduces the disability from migraine.

Neuropsychological and psychopathological features in headache

Migraine, pain experience, defensive strategies and psychiatric comorbidity: preliminary results in a cohort of 51 migraine patients

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Introduction Migraine is a frequent pain disorder that determines relevant disability, and severely affects quality of life disturbing individual and social functioning. It is known that migraine, especially when chronic, presents psychiatric comorbidity, and particularly anxiety, depression, and dependent behaviours like drug-abuse. Differently, little is known about the role of psychological mechanisms like defensive strategies in migraine, even if stress has been shown to be important in precipitating, maintaining and worsening migraine headache. Concerning this matter, an important role could be played by the subjective experience of pain as this aspect (strictly related to life-quality) is correlated to disease severity and psychiatric comorbidity in migraine. In this study we explored pain experience in migraine patients investigating also the potential relationship with psychological mechanisms (defensive strategies, anxiety) and psychiatric comorbidity.

Methods We studied patients affected by migraine (according to IHS criteria) consecutively recruited at our outpatient Headache Centre. All patients underwent the following examination protocol:

- Raven Coloured Progressive Matrices (CPM, 1981, tr. it. 1996), to exclude subjects with low (under 10th percentile) cognitive level, unable to correctly perform the other tests;
- Personality Questionnaire of Structured Clinical Interview for DSM axis I SCID-I and for DSM axis II (SCID-II) to assess psychiatric comorbidity;
- Questionario Italiano del Dolore (QUID, De Benedictis, 1988) for qualitative and quantitative assessment of pain perception;
- State-Trait Anxiety Inventory (STAI, Spielberger, 1970) for assessment of anxiety;
- Defense Mechanisms Inventory (DMI, Gleser, Ihilevic, 1993) that explores defensive strategies in the following five domains: TAO: turning against object; PRO: projection; PRN: principalization; TAS: turning against subject; REV: reversal.

Results We examined 51 patients and the results showed:

- QUID components: Sensorial: 33.2 ± 8.7 ; Affective: 37.2 ± 20.0 ; Valutative: 43.5 ± 21.5 with significant inter-components positive correlations ($p \leq 0.05$).
- 11 patients (24%) showed very high scores at the 0–5 points scale for pain perception.
- Psychiatric comorbidity was found in 4 patients (7.8%) for axis I and in 6 patients (11.7%) for axis II; marked personality traits were found in 14 (27.4%).
- DMI showed 33 (65%) symptomatic profiles with the following distribution: REV: 10 (19.6%), PRN: 8 (15.5%), TAO: 7 (13.7%), PRO: 4 (7.8%), TAS: 4 (7.8%).
- Anxiety scale: State anxiety: 53.0 ± 15.2 ; Trait anxiety: 53.6 ± 17.8 .

Correlation analysis showed that: marked personality traits or psychiatric comorbidity are significantly associated with higher anxiety ($p < 0.03$); Psychiatric comorbidity showed significant correlation with defensive strategies ($p < 0.003$).

Conclusions Pain perception and defensive strategies could play important roles in psychiatric comorbidity and chronicization of migraine.

Psychiatric comorbidity of migraine: a consultation-liason study in the Modena Headache Centre

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Introduction The association between headache and psychiatric disorders is undisputed, depression and anxiety being the commonest complaints [1]. There is a lack of data in the literature on the extent of psychiatric comorbidity in patients with different subtypes of chronic daily headache. Ten to 15% of the general population suffer from migraine and a certain percentage of these individuals will develop chronic daily headaches with medication-overuse [2]. This syndrome, referred to by the International Headache Society 2nd edition as medication-overuse headache (MOH), affects 4% of migraine sufferers overall and approximately 30% of patients attending Headache Clinics [3].

Methods A group of patients seeking treatment at the Headache Clinic of the University of Modena from November 2006 to December 2007 were included in the study sample if they met the International Headache Society [2] criteria for chronic migraine (code 1.5.1) or MOH (code 8.2). The sample was then divided into three groups: Group 1) patients suffering currently from migraine without a history of MOH (MIG group, $n=36$); Group 2) patients currently suffering from MOH ($n=14$); and Group 3) patients suffering from chronic TTH (TTH group= 6). A psychiatrist evaluated the patients according to the ICD 10 criteria, to assess the comorbidity of mood and anxiety disorders.

Results Fifty-six patients with chronic daily headache were recruited. The mean age was 43 years, 23% were male and 77% were female. Transformed migraine was diagnosed in 14 patients (25%) and chronic tension-type headache in 6 patients (10.7%), chronic migraine was found in 36 patients (64.3%). Patients with transformed migraine (71%) showed psychiatric comorbidity, including major depression (21.4%), neurotic stress-related somatoform disorder (28.2%), and generalized anxiety disorder (21.4%). Patients with chronic tension-type headache (33.4%) had psychiatric diagnoses, including neurotic stress-related somatoform disorder (16.7%), and generalized anxiety disorder (16.7%). Patients with

chronic migraine (72.3%) had psychiatric diagnoses including major depression (61.5%), generalized anxiety disorder (34.6%) and neurotic stress-related somatoform disorder (3.9%). Both depressive and anxiety disorders were significantly more frequent in women.

Conclusions Psychiatric comorbidity, especially major depression and anxiety disorders, was highly prevalent in patients with chronic migraine. When present, psychiatric disorders may complicate headache treatment and portend a poorer treatment response. We suggest that the treatment of psychiatric comorbidity is warranted to improve the outcome of headache management.

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Affective pictures perception in migraine patients: covariation of event related responses with autonomic arousal

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Introduction High-level cognitive activity, as it can be detected at the cortical level by electrophysiology, appears to be connected to autonomic output [1]. The aim of the study was to evaluate affective perception by the use of event-related potentials, heart rate and blood pressure outcome, measured during affective picture viewing [2] in a cohort of migraine patients compared to sex- and age-matched controls.

Methods Twenty 25–45 years of age, migraine without aura (MA) patients (15 females) were recorded in the inter-critical phase and compared with 20 sex- and age-matched controls. Twenty neutral (N), 20 pleasant (P) and 20 unpleasant (U) IAPS images [2] were selected, and submitted to subjects vision on a computer monitor in a random order (random –R– series) and in three series where only N, P, and U pictures were presented (N, P, U series). EEG was recorded by 32 scalp derivation, and at the same time EKG signal, SSR response, and EMG activity were acquired by Micromed Brain Quick apparatus. The systolic, diastolic and mean blood pressure values (SBP; DBP; MBP) were contemporary recorded by Porta Press Apparatus. A 20 min basal recording was first obtained, after which patients were requested to look at the monitor, where the IAPS images lasted for 6 sec, separated by a standard back panel with a white centre. The average latency, amplitude and habituation of the late positive potential (LPP) in the time window of 400–700 ms were evaluated, together with HR (beat/minute) and BP average values and their variations between the first and the last block of 3 slides in each pictures set.

Results U series determined larger LPP potentials in both patients and controls: in patients a significant habituation deficit was found for all the images, specially for the unpleasant ones. Similarly, HR

deceleration and MBP decrease appeared reduced between the first and last block of pictures, independently from their affective content, in controls, while in migraine patients unpleasant images caused a quite stable variation of both heart rate and blood pressure across the entire set of presentations.

Discussion and conclusions Deficit of habituation seems to affect resource allocation due to the motivational relevance of affective cues in migraine patients. This causes a reduced variation of vegetative changes induced by emotional arousal, suggesting a reduced pattern of organized variability and quite static and rigid levels of autonomic control in response to changing of environmental demands.

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Medication-overuse headache and drug addiction: a controlled study using MMPI-2

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Introduction According to the International Classification of Headache Disorders (ICHD-II), medication-overuse headache (MOH) is a form attributed to abuse of abortive medications, that may remit only when analgesics are withdrawn. Regarding the possible psychological factors, psychiatric disorders are known to be important contributors to the chronification of headache. MOH patients, like those with other forms of chronic daily headache, show a high frequency of psychiatric disorders and although personality factors are likely to be involved, studies are needed to explain the transition from drug use to drug abuse. Given the suspected broader involvement of behavioral and personality factors in drug abuse mechanisms, the study of psychological factors in MOH should not be restricted to psychiatric comorbidity. In fact, while the high prevalence of psychiatric disorders in MOH patients may be related to the presence of chronic pain, the presence of personality characteristics may be related to addiction and dependence behaviour [1, 2]. Very few studies have addressed the role of personality profile in MOH.

Objective The main aim of this study was to establish, using the MMPI-2, whether MOH patients have personality traits of dependence, and comparing them with drug addicted subjects (DA), episodic headache patients, and healthy controls.

Materials and methods Two headache samples from the C. Mondino Headache Centre (82 patients with MOH and 35 with episodic headache) and 37 DA patients were compared with 37 healthy controls. MMPI-2 was administered by expert psychologists. The headache complied with ICHD-II criteria. One-way Anova and Duncan post-hoc were performed ($p < .05$).

Results DA patients gave statistically significant scores (vs. headache and healthy samples) (Duncan’s post-hoc) on the main

scales measuring Depression (lower), Psychopathic deviate (higher), Hypomania (higher) and Social introversion (lower). On the sub-scales, the DA differed from the headache and healthy samples on the Depression (lower), Mac-R (higher), Potential addiction (higher) and Admission of dependence (higher) scales.

Discussion and conclusions MOH and episodic headache patients did not show clear cut differences in any main MMPI-2 scale. The hypothesis of common personality characteristics for MOH and DA patients linked to dependence characteristics and measured by MMPI-2 sub-scales was not confirmed, adding contrasting elements to the ongoing debate on dependent behaviour in MOH patients [1]. Our data suggest that MMPI-2 is not the best instrument for establishing the presence of dependence in MOH, while it is very helpful in DA. In MOH patients additional specific tests are needed.

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Primary headache: emotions about thoughts, thoughts about emotions

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Introduction Recent studies suggest a growing interest in the relationship between emotions and headache. Information about psychological aspects in headache patients in order to obtain a better compliance in pharmacologic treatment is both important and necessary. On the other hand, headache patients’ quality of life seems to be prejudiced by worries about the possible experience of pain more than pain itself [1, 2]. Aim of this study was to define whether specific emotional or meta-cognitive patterns could exist in headache and if these patterns could influence quality of life.

Materials and methods Forty-six patients with primary headache (HP, F:M=34:12) and 20 healthy controls (HC, F:M=10:10) underwent the following psychological questionnaires: Profile of Mood States (POMS), Short Form – 36 (SF36), Symptom Check List 90 (SCL90), STAI Y1 and Y2, and Beck Depression Inventory (BDI). Personal Meaning Evaluation Questionnaire (QSP), Meta-cognition Questionnaire (MCQ) and Anxious Thoughts Inventory (AnTI) were also administered. Non parametric analysis of data was performed.

Results No emotional or meta-cognitive differences between the groups emerged, even if specific patterns for men and women seem to appear. Nonetheless, different ways of thinking influence quality of life.

Discussion Fear of fear (meta-fear) about the possible experience of pain in headache highlights a general limitation in social life using avoidance behaviours [2]. According with the literature, these results confirm high anxiety levels [3], focusing on somatic symptoms and related worries. This fact illustrates that emotional and meta-cognitive patterns are similar in men and women, even if they influence perception of quality of life in different ways. In fact, the idea that one can maintain control over one’s own thoughts is specific to the female group, while clear presence of anxious thoughts appear in the male group together with depressive symptoms, which seem to have just a sub-clinical relevance.

Conclusions In conclusion, our data suggest that avoiding behaviours in headache patients could be influenced both by meta-cognitive impairment and/or by difficulty in the recognition of emotions.

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Tiner (Neuromuscular Emotional Relaxing Integrated Treatment) in catamenial headache

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Introduction We had thirty female subjects affected by Catamenial Headache, aged between 20 and 45 years, undergo Tiner (Neuromuscular Emotional Relaxing Integrated Treatment). We tried to evaluate a possible positive effect of our psychophysical treatment in reducing frequency and intensity of headache attacks, and in particular, in decreasing inability at a working, social and family level, and therefore, improving the patients' quality of life.

Methods Sixty female subjects underwent, prior to the study, a psychodiagnostic evaluation through the administration of the MIDAS scale (instrument which objectively measures the seriousness of a headache attack, it specifies the inability level and is suitable for identifying the appropriate therapy on the basis of the severity level of each patient). MIDAS showed values between 5 and 9 and, thus, our patients did not undergo any therapy which involved migraine drugs, excluding the headaches with minor (level 1) and major (levels 2–4) inability. Afterwards, the study group, including twenty subjects, underwent TINER every week, for three months, with a subsequent phase: every fifteen days for another six months. A control group, with the same number of people, did not carry out any programme. At the end of nine months, both the study group and the control group, underwent another evaluation.

Results The points, obtained comparing the first MIDAS with the last one, showed a decrease of 5 points in 15% of patients, 3 points in 20%, 2 points in 25%, 1 point in 25%, with an unchanged condition in 15% of cases of the study group. The control group did not reveal any significant decrease. Thus, the results were achieved only for the patients who underwent TINER. The patients improved the quality of their life, reduced the negative effects of the headache attacks in work, social and family environments and of the consequent unpleasant personal experience.

Conclusions TINER, seems to have a positive effect in the reduction of the frequency of headache attacks and the alleviation of their seriousness. We can assert that in the study group affected by Catamenial Headache, which underwent TINER, the quality of life improved significantly. This is a noteworthy result, above all, if we compare it with the unchanged situation of the control group.

Efficacy of a workplace cognitive and physical programme on psychosomatic symptoms in a working community with headache, neck and shoulder pain: a longitudinal, controlled study

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Introduction Patients suffering from different headache types usually complain of numerous accompanying symptoms, behavioural and somatic. This study was aimed at examining the effect of a workplace cognitive programme on psychosomatic symptoms in a working community.

Materials and methods Three hundred and eighty-four employees of the registry and tax office of the city of Turin, were distributed into two groups: study group (n=192) and controls (n=192). In all subjects data were taken of headache, neck and shoulder pain and the presence of 28 symptoms, mainly psychosomatic in nature (such as colitis, gastritis, sleep disorders, palpitations, etc.) was also assessed. These symptoms showed in previous studies a significantly higher prevalence in pain patients with respect to a normal population. An instruction programme was then administered to the study group: it consisted of brief shoulder and neck exercises, a relaxation exercise and instructions on how to reduce hyperfunction of the craniofacial and cervical muscles. After six months all subjects were re-examined and the presence of psychosomatic symptoms was assessed again. In the two groups the difference between the data at the baseline and those at the end was calculated and the data compared (Student's t test).

Results In the study group a significant reduction in headache frequency and analgesic consumption was observed [1] at the end of the study. Also the mean amount of psychosomatic symptoms decreased significantly ($p=0.002$) from the baseline (7.27 ± 5.19 SD) to the end (5.73 ± 4.77 SD). In the control group no significant difference was observed (baseline: 6.65 ± 5.07 SD; end: 6.55 ± 4.93 SD; $p=0.78$).

Conclusions The results of this 8-month controlled trial demonstrate that the administration of a simple cognitive instruction programme can significantly decrease psychosomatic symptoms in a working community. This finding may be the direct consequence of the cognitive programme and may be also partly due to the beneficial effects of such programme on the headache, neck and shoulder pain in the study population.

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Psychological characteristics of headache sufferers: defence mechanisms

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Introduction Many studies have been conducted in the past to identify the personality characteristics of headache sufferers, above all in migraine suffering patients, but their defence mechanisms are still not very clear. The purpose of this work was to investigate this aspect.

Methods The experimental sample was represented by 298 adult headache patients (241 females, 54 males, mean age: 36.4 ± 11.7 years; range: 12–68 years). The sample was composed of 227 migraine sufferers (208 MwoA, 19 Mwa), 64 patients suffering from tension headache (45 ETTH, 19 CTTH). The sample was

compared with a control sample represented by 311 healthy adults (192 females, 119 males; mean age: 38.7 ± 10.4 years; range: 15–71 years).

Instruments The 609 subjects were administered: Symptom Check List-90-Revised (SCL-90-R), Defense Mechanisms Inventory (DMI-short version) and Defense Style Questionnaire-40 (DSQ-40).

Results and conclusions The SCL-90-R showed a general symptomatology significantly higher in headache patients compared to the control group. Migraine suffering patients used in a significant manner masochism and to a lower extent projection (DMI). An explanation for this is found in the rigid educational environment from which these patients come from, preventing the external expression of aggressiveness (minimum utilization of projection) and causing them to turn against themselves (massive use of masochism). The DSQ showed that among migraineurs there is greater use of anticipation, since in this manner they are able to remove tensions somatically, in order to show themselves affectively more pleasant. Tension headache sufferers have greater recourse to annulment and to a lower extent to suppression with respect to the control group, since they appear to be unable to remove problems and/or retain disturbing feelings. From a psychiatric point of view, the characterization of patients suffering from migraine in handling intrapsychic conflicts with peculiar modalities, originating from disturbing perceptive and affective sources with respect to the general healthy population, appears to be confirmed.

Psychological short-term effects of the detoxification programme in chronic migraine patients with medication-overuse

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Background Chronic migraine (CM) represents a debilitating disorder and the first cause of an excessive use of symptomatic drugs. Since tolerance and addiction may sustain CM with drug abuse, the management of patients consists in the suspension of symptomatic drugs assumption. Therapeutic success (absence of headache or frequency reduction over 50% over a 6-month period) stands around 72%–74%. Peculiar psychological traits are present in CM patients, although it is unclear if they represent the consequence of chronic pain or a pre-existing psychological trait. These include: anxiety, depression, phobias, obsessive-compulsive symptoms, emotional lability, psycho-physiological disorders and anger [1]. According to many researchers, it is possible to define a personality profile in patients with CM: the attachment style is insecure and the temperament is indicative of avoidant personality. Furthermore psychological and behavioural features seem important in promoting and sustaining drugs abuse. The objective of this study was to evaluate the psychological short-term effects of the detoxification programme in a group of CM patients treated for medication-overuse.

Methods Fifteen female patients (mean age: 53.08, SD 8.09), affected by CM (according to IHS criteria) with medication-overuse underwent a standardized detoxification programme. A standardized psychological examination at admission and after a week of detoxification treatment was performed. The psychological assessment included: State and Trait Anxiety (Stai-X1 and Stai-X2), Personality (Eysenck Personality Questionnaire/R), Psychophysiology (QPF/R), Fear's Inventory (IP/R), Depression (QD Questionnaire), Phobias and Obsessive-Compulsive symptoms (Maudsley Obsessional-Compulsive Questionnaire/R) and State and Trait Anger (STAXI) tests. Statistical analysis was performed

using the paired t test. The level of statistical significance was taken as $p \leq 0.05$.

Results After a week of treatment, State anxiety and Emotion lability subscale scores were significantly reduced ($p < 0.05$). No significant statistical differences were found in Trait Anxiety, Personality, Fear's Inventory, Phobias and Obsessive-Compulsive symptoms, Depression and Anger scores.

Conclusions This study showed that, after 1-week therapy, CM patients with medication overuse present a significant reduction in anxiety and emotion lability. This effect cannot be attributed to the antidepressant effects of drug. Patient psychological traits might influence the results of the detoxification programme while the expectation, the doctor-patient relationship, the information about the therapy and the motivation might favour a good outcome. Our hypothesis is that admission to a hospital reduces stressful life events. Additional studies are needed to evaluate if these are long lasting results and might act to change the personality profile in long-term follow-up.

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Headache onset precedes anxiety and depression occurrence in patients from a tertiary Headache Centre

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Introduction Data from longitudinal studies on general population suggested on the one hand that suffering from baseline depression increases the risk of incident migraine but not the risk of other severe headaches; on the other hand, the risk of incident depression seems to be higher in subjects with baseline migraine [1]. Merikangas et al., in a previous study had suggested that anxiety might precede the headache onset and that headache in turn might be followed by depression [2]. The aim of this study was to verify retrospectively the possibility of a preferential order of incidence of psychiatric symptoms/disorders in relation to headache and the influence on headache course.

Methods A sample of 516 headache sufferers consecutively referring to the Headache Disorders Centre of Bari and receiving a diagnosis of primary headache according to diagnostic criteria of the International Classification of Headache Disorders (2004) were included [3]. A personal and familial medical history focusing on the natural history of headache, possible psychopathologic features and therapies were collected.

Results An association of headache with psychiatric comorbidity was found in 331 patients (64.14% of cases). In 42.59% of them anxiety and depression were comorbid, in 21.46% of headache patients anxiety was found as a single psychopathological factor, in the remaining 35.95% depression was the single comorbid factor. In all the three groups, headache onset preceded the occurrence of psychopathological symptoms. In most of the patients with concurrent anxiety and depression both disorders occurred at once, after the headache onset. This chronology of onset was observed either in migraine or in tension-type headache patients.

Conclusions The results of this study do not confirm the chronology of onset described in previous studies in the general population but seem to indicate that headache is in most cases the first disorder to occur. The retrospective design of this study might represent

a limit for the accuracy of data collected. The disagreement also might be due to different severity of headache in patients from the general population compared to tertiary headache outpatients. Thus, if headache may represent a predisposing condition to psychopathology remains a priority question for further studies.

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Migraine and psychoanalysis

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Introduction Migraine is a common, chronic, incapacitating neurovascular disorder, characterized by attacks of severe headache, autonomic nervous system dysfunction, and in some patients, an aura involving neurologic symptoms. Migraine headaches have a complex pathophysiology; both vascular and neuronal mechanisms have been proposed. Many authors, including Freud, have proposed a different pathophysiology of migraine. Initially, Freud's theories on the etiopathogenesis of pain and migraine focused on neurophysiological hypotheses, which are of historical interest. They were replaced by psychodynamic hypotheses which are still important for our current understanding of pain and headache.

Discussion There is no evidence for use of psychoanalysis in migraine therapy because it is not classified according to Evidence Based Medicine. It is evident, for medicine, that the symptom is something that must be relieved, but many times migraineurs live their condition as a life mark, and for this reason we have headache sufferers associations. An analytical cure is not just one of many kinds of psycho-knowledge with an objective that oscillates between the patient's well-being and an adaptive socio-educative solution. It is, rather, a new social bond, not influenced by previous subjective experiences – philosophical, religious or scientific – because it sets up a different structure of discourse and thus permits the subject to define and describe his/her own mode of enjoyment and, many times, migraine is just a form of enjoyment. If migraine can be a source of satisfaction, it can, above all, have the function of permitting the subject to stop thinking, of putting his body in motion, etc.

Conclusions Migraine can be considered “a disorder caused, at the most, by personal juncture between the subject and his/her sense of being alive”: When psychoanalysis analyses a choice of lifestyle, such as that to be a migraineur for example, it is on the condition that the process be applied “in a literal sense as treatment to a speaking, hearing subject” (Lacan). Jacques Lacan presents “psychoanalysis as the last flower of medicine, the tail of medicine, that is exactly the place where medicine can find refuge”. The taking charge by psychoanalysis, of the the medicine operating with the transference by psychoanalysis, supposes the reintroduction of the dimension of the subject in that field, not the migraine but the migraineur.

Symptomatic and prophylactic treatment in headache

Changes in orexins, neuropeptide Y, and leptin plasma levels correlated to weight increase consequent to flunarizine and amitriptyline prophylactic treatment in migraine

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Introduction Weight gain is a side effect commonly associated with drugs used for headache prophylaxis, in particular, amitriptyline (AMT) and flunarizine [1]. It has been reported that certain neuropeptides, such as orexins, neuropeptide Y (NPY) and leptin play an important role in the regulation of appetite and energy metabolism and therefore may be involved in weight increase during migraine prophylaxis [2].

Materials and methods Plasma levels of orexins A and B, leptin, NPY, and insulin were measured by RIA methods in 39 migraine patients with a body mass index (BMI) <25 and without any other disorder, with particular regard to endocrinological or metabolic diseases. Patients were randomly divided into two groups, receiving AMT or flunarizine ($n=24$ and $n=15$, respectively) for three months.

Results Plasma orexin A and B concentrations were significantly reduced by both drugs from the first to the third month of treatment (ANOVA: orexin A, $p<0.02$ and $p<0.001$; orexin B, $p<0.03$ and $p<0.003$, respectively). This reduction was more accentuated in patients treated with flunarizine, which had the greater mean weight increase. Conversely, plasma NPY, leptin and insulin levels were markedly increased, with the highest levels at months 2 and 3, particularly in the flunarizine group.

Discussion and conclusions Our results suggest that orexin A, NPY and leptin levels are affected by AMT and flunarizine treatment in migraineurs. In particular, the two drugs may cause a decrease in orexin and NPY levels by inducing leptin resistance, possibly by different mechanisms, and thereby result in an increase in serum leptin levels and BMI [2].

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Therapeutic effect of a low-carbohydrate fractioned diet as a treatment of migraine; follow-up at 6–24 months

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Introduction In the last few years insulin alteration has been reported in migraine [1, 2].

Objective The main aim was to evaluate the therapeutic effect on migraine by treating hyperinsulinism with a proper diet; to evaluate the effect of different glucose-insulin metabolic profiles, compared with controls; and to evaluate maintenance of the therapeutic effect of the diet over time.

Patients and methods This was an observational prospective controlled study. We recruited all the consecutive patients visited at the Headache Centre, suffering from migraine (IHS), and collected general, neurological, and haematological data. General, and standard oral glucose tolerance test with dosage of glucose and insulin (OGTT) were also carried out. Follow-up was at 3, 6, 12 months and 24 months in some case. Patients with abnormal metabolic profile were treated with a proper diet. Statistical analysis was as appropriate.

Results Over two years we recruited 319 patients (257 women, 63 men). Their mean age was 42 years; mean age of onset was 21 years, mean lasting was 22 years, and mean frequency was 12 days per month, with a headache severity index of 33. Two hundred and seventeen patients (68%) showed an alteration in the OGTT test, 169 resulted insulin resistance (IR), and 48 were insulin sensitive (IS). General characteristics of the patients did not significantly differ between the two studied groups. Body Mass Index (BMI) was also similar (24 and 23), such as associated diseases and drug use. In the OGTT altered group: analysis for subgroups showed that BMI was slightly lower in the IS group (21), and in the IR group it was 29; comparison of OGTT results at baseline and after diet showed a slight improvement of glucose and insulin values; it reached significant differences when considering the IR group ($p=0.001$); headache index improved and decreased from 33 to 11; with sub-group analysis the major improvement was in the IR group. At 6- and 12-month follow-up we assisted at a progressive worsening in headache index, but it remained significantly lower compared to the baseline values ($p=0.01$). In the group with a normal OGTT profile, the patients improved their headache index slowly over time, reaching the same index after 3 months (31 to 11), and the benefits lasted longer and was more constant.

Conclusions Diet therapy for patients with migraine and glucose-insulin alteration is useful and of no cost. It can be difficult to apply because it needs more compliance compared to a drug treatment, but we believe it is better than drugs, both for the patients and for the Health System. The long lasting benefits of the diet therapy support the theory that its efficacy, if real; the placebo effect could explain the more relevant improvements in the first months. Diet does also improve BMI and metabolism, and ameliorates patient health.

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Epidural blood patch to treat orthostatic headache by spontaneous CSF leak

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Introduction Spontaneous intracranial hypotension (SIH) generally results from spontaneous spinal CSF leakage (SCSFL). The treatment is usually conservative but epidural blood patch (EBP) has emerged as the most important nonsurgical treatment for SCSFL [1, 2].

Materials and methods We observed 66 patients with SCSFL between 1992 and 2007. Thirty-two patients (18 women and 14 men; age range: 31–69 years, mean age: 45 years) received lumbar EBP. Lumbar EBP was performed using 15 to 34 ml (mean 29) of autologous blood. In 12 patients the blood was mixed with gadolinium, they underwent spinal MRI post-EBP. In 13 patients the blood was mixed with iopamidol and multi-slice spinal CT post-EBP was performed. One patient who had three lumbar EBP underwent the first spinal MRI post-EBP and the second and third spinal CT post-EBP. All patients maintained a 30° Trendelenburg position during the procedure and for the following 24 hours after the procedure. Follow-up ranged from 6 months to 2 years.

Results All patients had orthostatic headache (OH). Other manifestations were nausea, vomiting, mild neck stiffness, tinnitus, blurred vision, diplopia, bilateral upper limb numbness and coma. CT myelography or spinal MRI or brain MRI or radionuclide cisternography showed CSF leakage sites in 17 patients, (four sites were at the cervical level, nine sites at cervico/dorsal level, one site at dorsal level and three at the lumbar level), in 15 patients the site of CSF leakage was unknown. In 31 patients brain MRI showed diffuse pachymeningeal gadolinium enhancement (neuroimaging of intracranial hypotension). All patients failed an initial conservative treatment which consisted of bed rest and rehydration over a period of 20 days to 13 months. Twenty-nine patients (90%) responded well to the first lumbar EBP. OH disappeared within 24 hours. Two patients with atypical SCSFL became asymptomatic after three lumbar EBP. One patient underwent a combined treatment, first lumbar EBP and then evacuation of the subdural haematomas. In 17 patients, spinal MRI (5 patients) or spinal CT (12 patients) post-EBP showed the blood patch spread from the lumbar to cervical epidural space.

Discussion and conclusions Our data confirm the efficacy of EBP in the SCSFL, suggest that the blood patch spread in the epidural space can be easily traced with spinal MRI or spinal CT, using blood mixed with contrast medium, and underline the importance of the Trendelenburg position to favour the blood patch spread from lumbar to cervical epidural space [3].

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Experimental evaluation study for the employment effectiveness of the association of riboflavin and niacin in the prophylactic treatment of migraine

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Introduction The purpose of this study was to provide a simple therapeutic method that was without contra-indications for the prophylaxis of migraine taking into consideration the association represented by nicotinic acid, vitamin B3 and riboflavin vitamin B2. Nicotinic acid fulfils its function after its conversion into nicotinamide adenine dinucleotide (NAD) or nicotinamide adenine dinucleotide phosphate (NADP), coenzymes for essential oxyreduction reactions for tissural breathing. Riboflavin is also an essential component of two coenzymes, the flavin-mononucleotide (FMN) and

the flavin-adenine-dinucleotide (FAD). The presence of both these substances is necessary for the functioning of biochemical mechanisms governing cellular metabolism. A decrease was recently demonstrated of fosforilization in the brain and of mitochondions of migraine-suffering patients between a crisis and the next one [1]. Even though this discovery is in line with the previous observations of reduction of the phosphocreatine and phosphate ratio in the brain of migraine suffering patients, this needs to be confirmed since it may represent the link between behavioral factors and the unbalance of brain oxygen, and the secondary activation of the trigemino-vascular system [2]. This therapeutic choice has already been made by several authors in the past [3].

Objective Oral administration of 50 mg nicotinamide + 2.5 mg of riboflavin was administered twice a day for 26 weeks. After authorization by the ethic committee and informed consent, 50 patients entered the study, (33 females, 17 males; average age: 37 ± 12 years, range 18/60 with MwA, IHS 2004) after 4-week wash-out period.

Methods End points were verifying the reduction of the frequency, duration, and the use of symptomatic medications per month. The data were compared to T0 and T26 for riboflavin/niacin (RN) ($n=25$) and placebo (PL $n=25$).

Results All parameters studied showed a reduction in: frequency (RN $8.9 > 4.7$, PL $8.1 > 5.9$), duration (RN $7.2 > 4.5$, PL $7.9 > 6.5$), and symptomatic medications (RN $5.7 > 3.5$, PL $7 > 5$). In both groups, there was a reduction in the parameters studied, but only if the frequency difference was statistically significant in favour of the drug ($p < 0.05$). Only one patient treated with placebo presented side effects.

Conclusions The association riboflavin/niacin, has proven effective for prophylaxis in migraine, even if the results are significant only for frequency; on the other hand, the absence of side effects makes it easy to use.

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Low dose amitriptyline in prophylaxis of migrainous vertigo

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Fifty patients, 34 females and 16 males with ages ranging from 18 to 46 years, were selected for the study carried out from January 1st 2006 to December 31st 2007. The patients had been diagnosed with migraine with aura of the vertiginous type and were attending headache centres. Tension-type headache alone or migraines with aura cases were excluded from the study. In each patient the migraine attack (at least 3 attacks occurring each month) followed a mixed vertiginous syndrome with vagal symptoms. The patients were all treated with a daily dose of 10 mg of amitriptyline administered in the evening with follow-up after the 1st, the 3rd, the 6th and the 12th month and monitored through a daily journal kept by each patient in order to record headache attacks and collateral symptoms. After a month, 60% of the patients reported a significant reduction in the frequency of migraine and vertigo attacks. In the non-responsive group,

the dose was doubled to 20 mg daily of amitriptyline, with success in 90% of cases. Only low entity collateral effects were noted and evident only among the patients treated with a 20 mg daily dose of the drug. Hence, we consider that this type of treatment is valuable in the prophylaxis of migrainous vertigo.

Patterns of triptan utilization in the general population

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The rate of migraine patients using triptans is often estimated from studies of selected migraine populations, taken from specialist consultation. Poor data exist about the real utilization of triptans among the general population. The largest published study concerns about 1/10 of the Italian population [1]. A detailed description of drug utilization pattern was carried out in a population resident in Tuscany (Healthy Authority 11, Empoli) in 2005 [2]. A study on this population was performed in the period 2005–2006 (TRIPTEMP study), with the aim to improve the understanding of the pattern of triptan utilization. Marginal variations were found in triptans users regarding sex and age distribution when comparing 2005 and 2006, but other important items must be underlined. Firstly, among 921 patients that used a triptan in 2005, 432 (46%) had not taken any triptan in 2006 (past users); 79% of these patients, during 2005, had taken 1–2 packages, while only 24 subjects had taken two types of triptans. Secondly, among 1022 patients who used a triptan in 2006, 531 (52%) were naïve and did not take triptans in the preceding year (new users); 407 (76%) of these patients had used 1–2 packages. Thirdly, the analysis of the frequency of utilization highlights that 50 subjects in the years 2005–2006 had utilized more than 120 DDD/year; they can probably be classified as triptan abusers, with an expenditure of 34% of the total. In conclusion, analysing data coming from Italian and world populations, the following findings emerge: 1) a very low percentage of migraine patients is treated with triptans; 2) if triptans are used, these drugs are prescribed only once in a year in a large number of cases; 3) a high turnover (high percentage of past users and new users) is not associated with a substantial increase in the percentage of users, in the years; and 4) a large amount of triptans was prescribed to few subjects (abusers). This data clashes with both the proven efficacy of these drugs [3], and with studies showing the superior grade of satisfaction of patients for triptans compared to non-triptan drugs. It is clear that there is a need for a new approach to headache problems, and a closer collaboration between general practitioners and specialists. This task force will allow the "iceberg" headache to emerge and consequently the optimal use of triptans, an important, but still underused, therapeutic tool.

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Short-term effectiveness of simple advice as a withdrawal strategy in simple and complicated medication-overuse headache

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Objective The aim of this study was to compare the effectiveness of intensive advice to withdraw the overused medication as a withdrawal strategy in patients with simple and complicated medication-overuse headache (MOH) having migraine as primary headache.

Methods One hundred consecutive patients (82 females, mean age: 39±12 years) fulfilling the appendix ICHD-II criteria for MOH participated in the study. Exclusion criteria were co-existent severe medical or psychiatric illnesses, treatment with migraine prophylactic drugs within the past three months and overuse of opioids, and barbiturates containing agents. MOH was defined as complicated in patients satisfying at least one of these criteria: a) a current diagnosis or history of co-existent, significant and complicating medical illnesses; b) a current diagnosis of mood disorder, anxiety disorder, eating disorder or substance addiction disorder; c) relapse after previous detoxification treatment; and d) psycho-social and environmental problems. Withdrawal therapy was considered successful if, after 2 months, the patient had reverted to an intake of symptomatic medication lower than 10 days/month.

Results Fifty-one patients had simple MOH and 49 patients had complicated MOH. Eleven patients dropped out from the study (simple MOH=5.6%, complicated MOH 16.3%, $p>0.05$). By considering all the patients enrolled in the study we were able to detoxify 77% of the patients, 90.2% of patients with simple MOH and 63.2% of patients with complicated MOH ($p<0.01$).

Conclusions Simple advice is highly effective in simple MOH and effective in the majority of complicated MOH patients, and should be regarded as the first step in a step-care approach to managing MOH.

Use of a formulation containing feverfew (*Tanacetum parthenium*) and chaste tree (*Vitex agnus castus*) in the symptomatic treatment of migraine

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Introduction Acute attacks of migraine are usually treated with traditional drugs (triptans being the most important of them up to

now), but there are also other available approaches to healing, that belong to the so-called alternative medicine (homeopathic or herbal medicine products). Feverfew (*Tanacetum parthenium*) has been used with good results in the prophylactic treatment of migraine and chaste tree (*Vitex agnus castus*) in the treatment of premenstrual syndrome. It seems that the addition of Mg to these substances could increase their speed of action. Therefore we decided to evaluate a formulation containing Feverfew (120 mg), Chaste Tree (80 mg), Magnesium Oxide (85 mg), Vitamin E (8 mg) (PREMEDOL®), for the treatment of acute attacks of migraine.

Materials and methods A group of female patients (age 18–65 years), suffering from migraine without aura (MO) according to the ICHD-II criteria, with minimum 4 migraine attacks per month in the previous 3 months, referring to University of Turin Headache Centre, were studied. They were divided into three groups assuming the formulation at different dosages in 3 consecutive migraine attacks: two tablets at the beginning of each attack and a third after one hour, if the pain was still present (Group A), two tablets plus two (group B), one tablet plus one (Group C). In case of inefficacy, they were told to assume their usual medication 2 hours after the second assumption. They were also asked to express their satisfaction using a 0-to-5 evaluation scale.

Results All the patients (100%) assumed the formulation in minimum 2 attacks. In Group A 7 (70%) patients had total relief from pain in 1 to 2 hours from the assumption of the formulation. Two (20%) had a partial relief from pain, therefore they used a rescue medication; only one patient (10%) did not have any result from this treatment, in all 3 attacks treated. The results were compared with those of the other two groups. No particular side effects were referred. The patients' satisfaction degree varied from 1 to 5.

Conclusions and discussion From the results of this preliminary study, this formulation seems to be effective in the symptomatic treatment of migraine attacks. If these preliminary data will be confirmed by further studies on wider populations, this compound (formulation) could be a valid alternative for symptomatic treatment of migraine attacks, especially for those patients who have important side-effects with the traditional drugs (triptans or FANS).

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