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GENETIC ASPECTS OF MIGRAINE

SINGLE NUCLEOTIDE POLYMORPHISMS ON THE CACNA1E GENE IN SUBTYPES OF MIGRAINE WITH AURA

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Background Familial Hemiplegic Migraine (FHM), Sporadic Hemiplegic Migraine (SHM), and Basilar-type Migraine (BM) are phenotypically similar subtypes of migraine with aura (MA), differentiated only by motor symptoms, which are not present in BM. They are as well the only subforms of migraine where genetic defects have been found. FHM1 and some cases of SHM are characterized by mutations on the CACNA1A gene (chromosome 19p13), coding for the main subunit of the P/Q-type Ca²⁺ channels. Mutations on the ATP1A2 gene (chromosome 1q23), coding for the main subunit of the Na⁺/K⁺ pump have been found in FHM2 and in one family affected by BM. However, some FHM patients do not bear mutations on these genes, so that at least a third FHM locus is expected (FHM3). One study identified an FHM locus on chromosome 1q31, which contains the CACNA1E gene, coding for the main subunit of R-type Ca²⁺ channels, similar in function and location to the P/Q-type. A linkage to the 1q31 locus has been suggested also for common forms of migraine.

Methods We searched for variations in the CACNA1E gene in a large group of migraineurs (*n*=111; migraine without aura (MO)=29; migraine with typical aura (MA)=56; Basilar-type Migraine (BM)=9; Sporadic Hemiplegic Migraine (SHM)=11; Familial Hemiplegic Migraine-(FHM)=6; and in a control group *n*=104). Screening was performed by direct sequencing on blood genomic DNA.

Results We identified a novel single nucleotide polymorphism (D840E) in exon 19 of the CACNA1E gene. It was present in 14.4% of control subjects and in 18% of migraineurs. It was significantly more represented in FHM, SHM, and BM patients (34.6%) than in MA patients (8.9%, *p*=0.01) and control subjects (*p*=0.03).

Conclusions In this study we report a novel polymorphism in the CACNA1E gene (D840E), which was particularly represented in some subtypes of migraine with aura, such as FHM, SHM and BM. This finding supports the hypothesis that abnormalities on locus 1q31 and particularly on the CACNA1E gene may represent the genetic basis for some subforms of migraine with aura and that CACNA1E is a suitable candidate for FHM3.

LACK OF VARIATIONS IN THE CACNA1A GENE IN PATIENTS AFFECTED BY SUBTYPES OF MIGRAINE WITH AURA

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Introduction Mutations in the CACNA1A gene on chromosome 19p13, encoding a neuronal calcium channel subunit, have been found in patients affected by Familial (FHM1) [1] and Sporadic Hemiplegic Migraine (SHM) [2]. Some families with FHM (FHM2) [3] and Basilar-type Migraine (BM) [4] bear mutations on the ATP1A2 gene (chromosome 1q23). These findings suggest that FHM, SHM and BM are not only phenotypically similar subtypes of migraine with aura but also allelic disorders. Sib-pair [5, 6] and linkage studies [7] suggested that abnormalities on the CACNA1A gene may also be at the basis of common forms of migraine such as migraine without and with typical aura. In our study, we screened for CACNA1A gene variations in a group of probands with FHM, SHM or BM and compared them to migraine patients with typical aura (MA), migraine patients without aura (MO), and control subjects.

Methods A total of 120 migraine patients (MO (*n*=33), MA (*n*=59), FHM (*n*=11), SHM (*n*=7), BM (*n*=10)) and 124 control subjects were enrolled and studied for gene screening after having obtained their informed consent. Complete screening of the CACNA1A gene was obtained in 3 BM patients and 1 SHM patient. Two patients with FHM were screened for the mutations known in FHM [2]. The remaining patients and controls were screened only for the variations found in the above preliminary patient groups.

Results None of the known mutations were found in the studied subjects. Two new single nucleotide polymorphisms, E918D and E993V, were identified in the CACNA1A gene with similar prevalence in both migraine patients (24.4% and 27.3%, respectively) independently of subtype diagnosis and in controls (27.4% and 27.7%).

Conclusions CACNA1A gene mutations reported in the literature were not confirmed in our BM, FHM and SHM patients. The variations we described are polymorphisms, since they were highly represented in MO and MA patients and in control subjects as well. Our findings confirm that CACNA1A gene variations are not present in most migraine patients, even affected by subtypes of migraine with aura supposed to be allelic disorders of FHM.

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INVESTIGATING THE ASSOCIATION BETWEEN NOTCH3 POLYMORPHISM AND MIGRAINE

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Background It has been recently demonstrated that migraine is characterized by subclinical brain infarctions and white matter lesions. Several genetic risk factors have been associated with migraine, but no study has unravelled a possible relationship between migraine and Notch3, which is involved in vascular damage. Mutations in the Notch3 gene have been demonstrated to be pathogenetic for Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), a small vessel disease of the brain characterized by migraine.

Objective The aim of the present study was to evaluate whether the functional Notch3 polymorphism T6746C, which is not causative for CADASIL, might be a risk factor for migraine.

Methods One hundred and fifty-six migraine patients and 128 headache-free healthy volunteers entered the study. Demographic and clinical characteristics were carefully recorded, and a neurological work up was performed. Moreover, each subject underwent blood sampling for Notch3 genotype determination.

Results Notch3 genotypes as well as allele frequencies did not differ in migraine patients compared to controls, even adjusting for the presence of possible confounders. No difference was found either in migraine patients with or without aura.

Conclusions These findings support the view that the functional polymorphism T6746C in the Notch3 gene is not involved in increasing the risk of migraine or migraine subtypes.

HOMOCYSTEINE AND MIGRAINE: CORRELATIONS WITH CLINICAL, NEUROPHYSIOLOGICAL AND NEURORADIOLOGICAL FEATURES

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Introduction Increased homocysteine levels are associated with various pathological conditions in humans, including stroke and cardiovascular disorders. An association between the homozygous C677T mutation in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene and serum homocysteine levels [1] has been detected. In previous studies, an over-representation of the 677T allele was observed in migraine patients compared to controls, specifically for the migraine with aura (MA) subtype [2]. Homocysteine acts as an excitatory amino acid and may influence the threshold and the evolution of migraine headache.

Objective This study was designed to determine the influence of homocysteine levels and the homozygous C677T mutation on: (1) the factors predisposing to migraine, evaluated with the steady-state visual-evoked response and the habituation of Contingent Negative Variation (CNV); (2) the severity of migraine, evaluated with the MIDAS scale and the mean frequency of headache in the last 3 months; and (3) the MRI picture.

Methods The MTHFR C677T variant was genotyped in 75 migraine without aura (MO), 15 MA patients, and 100 controls. In all cases, CNV habituation and somatosensory visual-evoked potentials (SSVEPs) to medium and high frequency stimulation patterns were evaluated; twenty controls negative for the MTHFR gene were admitted for neurophysiological examination. Eighty patients were also admitted for MRI study.

Results We observed an over-representation of the 677T allele in migraine patients compared with controls, more evident for the MA

subtype: the MTHFR variant was also associated with reduced habituation pattern of CNV and enhanced photic driving. Higher levels of homocysteine were linked with earlier onset of migraine, higher frequency of headache, and multiple gliotic, peri-ventricular areas on MRI.

Discussion The MTHFR variant seems to be linked with greater severity of both MA and MO and increased migraine susceptibility: this finding may be reinforced by increased levels of homocysteine, which may cause impaired release of nitric oxide and increase the firing rate of trigeminal neurons, factors involved in the initiation and maintenance of migraine.

Conclusions The MTHFR gene variant seems to enhance the susceptibility to migraine and to worsen its evolution.

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PHYSIOPATHOLOGICAL ASPECTS OF HEADACHES I

DIFFERENT BEHAVIOUR OF THE SOMATOSENSORY HIGH-FREQUENCY (600 HZ) THALAMO-CORTICAL ACTIVITY IN MIGRAINE PATIENTS: DURING AND IN BETWEEN ATTACKS

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Background A deficit of habituation for different sensory modalities, including somatosensory, characterizes migraine patients between attacks. Interestingly, this abnormal cortical information processing normalizes during an attack. Since the exact mechanisms of this electrophysiological phenomenon are still under debate, we have studied the high-frequency oscillations (HFOs) embedded in somatosensory evoked potentials (SSEPs) because they are thought to reflect spike activity in thalamo-cortical cholinergic fibers (early HFOs) and in cortical inhibitory GABA (gamma-aminobutyric acid)-ergic interneurons (late HFOs).

Subjects and methods Forty-two untreated migraine patients with (MA) and without (MO) aura were recorded during ($n=13$, 9 MO, 4 MA) and between attacks ($n=29$, 14 MO, 15 MA) and compared with 15 healthy volunteers (HV). SSEPs were filtered off-line (digital band-pass between 450 and 750 Hz) to extract the two HFO bursts from the broad-band contralateral N20 somatosensory cortical response, obtained always by right median nerve stimulation.

Results Amplitudes and latencies of conventional broad-band SSEPs recorded in migraine patients between attacks from cervical and parietal active electrodes were not significantly different from those found in HV. In contrast, maximum peak-to-peak amplitude and area under the rectified curve of the early HFO burst were significantly smaller in both MO and MA patients than in HV. There was no significant difference in the later HFO burst between migraineurs and HV. During attacks, all electrophysiological measurements in migraineurs were similar to those found in HV.

Discussion These results support the hypothesis that a reduced pre-activation level of sensory cortices explains the lack of habituation phenomenon in migraineurs, and not cortical hyperexcitability or reduced intracortical inhibition.

Conclusions These results suggest that evoked activity in thalamo-cortical excitatory cholinergic afferents is interictally decreased in both migraineur groups, but normalises during an attack; whereas intracortical inhibition, as indexed by the late HFO burst, is normal at any time.

THE DIFFUSE NOXIOUS INHIBITORY CONTROL SYSTEM IN CHRONIC MIGRAINE TESTED BY MODULATION OF THE BLINK REFLEX BY REMOTE PAINFUL CONDITIONING STIMULI

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Introduction A dysfunctional activation of brainstem structures inhibiting pain transmission was postulated in chronic migraine [1]. The R2 component of the blink reflex is a very tempting model to explore trigeminal nociception [2]. The aim of the study was to test the function of the diffuse noxious inhibitory control system (DNIC) in chronic migraine, exploring the R2 suppression induced by painful stimulation of the hand, obtained by topical application of capsaicin.

Methods Thirty headache patients were selected, 10 were affected by migraine without aura, 10 by chronic migraine and 10 by chronic migraine with analgesic overuse. Ten control subjects were also evaluated. All patients were free from migraine during the evaluation. The blink reflex was elicited by electrical stimuli delivered to the right supraorbital nerve, settled at an intensity 2 mA over the threshold of the R2. Therefore, the R2 response was obtained 10 min and 20 min after the application of 1 ml of 3% capsaicin in a cream base (Teofarma) on the skin of the dorsum of the right hand, within an area of 3 cm². All patients were requested to rate the pain induced by capsaicin using a 0–100 visual analogue scale (VAS).

Results In control subjects the integral of R2 was reduced by about 15%, while the rate of R2 suppression after conditioning painful stimulation was on average 12% in migraine without aura patients, 7% in chronic migraine, and 2% in chronic migraine with analgesic overuse. Chronic migraine rated the capsaicin elicited pain with higher VAS scores with respect to controls. In the whole migraine group, the rate of R2 suppression was significantly reduced with the increase of illness duration and headache frequency. The rate of R2 suppression was also significantly correlated with the subjective rating of capsaicin induced pain in patients and controls.

Discussion and conclusions These data could suggest that the dysfunction of inhibitory control of pain may be intrinsic to migraine, but it can predispose to chronic migraine and analgesic overuse. It may be linked with the phenomenon of generalized hyper-algesia, which may persist outside the attack, leading to a self-outstanding circuit favouring the maintenance of headache.

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INTERICTAL INHIBITION OF THE NOCICEPTIVE SPECIFIC R2 BLINK REFLEX COMPONENT IS NORMAL IN MIGRAINE WITHOUT AURA PATIENTS

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Background In migraine patients, sensitisation of the spinal trigeminal nucleus neurons has been hypothesised during an attack (Burstein et al., *Brain* 2000; Kaube et al., *Neurology* 2002). There is also some evidence that such sensitisation could persist for some time between attacks. A deficit of habituation was detected in migraineurs for a brain stem reflex, the nociceptive specific blink reflex (nBR) (Katsarava et al., 2003); the question arises whether this phenomenon could be related to peripheral or central sensitisation in the trigeminal system. The R2 response can be suppressed by prior stimulation of the supraorbital nerve and its recovery curve after paired stimuli depends on the excitability of the trigemino-facial circuit. Moreover, the R2 response can be suppressed also by peripheral nerves (Rossi and Scarpini, 1992), via activation of inhibiting central reticular nuclei (Valls-Solé et al., 1994). In order to shed light on the mechanisms of the interictal brainstem dysfunction in migraine, we have studied recovery curves of the R2 component of the nBR after conditioning by supraorbital or index finger stimuli in untreated migraine without aura patients (MO) between attacks and in healthy volunteers (HV).

Subjects and methods We recorded the recovery curve of the R2 nBR in 14 MO patients and in a group of 15 HV, in a first session by paired supraorbital identical stimuli, and in a second after a single shock delivered through ring electrodes to phalanges I and II ipsilateral to the preceding supraorbital stimulus. Both conditionings were performed at interstimulus intervals (ISI) ranging from 50 to 600 ms, which allowed computation of a recovery curve.

Results The nBR recovery curves were normal for both the paired supraorbital and the peripheral index finger stimuli in migraineurs compared to healthy volunteers.

Conclusions These results are not in favour of persistent interictal sensitisation in the spinal trigeminal sensory system. They also suggest that the control of medullary R2 interneurons, notably by descending brainstem pathways, is normal in migraine between attacks. Therefore, neither central nor peripheral sensitisation are likely to be responsible for the interictal habituation deficit of the nociceptive blink reflex in migraine patients.

HABITUATION DEFICIT OF THE VISUAL-EVOKED GAMMA BAND RESPONSES IN MIGRAINE PATIENTS BETWEEN ATTACKS

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Background Two abnormal visual information processings characterize migraine patients between attacks: habituation deficit to repetition of the same stimulus, and the experience of more discomfort during visual stimulation, e.g. environmental light and pattern reversal on a screen. Pre- and post-synaptic or pre-cortical and cortical contributions have been hypothesized in the generation of visual-evoked oscillations in the gamma frequency range (GFOs, 20–60 Hz) (Carozzo et al., 2004). Moreover, these GFOs may underlie the perception of visual discomfort (Adjamin et al., 2004).

Subjects and methods We extrapolated the GFOs from the broadband visual-evoked potentials (VEPs) with an off-line band pass digital filter (20–35 Hz) in a group of healthy volunteers (HV, n=15), and in a group of migraine with (MA, n=15) and without aura (MO, n=15) patients between attacks. We analysed peak-to-peak amplitude and habituation (the amplitude change (%)) between the 1st and 6th block of 100 sequential averaged responses) of the conventional broadband N1-P1 and every 6 peaks of GFO bursts evoked by a checkerboard pattern.

Results Amplitude of the 3 early components in the 1st block (100 sweeps) was significantly increased only in MA patients ($p=0.03$). There was significant habituation deficit of the late GBO peaks, but not of the early ones, in migraineurs (MA and MO) compared with HV ($p<0.05$).

Conclusions The lack of habituation of the late GFO burst mimics that of the broad-band VEP and suggests that postsynaptic mechanisms are responsible for this most reproducible abnormality of sensory processing in migraine. However, it could also be hypothesized that the increased amplitude of early GFO is related to the visual discomfort commonly experienced in migraineurs, more frequently in MA.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) MODULATION OF THE VISUAL CORTEX OF HEALTHY SUBJECTS UNDERGOING LIGHT DEPRIVATION: A HUMAN MODEL TO STUDY THE PATHOPHYSIOLOGY OF MIGRAINE

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Introduction We reported paradoxical facilitation by 1 Hz rTMS in the visual cortex of migraineurs with aura and interpreted these results as due to inefficiency of the inhibitory circuits, unable to be up-regulated by low-frequency rTMS [1, 2]. Light deprivation (LD) is known to increase visual cortical excitability through down-regulation of GABA circuits. On this basis, we investigated rTMS modulatory effects in normal subjects undergoing LD with the following aims: first, to explore further the effects of LD on visual cortex excitability; and second, to evaluate if, in a condition of reduced inhibition such as LD, healthy subjects show paradoxical effects like those reported in migraineurs.

Subjects and methods Six healthy subjects reporting reliable induction of phosphene by occipital TMS underwent 60 min of complete LD. Phosphene threshold (PT) was measured before (T0), after 45 min (T1) and 60 min (T2) of LD, and then every ten minutes after light re-exposure until recovery to T0 values. Repetitive TMS (at 1 Hz or 10 Hz) was applied in separate sessions in the last 15 min of LD. PTs significantly decreased after 45 min of LD. rTMS differentially modified the effects of 60 min LD on PTs depending on stimulation frequency. 1 Hz rTMS did not change the decreasing of PT values as observed in baseline condition, but significantly prolonged the time to recover T0 PT values after light re-exposure. By contrast, 10 Hz rTMS significantly increased PT and the time to recover T0 PT values after light re-exposure was shortened.

Conclusions The results of this study show that the modulatory effects of different rTMS frequencies on visual cortex critically depend on the pre-existing excitability state of inhibitory and facilitatory circuits. Indeed, during LD healthy subjects behave like migraineurs and this could provide a useful human model to study the pathophysiology of migraine.

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MOTOR CORTEX EXCITABILITY TO FOCAL TRANSCRANIAL MAGNETIC STIMULATION (TMS) IN UNILATERAL MIGRAINE PATIENTS

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Introduction Motor cortex excitability changes have been reported in migraine and numerous studies have yielded interesting, but partly controversial results. We employed focal TMS to evaluate motor cortex excitatory and inhibitory properties in unilateral migraine patients.

Patients and methods Motor Evoked Potentials (MEPs) were recorded from the ADM muscle of 14 patients (40 ± 8.2 years) with unilateral migraine with or without aura (frequency attack 1–7/month). TMS was performed 2 days after the last attack. Seven patients had a post-TMS headache within 24 hours following the TMS recording (subgroup A = post-TMS attack), whereas 7 patients did not (subgroup B = no post-TMS attack). The following TMS parameters were analysed in both hemispheres and compared to those of 10 healthy subjects: (a) resting motor threshold (RMT); (b) cortical silent period (CSP) duration at threshold (100%) and from 110% to 180% of threshold values; (c) short- (S-ICI=1–3 ms) and long- (L-ICI=80 ms) intracortical inhibition to paired-TMS.

Results RMT, S-ICI and L-ICI were not significantly different between the two subgroups of patients and between patients and controls. CSP duration at threshold was significantly shorter in subgroup B (no post-TMS attack) than A (post-TMS attack; $p<0.05$). In subgroup A, CSP duration increased linearly from 110% to 180% of threshold intensity. Such a stimulus intensity/silent period duration curve was very similar to that observed in normal subjects. Conversely, in patients without post-TMS attack, the linear CSP progression was interrupted at TMS intensities of 140% above threshold.

Discussion Abnormalities of inhibitory motor cortex circuits as revealed by CSP duration analysis were found in both hemispheres of patients with no migraine attack after TMS recordings. In contrast, in patients with post-TMS headache, no abnormalities were observed.

Conclusions Our findings confirm that the motor cortex is dysfunctioning interictally in unilateral migraine. Furthermore, from our data we speculate that a “time window” could exist next to the migraine attack, during which motor cortical inhibitory mechanisms tend to normalise.

PHYSIOPATHOLOGICAL ASPECTS OF HEADACHES II

CEREBROSPINAL FLUID LEVELS OF ANANDAMIDE AND PALMITOYLETHANOLAMIDE SUGGEST A FAILURE OF THE ENDOCANNABINOID SYSTEM IN CHRONIC MIGRAINE WITH AND WITHOUT ANALGESIC OVERUSE

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Background Cannabinoid receptors and their endogenous ligands constitute a novel modulatory system that is involved in specific brain functions, such as control of movement, memory, neuroendocrine regulation, and also nociception [1]. Based on experimental evidence of the antinociceptive action of endocannabinoids and their role in modulating trigeminovascular system activation, we hypothesized a dysfunction of this system in chronic migraine.

Objectives We determined the levels of the endogenous cannabinoids arachidonylethanolamide (anandamide, AEA), palmitoylethanolamide (PEA) and 2-arachidonoylglycerol (2-AG) in the cerebrospinal fluid (CSF) of 15 patients with chronic migraine (CM), 15 patients with probable chronic migraine and probable analgesic-overuse headache (PCM+PAAH), and 15 controls.

Methods Endogenous cannabinoids were purified from CSF by high-performance liquid chromatography, and quantified by isotope dilution gas-chromatography/mass-spectrometry. CGRP levels were also determined by RIA method and nitrites by HPLC.

Results CSF concentrations of AEA and PEA were significantly lower in CM and PCM+PAAH patients than in controls ($p < 0.01$ and $p < 0.02$, respectively). In contrast, the levels of 2-AG were below detection in both patient and control groups. A negative correlation emerged between AEA and PEA and both CGRP and nitrite levels in both patient groups. **Conclusions** Reduced levels of anandamide and palmitoylethanolamide in the CSF of CM patients suggest failure of the endogenous cannabinoid system and intercellular signalling that may contribute to chronic head pain, which seems to be related to increased CGRP and NO production. This can be related to a failure of the inhibitory role of AEA on trigemino-vascular system activation via CB(1) receptors localized on fibres in the spinal trigeminal tract and spinal trigeminal nucleus caudalis. The failure of the inhibitory role of AEA and also of PEA can therefore contribute to maintaining central sensitization in chronic head pain together with NGF and BDNF release via glutamatergic transmission, reflected in higher levels of the sensory neuropeptide CGRP and NO production. The above findings support the potential role of the CB(1) receptor as a possible therapeutic target in these patients [2].

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NOCICEPTIN LEVELS IN CEREBROSPINAL FLUID OF CHRONIC MIGRAINE AND FIBROMYALGIA PATIENTS

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Study background Nociceptin is the endogenous ligand of the G-coupled naloxone-insensitive ORL-receptor. An increased expression of both nociceptin and ORL(1) receptors has been demonstrated in the dorsal horn of rat spinal cord in experimental pain models, thus indicating the involvement of the nociceptin/ORL(1) system in the mechanisms of pathological pain [1].

Objective The present study was aimed at investigating the cerebrospinal fluid (CSF) levels of nociceptin and PGE₂ in 20 chronic migraine (CM) patients, 20 patients with probable chronic migraine (PCM) and probable analgesic-abuse headache (PAAH), and 20 patients affected by primary fibromyalgia syndrome (PFMS). Control values for nociceptin and PGE₂ were obtained from the CSF of 20 subjects, for whom laboratory and instrumental investigations excluded diseases of the central and peripheral nervous systems.

Methods CSF nociceptin and PGE₂ levels were determined by sensitive immunoassays.

Results Nociceptin and PGE₂ levels were significantly higher in the CSF of patients with CM, PCM+PAAH and PFMS compared with controls (nociceptin = $p < 0.01$, $p < 0.02$, $p < 0.01$; and PGE₂ = $p < 0.03$, $p < 0.02$, $p < 0.01$, respectively), without significant differences among patient groups. A significant correlation emerged between CSF nociceptin and PGE₂ levels in CM ($R = 0.62$, $p < 0.01$) and PCM+PAAH ($R = 0.60$, $p < 0.02$) patients and also PFMS patients ($R = 0.48$, $p < 0.01$).

Discussion Nociceptin/orphanin FQ (noc/OFQ), the endogenous ligand and for the orphan ORL(1) (opioid receptor-like1), has been shown to be anti- or pronociceptive and modifies morphine analgesia in rats after central administration. A pronociceptive action of nociceptin related to PGE₂ secretion can be hypothesized in both chronic migraine and fibromyalgia, where it seems not to be influenced by analgesic abuse but rather is related to chronic pain per se [2].

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EFFECTS OF DISTRACTION ON ANALGESIA AND SPATIAL DISCRIMINATION OF PAINFUL STIMULI IN MIGRAINE

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Introduction In a previous study on laser-evoked potentials (LEPs) in patients with migraine without aura (MO) and chronic migraine (CM), a reduced effect of distraction in suppressing the cortical response to painful stimuli was detected in both MO and CM [1].

Objective The aim of this study was to test the effects of arithmetic tasks on spatial discrimination of painful laser stimuli and pain sensitivity in a cohort of MO and CM patients, compared to healthy controls.

Subjects and methods Ten MO and 10 CM patients were examined in a pain-free period and compared to 10 age- and sex matched controls. Four series of 20 laser pulses were applied on the dorsum of the left and right hands, onto two parallel lines located on the ulnar and radial side. All subjects were asked to perform spatial discrimination tasks (ulnar or radial side) after each laser stimulus, using two levels of task difficulty to emphasize the sensory-discriminative aspect of pain, also specifying the subjective pain rating according to a visual analogue scale 0–100. In 1 run taken randomly for both hands in the two levels of task difficulty, spatial discrimination tasks were contrasted with active distraction by mental arithmetic, consisting of serial subtractions of four-digit-numbers in steps of 7 or 9. Electroencephalogram (EEG) was recorded by 25 electrodes, placed at the 19 standard positions of the international 10/20 system, with 6 adjunctive electrodes.

Results The discrimination ability was the same across the three groups, but the effects of distraction on pain sensitivity was significantly reduced in both MO and CM groups in respect to controls. CM patients showed a slightly reduced ability in arithmetic tasks in respect to controls, and the effects of distraction on spatial discrimination was reduced in respect to normal controls. The rate of amplitude suppression of LEPs was also reduced in CM patients during mental arithmetic tasks.

Discussion and conclusions A reduced analgesic effect of distraction was confirmed in migraine: in CM patients, a slightly reduced arithmetic ability was linked with higher spatial discrimination of painful stimuli. This phenomenon may be attributed to enhanced activation of the cortical areas underlying the attentive components of pain, and it may also be favoured by slight cognitive impairment linked with the progression of migraine.

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ENHANCED TRIGEMINO-CERVICAL-SPINAL REFLEX RECOVERY CYCLE IN PAIN-FREE MIGRAINEURS

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Introduction Trigemino-cervical-spinal reflexes (TCsRs) are part of a complex nociceptive response involving the cervical and the upper

limb muscles, and are modulated by supraspinal inhibitory pathways; it may thus be possible to use TCSRs to explore the trigeminal system in migraineurs. The aim of the present study was to evaluate TCSRs in a group of migraine patients during the pain-free period.

Patients and methods Forty-three migraine patients, 32 without aura (MO), and 11 with aura (MA) and 30 age- and sex-matched healthy subjects took part in the study. TCSRs were obtained by stimulating the supraorbital nerve (SON) and recording from the semispinalis capitis muscle and the biceps brachii. The latency (L, ms), area (A, mVms) and recovery cycle of the reflexes were recorded. The effects of heterotopic painful stimulation on the neurophysiological parameters were studied by a validated cold pressor test (CPT).

Results No significant changes were found between either migraine patients and controls or MO and MA patients in the mean values of L and A of TCSRs (*t*-test, $p>0.05$). The recovery curve of the trigemino-cervical reflexes (TCRs) was significantly faster in migraine patients than in controls, while no differences were found in the trigemino-spinal reflexes (TSRs) (*t*-test, $p<0.01$). Activation of the diffuse noxious inhibitory controls (DNICs) through the CPT induced a significant reduction in the areas of the TCRs and TSRs in both migraine patients and controls (paired *t*-test, $p<0.01$), though the extent of this reduction did not differ significantly between migraineurs and controls (*t*-test, $p>0.05$).

Conclusions Our data suggest that the pain-free period in migraine patients is characterised by hyperexcitability of the trigeminal pathways and of their anatomical and functional connections with the upper cervical cord neurons, and that this abnormal hyper-excitability does not appear to be due to a lack of supraspinal inhibitory modulation.

NEUROENDOCRINE FUNCTION IS ALTERED IN PATIENTS WITH CHRONIC MIGRAINE AND MEDICATION-OVERUSE HEADACHE

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Introduction Chronic migraine (CM) is a major health problem. CM is frequently associated with psychiatric comorbidity, like anxiety and depression, and often complicated by overuse of acute medication drugs. The effects of analgesic overuse on endocrine functions in CM patients are still unknown. The purpose of this study was to investigate neuroendocrine function in patients with CM and medication-overuse headache (MOH).

Subjects and methods Eighteen patients (15 women, 3 men; mean age \pm SD = 44.3 \pm 9.9 years) with CM and MOH, diagnosed according to ICHD-II criteria, and 18 healthy controls (15 women, 3 men; mean age \pm SD = 40.3 \pm 7.9 years) received intravenous administration of GHRH, hCRH, and TRH. Plasma concentrations of GH, TSH, ACTH and cortisol were measured in a 90 min period after administration of the specific releasing hormones.

Results Hormonal baseline concentrations were similar in both groups. GH response to GHRH was significantly reduced in patients with CM-MOH in comparison with controls. After hCRH administration, ACTH and cortisol concentrations were significantly higher in patients than in controls. A significant positive correlation ($r=0.61$, $p=0.028$) between duration of disease and altered hormonal response was found.

Discussion Our study indicates that, in patients with chronic migraine and abuse of analgesic drugs, hypothalamic control of corticotropic and somatotrophic functions is significantly altered. These findings are in accord with a previous study showing an abnormal pattern of spontaneous hypothalamic hormonal secretion in patients with CM. A relationship between altered hormonal secretion and some of the clinical symptoms of patients with CM-MOH may be hypothesised.

Conclusions Our data support a role for the hypothalamus in the mechanisms of migraine chronicity and suggest the need for additional studies evaluating the relationship between abuse of antimigraine drugs and hormonal alterations in chronic migraine.

CLINICAL ASPECTS OF HEADACHES I

PREVALENCE OF HEADACHE IN A GROUP OF 1000 PATIENTS AT FIRST VISIT TO A TERRITORIAL NEUROLOGICAL CENTRE

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Introduction Headache is one of the most common types of neurological symptoms that patients complain of to the neurologist; in fact, previous studies suggest that headache is one of the main reasons for visiting a neurological office. Our clinic is in Bagheria (Sicily) and serves a population of more than 80 000 people. The aim of this study was to determine how many patients at first visit had headache as a dominant symptom.

Patients and methods We retrospectively analysed the clinical records of 1000 consecutive patients who came to our office for the first time for a neurological examination. We did not use any other criterion for selection.

Results The mean age of Group A was 60 years (range 18–94); 590 (59%) were woman, 410 (41%) men, and 46.1% of patients were over 65 years of age. Headache was the reason for the visit in 176 (17.6%) patients (50 M, 126 F). Group B was composed of patients aged 18 to 65 years (mean age 45), 330 women and 209 men, of whom 139 (25.8%) suffered from headache (28 M; 101 F). In Group A, 12.2% of males and 21.3% of females suffered from headache, whereas in Group B, 13.4% of males and 30.6% of females were affected by headache. The males who had headache were 12.19% in Group A and 13.39% of all in the Group B, the females were 21.3% in Group A and 30.6% in Group B.

Discussion and conclusions This epidemiological study confirms that headache is the most common reason for visiting in adult neurological patients and the prevalence of this disease increases in the group aged 18 to 65 years. In terms of percentages, there was a small difference between the two male age groups ($>1.20\%$ in Group B), whereas we found a major female preponderance in Group B ($>9.3\%$). Presumably, migraine prevalence increases more rapidly in women, from menarche to about the age of 40 due to alterations in hormonal levels, after which prevalence decreases with respect to men.

EVALUATION OF HEADACHE FREQUENCY: A COMPARISON BETWEEN TWO METHODS

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In the management of the headache patient an accurate evaluation of headache frequency is very important for many different reasons (e.g., to decide if a prophylactic treatment is necessary, to identify the best drug to be used, to evaluate treatment efficacy, etc.). It is possible to obtain this information directly from the patient's history, or from the patient's headache diary. To determine if these two methods are equiv-

alent, a group of 523 headache patients (390 females and 124 males, age range 15–71 years, mean age \pm SD = 37.42 \pm 12.42 years), of whom 250 (190 females and 60 males, mean age \pm SD = 35.86 \pm 12.05 years) suffering from migraine without aura (MO) and 273 (209 females and 64 males, mean age \pm SD = 38.83 \pm 12.8 years) suffering from coexisting MO and episodic tension-type headache (ETTH), diagnosed according to ICHD-II criteria, were studied. All patients were asked how many days with headache they usually had in a 4-week period. Then, each patient had to record all the days in which he/she experienced headache in a 4-week period headache diary. Headache frequency assessed by an interview was compared with that obtained from the diary. The two data were considered corresponding when the difference did not exceed 2 days (more or less), otherwise they were considered not corresponding. The patients in both groups were also subdivided into subgroups based on age and sex. In 295 (56.4%) patients, the headache diary data matched those provided by the interview. This correspondence was almost the same in all the different groups studied. When the data did not correspond, patients suffering from coexisting MO and ETTH generally recorded a higher number of days with headache in the diary than the one derived from the interview more often than MO patients ($p < 0.001$). In conclusion, while both these methods can be used to determine headache frequency, they do not correspond exactly. Since, in our experience, both methods can be imprecise, it is always better to combine them.

EMOTIONS IN PRIMARY HEADACHE: A PRELIMINARY STUDY

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Background Recent studies suggest a growing interest in the relationship between headache and psychological aspects [1, 2]. In order to underline that psychological information might be useful in treating such patients, we analysed both psychological symptoms and the emotional profile of our headache patients. A further aim of this study was to define if emotional or psychopathological traits might influence perception of quality of life. We report our preliminary data on the first patients.

Patients and methods Five female patients with primary headache (3 migraine without aura (MO); 1 tension-type headache (TTH); 1 analgesic rebound headache (ARH)) were studied with a global psychological assessment. Minnesota Multiphasic Personality Inventory-2 (MMPI-2), Cognitive Behavioral Assessment (CBA), Profile of Mood States (POMS) and Short Form-36 (SF36) were administered. Patients also underwent a psychological-clinical interview. Non parametric correlations (r Pearson), qualitative analysis of data and clinical profile observation were performed.

Results Our patients showed high levels in MMPI-based scale 1 (Hypochondriasis), 7 (Psychasthenia) and 8 (Schizophrenia), in MMPI-content scale HEA (Health Worry), in POMS-factor T (Tension-anxiety) and A (Anger). On the contrary, they showed low levels in SF36-subcales RF, DF and AS. CBA did not add any significant information. SF36-AS subscale correlates with MMPI-based scale 3 (Hysteria: $r = -0.936$, $p = 0.019$), MMPI-content scale HEA ($r = 0.881$, $p = 0.049$) and POMS-V factor ($r = 0.947$, $p = 0.014$). POMS-T factor correlates with MMPI-based scale 6 (Paranoia: $r = 0.939$, $p = 0.018$), MMPI-content scale ANG ($r = 0.988$, $p = 0.002$) and POMS-D factor ($r = 0.948$, $p = 0.014$).

Discussion According to the literature, our patients confirm high anxiety levels in formal psychological testing [3]. This agrees with the diagnosis of anxiety disturbances according to DSM-IV, as emerged from the psychological-clinical interview, even though some subclinical depressive symptoms might appear. Our data suggest that quality of life is not influenced primarily by pain perception itself, but by worries

about pain-related fear. This seems to limit social interactions by avoidance behaviour [4] and to determine general reduction of self-esteem. Moreover, our patients showed an important impairment in emotional focusing due to a more selective attention to somatic symptoms and mental distress.

Conclusions Our data may suggest that individual cognitive-behavioural psychotherapy and/or supervised mutual self-help groups could be the right tools to improve emotional recognition in headache patients. This might influence quality of life perception and the compliance to medical treatment.

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WORK-RELATED INJURIES AND HEADACHE AMONG HOSPITAL EMPLOYEES

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Introduction The Constitution regulates and protects workers also in work accidents. The work accident is defined as an accidental event that happens from a violent cause during work which causes an injury.

Aim The objective of the present study was to monitor the headache frequency in a hospital environment in employees who had reported work-related injuries.

Subjects and methods This open, observational, and prospective study was conducted at the IRCCS “C. Mondino” of Pavia, from January to December 1990, involving 252 hospital employees. All employees who had reported accidents, including employees who were never absent from work (0 days prognosis) were considered. The study involved all patients with headache visited by an occupational physician for injuries which occurred while working. A schedule for nosographic framing of headache based on IHS criteria (1988) was administered to workers who suffered from headache during the periodic control visits (Health Survey Protocol).

Results A total of 156 work-related accidents were registered, with an accident incidence of 1 per month, and 1847 total days of absence from work (mean days/injury 11.84). In the injured population (64 M, 92 F; mean age 34.3 \pm 6.8 years), 41 were headache sufferers (13 M, 28 F; mean age 38 \pm 8.7 years). The headache subtype distribution was: 2 episodic cluster headaches, 15 episodic tension headaches, and 24 migraine without aura. Among these, 5 migraine without aura and 3 episodic tension headache subjects had 2 injuries and 1 migraine without aura subject had 3 injuries. The most frequent accident was the needle prick, and the most serious was that occurring during working activities or “in itinere”.

Discussion Data show that the frequency of headache among workers who suffered an injury is 26.2%. The reduction in attention and the disability induced by headache or by post-pharmacological effects may be identified as possible risk factors that cause accidents in workers who suffer from headache.

Conclusions It is useful that occupational physicians investigate individual headache susceptibility during both the pre-hiring phase and

routine control visits, also in relation to the employee's work activity. This study will continue to monitor the presence and/or absence of headache at the time of injury to further study the relationship between headache and work injuries.

HEADACHE CENTRE IN AN EMERGENCY DEPARTMENT: A FOLLOW-UP STUDY ON THE EVALUATION OF CLINICAL AND DISABILITY IMPROVEMENT IN A MIGRAINE SAMPLE

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Introduction Headache accounts for 1%–3% of admissions to an emergency department (ED). The majority of patients who present to an ED with acute primary headache have migraine and little is known about their disability.

Aim The aim of this study was to evaluate the clinical impact of the collaboration between headache centre (HC) and ED in the diagnosis and treatment of migraine. In particular, we aimed to evaluate the disability of this population before and after a three-month period of therapy in a headache centre (HC).

Patients and methods All the patients admitted to our HC within 48h after discharge from an ED were included. At admission to our HC, patient data were collected on the basis of International Headache Society 2004 criteria (ICHD-II) and they underwent the Migraine Disability Assessment (MIDAS) (T0). A clinical evaluation was performed at 30 (T1) and at 90 (T2) days from baseline, and at the T2 visit, disability was again re-evaluated with the MIDAS scale.

Results Out of 252 patients admitted to our HC, 202 (47 M/155 F; age 36±14 years) met ICHD-II criteria for migraine or its complications (e.g. status migrainosus and/or chronic migraine). Seventeen percent of migraineurs had previously seen a headache specialist and 13% had used a triptan before. We observed a T2 follow-up visit in 52% of migraineurs. From a clinical point of view, we observed a significant reduction in days/months with headache from 15 at T0 to 5 at T2 ($p<0.001$). In regards to MIDAS, high level grades at baseline visit (65% of migraineurs at grade IV) and a significant reduction of the MIDAS scores at T2 follow-up visit ($p<0.0001$) were found.

Conclusions Our data confirm that migraine represents the most frequent primary headache observed in ED and that it is an under-diagnosed and under-treated pathology associated with a high level of disability. In fact, the high percentage of "treatment naïve" patients may be the main factor responsible for the disability of this peculiar migraine population. The reduction of headache frequency after 3 months of headache centre therapy together with the improvement in quality of life as observed in our migraine population support the importance of a strict collaboration between the HC and the ED in the diagnosis and therapy of primary headaches.

"HEADACHE WEEK": A MEETING BETWEEN PATIENTS AND EXPERTS

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Objectives To better understand patients' questions about their headache, we held free meetings in a headache centre for one week.

Methods In a headache centre, several pain experts were available to answer questions from patients about paediatric and adult headaches by phone, mail or direct contact. This "Headache Week"

was publicized through journals and posters in hospitals and medical offices.

Results During the week 182 people contacted us, 113 by phone, 58 by direct contact and 11 by mail. Thirty-three questions regarded paediatric headaches, 127 were made by patients under 55 years of age and 22 by patients over 55 years. One hundred and thirty-six were females and 46 were males. In this group 133 subjects had migraine, 19 chronic daily headaches, 26 unclassifiable headaches, and 4 other primary headaches. The most surprising data were that 78% of the population, even though suffering from high frequency headaches for several years, had never visited a headache centre or specialist and had never followed a preventive therapy for their headache. The major question concerned where they could be visited. Only 22% of the subjects had been just visited in a headache centre or by a neurologist or other pain specialist. The other most frequent questions regarded information about other headache centres, new preventive and symptomatic therapies and potential vascular risks factors.

Discussion These data suggest that our initiative to carry out a "Headache Week" has been surprisingly useful, not only to answer questions regarding doubts or curiosities by subjects who had only been visited by a pain specialist but also to identify the population of headache patients who had never gone to a specialist and who often relied on self-medication, risking pharmacological abuse of symptomatic drugs. The scientific data show that 30% to 70% of headache patients has not been visited by the doctor and that only 4% had gone to a pain specialist. For these reasons, similar initiatives can probably help to direct these patients to a headache centre and to better inform the general physicians about the headache centres and the usefulness of a correct symptomatic or prophylactic therapy for headaches.

CLINICAL ASPECTS OF HEADACHES II

INCREASED VARIANTS OF THE CIRCLE OF WILLIS IN MIGRAINEURS

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In recent years, some authors have described an increased proportion of patent foramen ovale in migraineurs, suggesting the possibility of a dynamic mechanism in sustaining migraine. Other authors have reported an increased number of lacunar lesions in some categories of migraineurs, without any reasonable source of the lesions themselves. In consideration of this information, we studied over 100 patients with different types of headaches. We recruited 131 patients with headache and 18 controls, recruited among patients who underwent MRI for other reasons. Among patients with headache, 68 patients were migraineurs, 25 had migraine plus another type of headache, and 38 had a different type of headache. Thirty (44%) of migraineurs had anatomical variants of the circle of Willis; in this group, 9 had ischaemic cerebral lesions, whereas only 3 of 13 were without variants. Among the group of patients with both migraine and another type of headache, 40% had anatomical variants, whereas only 21% of patients with other types of headaches and 18% of controls showed anatomical variants. The significantly higher percentage of anatomical variants of the circle of Willis in patients with migraine supports the hypothesis that vascular dynamic alterations are associated with migraine; it may be either an epiphenomenon with possibly a gene-related linkage, or due to the presence of an anatomical arterial abnormality that could influence headache through vascular dynamic modifications.

THE ROLE OF NEUROIMAGING IN THE EVALUATION OF HEADACHE PATIENTS: IMPLEMENTATION AND VALIDATION OF THE ITALIAN DIAGNOSTIC GUIDELINES

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Introduction In 2001 the Ad Hoc Committee of the Italian Headache Society published the Italian Diagnostic Guidelines for Migraine and Cluster Headache [1]. They were based on the diagnostic criteria of the International Classification of Headache Disorders and provided additional indications on when neuroimaging procedures are required to formulate a correct diagnosis and to exclude secondary headaches. The primary goal of this study was to implement the diagnostic guidelines for migraine and to validate them on headache patients referring to a tertiary headache centre. The secondary goal was to evaluate the frequency of white matter lesions whose association with migraine is still a controversial matter [2].

Subjects and methods All adult headache sufferers consecutively referred to the Headache Disorder Centre, University of Bari in a one-year period were enrolled. According to the Italian diagnostic guidelines, which were extended also to other types of headaches besides migraine, magnetic resonance imaging was recommended: (a) in the presence of focal signs at the neurological examination; (b) to patients without neurological signs but showing additional risk factors in their headache history (association with systemic and/or neurological symptoms, changes in severity, frequency or clinical features of headache attacks, new onset of headache after the age of 40 years, recent onset, progressive worsening course, headache worsening after Valsalva manoeuvre, and headache not responding to adequate therapies).

Results Specific lesions were found in 13.9% of cases: (venous angioma 1.9%, cerebellar tonsillar ectopy 1.9%, meningioma 0.8%, pineal gland cyst 0.2%, silent stroke 2.7%, aneurysm 1.5%, and pituitary microadenoma 0.4%). Among aspecific lesions, white matter hyperintensities were observed in 15.4% of cases. Among extracranial lesions sinusitis was the most frequent (13.5%). All patients with silent stroke were migraineurs. No difference was found in the occurrence of white matter lesions according to headache type, headache duration, attack frequency, or concomitant therapy, whereas a more elevated frequency was associated with older age, smoking and hypertension.

Discussion and conclusions Our results showed that the Italian diagnostic guidelines are highly sensitive and furnish a correct diagnosis. The finding of specific lesions allows the physician to plan subsequent controls and therapies. These results confirmed that magnetic resonance imaging is not recommended routinely but only in those cases with additional risk factors for secondary headache. The association between silent stroke and migraine suggests that migraine might be a vascular risk factor. The results concerning white matter lesions did not support the hypothesis of a strong link with migraine so further studies are needed on this topic.

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HEADACHE AND EPILEPSY: DIAGNOSTIC CHALLENGE AND THERAPEUTIC OPPORTUNITY

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Introduction Headache and epilepsy are chronic neurological disorders with recurrent attacks [1]. Both can include clinical features, such as: visual disturbances, changes in mood, behaviour, consciousness and focal sensory or motor symptoms/signs. Sometimes the differential diagnosis may be difficult. In other cases the two disorders are associated. The exact prevalence and nature of this comorbidity are not yet well known. In recent years antiepileptic therapy has been extended also to headache prophylaxis. This study was carried out with the aim of assessing the prevalence of headache in patients referring to tertiary centres for epilepsy care and of evaluating the influence of anticonvulsant drugs on headache progression.

Subjects and methods This cross-sectional study was conducted in the Neurologic Clinics of Bari, Milan, Pisa and in the Psychology Clinic of Pisa. A broad sample of adult epileptic patients consecutively referring to the centres was enrolled. Subjects with mental retardation, or any other psychical and/or medical condition that could limit their cognitive performance were excluded. A detailed medical history was collected. Patients underwent physical and neurological examinations, and when necessary, appropriate diagnostic testing. All patients were asked the following question: “have you ever suffered from headache?” If the answer was “yes”, a specific headache questionnaire was administered. Headache was diagnosed according to the criteria of ICHD-II [2]. Headache was considered as chronic when attack frequency was 15 days or more a month for at least 3 months. Data were analysed by means of SPSS 11.0 for Windows.

Results About 23% of patients complained of headache attacks related to seizures; in particular, 5% of headache attacks developed during a seizure, 30% of them were preictal and 65% were observed in the postictal period, while for the most part attacks were migraine-like. Headache and epilepsy were comorbid in 29% of patients. Epilepsy followed by headache occurred in 60% of patients. Headache onset followed by epilepsy onset was observed in 20% of patients. In the remaining 20% of cases the two disorders began at about the same time. The prevalence of migraine was about 12%. No chronic headache was observed in the sample.

Discussion and conclusions Results confirm that headache and epilepsy are strongly associated. Neuronal hyperexcitability and low attack threshold might be involved in both disorders. In this sample, chronic headache prevalence was lower than in the general population [3], suggesting a possible protective role of antiepileptic drugs not only toward epilepsy but also toward headache progression.

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MIGRAINE WITH AURA AND ISCHAEMIC STROKE

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Migraine with aura is considered a risk factor for ischaemic stroke in young people. The relative risk increases in the presence of additional factors, such as smoking, oral contraceptive therapy, and alterations of

coagulability, particularly activated protein C resistance and factor V mutation. A 39-year-old man was admitted to the Emergency Department because of the onset in the previous 5 hours of a severe pulsating headache accompanied by nausea, vomiting, photo- and phonophobia. Hemianoptic visual disturbances and a left hemisindrome preceded the headache phase. He previously suffered from sporadic hemiplegic migraine, according to the ICHD-II criteria. The persistence of the neurological symptoms and the worsening of the headache, despite the abortive treatment with triptans, which usually resolved the crisis, led the patient to medical observation. The neurological examination confirmed the presence of a left hemisindrome with a homonymous hemianopia; consequently, a direct brain CT scan was performed, which did not reveal any alteration. The presence of an ischaemic stroke in the region of the right middle cerebral artery was detected with a second brain CT scan, performed 20 hours after onset of the symptoms. Routine laboratory tests, auto-antibodies (including antiphospholipid antibodies), homocysteinemia, ECG, transthoracic and transoesophageal echocardiography, and Doppler ultrasound of the supraortic and intracranial vessels resulted normal. An activated protein C resistance led to investigate the presence of a factor V mutation, which revealed a homozygous point mutation, G-A1691. In the following days, the neurological examination improved, and the patient was discharged with anticoagulant therapy. Although several studies indicate a relationship between genetic prothrombotic abnormalities and migraine, this correlation is not demonstrated by definitive evidence. Nevertheless, it is useful to perform a complete haemocoagulative screening in patients suffering from migraine with aura. Furthermore, the persistence of aura symptoms in patients with a well-known diagnosis of migraine with aura should be carefully investigated.

MIGRAINE AND MULTIPLE SCLEROSIS: THE ROLE OF BRAINSTEM DEMYELINATING LESIONS IN THE CAUSATION OF HEADACHE

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Background Few studies investigated the prevalence of migraine, diagnosed according to the diagnostic criteria of the International Headache Society (ICHD-II), in patients with multiple sclerosis (MS). In case-control studies, prevalence was significantly higher in MS patients than in controls and ranged from 21% to 27%. Some studies have highlighted the role of brainstem grey matter dysfunction in generating migraine attacks. In patients with MS, the brainstem is frequently affected by demyelinating lesions, which could interfere with brainstem antinociceptive functions.

Objective To study, by quantitative analysis of MR images, the extension of demyelinating lesions in the brainstem of patients with MS (diagnosed according to McDonald's Criteria) with or without migraine. **Patients and methods** Eighty-one patients (53 F and 28 M) with MS underwent a 1.5 tesla brain MRI examination of the brain. Axial images were obtained with 5mm slice thickness using PD/T2 weighted SE sequences. T2-lesion load (LL) was calculated by an investigator blinded to patient's clinical status using a highly reproducible, semiautomated local thresholding technique for lesion segmentation. Migraine was diagnosed according to the ICHD-II.

Results Fifteen of 27 (55.5%) MS patients with migraine compared with 25/54 (46.3%) MS patients without migraine had demyelinating lesions in the brainstem ($p < 0.05$). The OR for a MS patient with a demyelinating lesion in the brainstem suffering from migraine was 1.45 (C.I. 95% 1.15-1.8). Brainstem mean T2-LL did not differ in MS patients with or without migraine (0.222 ml vs. 0.175 ml, $p = NS$). No differences were found between MS patients with or without migraine when calculating the mean T2-LL separately in the midbrain, pons, and

medulla oblongata. There was no relationship between the predominant side of migrainous headache and the demyelinating lesion side in the brainstem.

Conclusions MS patients with demyelinating lesions in the brainstem are at risk for migraine. The extension and the side of demyelinating lesions seem to have less impact.

PHARMACOEPIDEMOLOGY OF DRUG USE IN HEADACHE PATIENTS: COMPARISON BETWEEN SUFFERERS OF MEDICATION-OVERUSE HEADACHE AND MIGRAINE

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Introduction Chronic headache patients often overuse symptomatic drugs while episodic headache patients usually take drugs in a very cautious way. It is unknown if the differences between the two groups of headache sufferers concern only the amount or also the type of drug used.

Objective Our aim was to compare the pharmacological habit between medication-overuse headache (MOH) and migraine patients.

Subjects and methods We compared all drugs taken by (a) 138 MOH patients (F/M=5.3; mean age \pm SD: 51 \pm 7 years), consecutively admitted to the in-patient ward of the Headache Centre of the University of Modena and Reggio Emilia, and; (b) 78 migraine patients (F/M= 2.3; mean age \pm SD: 37 \pm 10 years) consecutively referred to the outpatient ward of the Centre. Data were collected by means of a standardized clinical chart and recorded in an appropriate database. The study was carried out between June 2004 and March 2005.

Results There were large differences in the types of symptomatic medications used between MOH and migraine patients. In particular, MOH patients concomitantly took more than one type of symptomatic drug: triptans, 43.5%; NSAIDs, 42%; association of indomethacin, prochlorperazine and caffeine (IPC), 14.5%; and weak opioids, 10%. Migraine patients used: NSAIDs, 56%; triptans, 30%; IPC, 5%; and other analgesic combinations, 2.6%. In both groups, the most used drugs were nimesulide and sumatriptan, respectively, among NSAIDs and triptans. Fifty-eight percent of MOH, and only 20% of migraine patients were following prophylactic treatments. More than 71% of MOH patients were also using other medications: antihypertensive agents, 27.5%; benzodiazepines, 27%; antidepressants, 23%; hormones, 23%; antileptic agents, 7%; and antiplatelet agents, 6%. Among migraine patients, 54% were also using other medications: hormones 33%; antihypertensive agents, 8%; antidepressants, 10%; and benzodiazepines, 5%.

Conclusions Even if MOH often evolves from migraine, our study indicates that the pharmacoepidemiology of drug use was different between the two headache forms: MOH patients overused triptans more than NSAIDs and took multiple medications; migraine patients took mainly NSAIDs for acute treatment, did not use weak opioids, and took fewer other medications.

CLINICAL ASPECTS OF HEADACHES III

MEASURING THE DISABILITY IN MIGRAINE

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Disability has been defined by the World Health Organization (WHO) as "any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being". In 2001,

WHO published the annual World Health Report, using the methodology of the Global Burden of Disease study. In this Report, WHO identified migraine among the top 20 leading causes of years of life lived with disability (YLDs) in all ages, ranking 12th in females and 19th in both sexes. Disability refers to the impact of illness on the ability to work and function in various settings and roles. Information on disability in migraine complements the diagnosis by helping the physician to assess the need for treatment. Reduction in headache-related disability is one of the main goals of the US Headache Consortium Guidelines, which recommend a stratified care approach based on the level of disability. To measure the impact of migraine, parameters must be defined that capture the personal burden on the sufferer and the economic burden on society. Disability in headache sufferers can be measured with a variety of generic and specific instruments. Generic tools address a broad range of life aspects related to health. These instruments can be used for many diseases and allow for comparison with healthy controls and other disease populations. However, the generic instruments are often too broad-based to be responsive to changes in a particular disorder. The specific tools address in-depth issues more focused on patients' concerns and are more likely to be responsive to therapeutic interventions. The most commonly used generic instruments are the Medical Outcome Study 36-item Short Form (SF-36) and the more recent versions, SF-12 and SF-8. Among the various specific instruments, the following tools have been most extensively studied and used: the Henry Ford Headache Disability Inventory (HDI), the Migraine-Specific Quality of Life Measure (MSQOL), the Migraine-Specific Quality of Life Questionnaire (MSQ) and its reviewed new version (MSQ Version 2.1), the Migraine Disability Assessment (MIDAS), also modified for children and adolescents (PedMIDAS), the Headache Needs Assessment (HANA), and the web-based Headache Impact Test (HIT) and its derived paper-based short form HIT-6. The use of impact instruments can improve communication between patients and physicians, aid in the assessment of migraine severity and in the prescription of an individualised treatment plan in concert with other clinical assessments, and in the monitoring of the response to therapy.

COMORBIDITY IN MIGRAINEURS IN COMPARISON WITH PATIENTS AFFECTED BY DIFFERENT TYPES OF HEADACHES

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We evaluated 152 consecutive patients referred to the headache service of our hospital, recording any diseases other than headache in order to identify any differences in prevalence of such pathological conditions that could be related to migraine. Of our patients, 84 (70 F, 14 M) were affected by migraine, 26 (23 F, 3 M) by migraine plus another headache type, and 42 (31 F, 11 M) by headache different from migraine. Among the migraineurs, 15 patients had no other pathologies, of whom only 1 patient had a headache frequency of more than 15 days per month, and 3 had a headache frequency of 10 days per month. Among the patients with migraine and another headache type, only 1 patient did not have any other disease, and only 2 patients affected by another headache type did not have other diseases. Different categories of diseases were evaluated in all groups (disorders of coagulation, orthopaedic, facial, cervical and spinal disorders, ophthalmic and otorhinolaryngoiatric, systemic diseases, psychiatric disorders, epilepsy, pathologies that provoke brain lesions, metabolic and endocrinologic diseases, and others). Comorbidity did not differ in the

three patient groups, except for the absence of additional pathologies in patients with migraine with low frequency of headache. This suggests that migraine is primarily an episodic disease, that is, its worsening should be correlated with the common causes of other headaches.

THE INFLUENCE OF PSYCHIATRIC COMORBIDITY ON MIGRAINE-RELATED DISABILITY IN A CLINICAL POPULATION OF PATIENTS WITH MIGRAINE WITHOUT AURA

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Background Previous studies have revealed that migraine-related disability, as measured by the MIDAS Questionnaire, does not reflect only migraine intensity and frequency. Factors other than migraine severity may play a role in determining individual variation in disability levels. **Objective** To define predictors of migraine-related disability in patients referred to a specialty headache clinic focusing on psychiatric comorbidity and personality characteristics.

Results Two hundred and thirty-three consecutive patients, suffering from migraine without aura, were evaluated using MIDAS, BDI for depression symptoms, STAI – T and STAS – T for trait anxiety and anger, TAS – 20 for alexithymia and SCID-I for the categorical diagnosis of axis I psychiatric disorders. Multiple regression analysis showed that disability was higher in those patients experiencing a higher number of headache days per month, more severe pain intensity, more severe depressive symptoms, and more prolonged migraine attacks. Other independent predictors of the total MIDAS score were female gender and having a full-time employment. The model was highly significant ($F=18.96$, $p<0.00001$) and explained 35% of the observed variance (adjusted R^2).

Conclusions Our findings demonstrate that, with the exception of depression symptoms, psychiatric comorbidity has a limited influence in modulating the impact on everyday functioning.

ACCOMPANYING SYMPTOMS AND PSYCHIATRIC COMORBIDITY IN MIGRAINE AND TENSION-TYPE HEADACHE PATIENTS

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Introduction It is well known that headache is frequently accompanied by physical and psychiatric complaints. The association between headache and psychiatric disorders has been extensively explored, the most common being anxiety and depression, as demonstrated by epidemiological and prospective studies. The aim of this study was to assess in patients with migraine and both episodic and chronic tension-type headache the prevalence of accompanying symptoms and their relationship with depression and anxiety.

Patients and methods A psychological assessment (Axis I, DSM-IV) was performed and 21 accompanying symptoms were investigated in 506 patients with: episodic migraine (EM, $n=231$), chronic migraine (CM, $n=102$), episodic tension-type headache (ETTH, $n=83$) and chronic tension-type headache (CTTH, $n=90$). The following issues were analysed: differences in number of symptoms among the groups and in patients with and without psychiatric comorbidity (respectively, by means of the Kruskal-Wallis test and the Mann-Whitney Rank Sum Test); relationship between symptoms and headache type (by means of a Discriminant Analysis and a Logistic Regression Model); and association between symptoms and psychiatric comorbidity (by means of the Fisher Exact Test).

Results Among the groups, the mean number of symptoms did not differ significantly, but it was significantly higher in patients with psychiatric comorbidity. The following associations were found: tinnitus, cramps with EM; back pain with ETTH; vaginism/frigidity, circulatory disorders and nail/hair fragility with CM; and oral parafunctions with CTTH. Psychiatric comorbidity was significantly associated with most of the symptoms, especially in EM.

Discussion Our results confirm that in a large and homogeneous cohort of patients with migraine and both episodic and chronic tension-type headache, a remarkable number of accompanying symptoms, most of them psychosomatic in nature, are frequently reported. The finding of a significant association between depression and/or anxiety and most of the symptoms clearly suggests that, in migraine patients, psychiatric comorbidity may consistently affect the burden of accompanying symptoms.

Conclusions In conclusion, depression and anxiety in headache patients and particularly in EM, play a significant role in the expression of physical complaints, whose increased burden could represent a factor by which psychiatric disorders may influence the migraine history, thus facilitating its chronicity. This is also relevant for correctly planning treatment strategies.

COGNITIVE FUNCTIONING IN SIDE-LOCKED AND SIDE-SHIFTING MIGRAINE PATIENTS

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Introduction One of the main features of migraine is represented by the unilateral location of pain during attacks. Nevertheless, the data regarding the constancy and the frequency of the unilateral location of pain suggest that only 20% of patients report unilateral pain persisting for the whole attack, thus, a side-locked location is infrequent. There is little evidence regarding cognitive functioning in migraine patients. Namely, possible differences in the cognitive profile between migraineurs with right and left side-locked pain have rarely been explored. The aim of the present study was to investigate the relationship between the unilateral pain (with or without side-shifting) and neuropsychological assessment in patients with migraine.

Patients and methods We recruited 35 patients (28 females and 7 males) (mean age 38.0 years, range 20–56; mean disease duration 18.5 years, range 1–37) affected by migraine without aura (MO) ($n=30$), migraine with aura (MA) ($n=2$), or both MA and MO ($n=3$) with unilateral pain during attacks. Patients were not receiving preventive treatment and had a monthly frequency of 2–8 attacks over the 12-month period preceding the evaluation. Neuropsychological assessment was obtained using 24 standard tests and a computerized task to investigate verbal and visual-spatial short-term and long-term memory, executive functions, visual-spatial and language abilities, abstract reasoning and attention processes. Patients were divided into 3 groups according to the location of pain: right side-locked patients ($n=17$), left side-locked patients ($n=11$), and right-left side-shifting patients ($n=7$).

Results No statistically significant differences were found in neuropsychological test scores among groups (One-way ANOVA; all $p>0.10$). Moreover, no correlations were found between cognitive tasks and any of the clinical features (i.e. age at onset of migraine, mean disease duration, and mean attack frequency) ($p>0.10$).

Conclusions In conclusion, our preliminary data suggest that neuropsychological performances in migraine patients seem to be not related to the side of pain, although strictly unilateral.

DIAGNOSTIC CRITERIA OF TENSION-TYPE HEADACHE

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Introduction The "tension-type headache" is one of the most common forms of headache: it has a lifetime prevalence of 69% in males and 88% in females [1]. At present, the treatment for patients who suffer from these disorders has increasingly required the need of a collaborative team approach. The differential diagnosis is based on clinical criteria regarding quality, localisation, and pain duration as well as lack of autonomic symptoms.

Materials and methods According to the International Classification of Headache Disorders, (ICHD-II), "tension headache" belongs to the "primary headache" forms and is distinguished according to the frequency of attacks in "episodic sporadic headache" (EsTTH); "episodic frequent" (EfTTH) or "chronic" (CTTH). A common characteristic of the three forms is the frequent connection with tension and/or pain of the cranio-cervico-mandibular muscles, which is often related to hypertrophy, dysfunctions, dental abrasion, mandibular movement limitation or dental malocclusion [2]. It is very important to identify and correctly diagnose possible dental elements involved in the field of headache disorders in order to begin correct therapy. To attain this goal, our team prepared a specific protocol including medical history, clinical and instrumental examinations.

All the patients underwent clinical examination in two phases by the same examiner:

- Extra-oral examination included recordings of pain in the jaw, temples, face, preauricular area or inside the ear, at rest or during activity, combined with tenderness on palpation of the masseter, anterior temporalis, sternocleidomastoid, and anterior digastric muscles.
- Intra-oral examination focused on health and dental failure, dental mobility, occlusion according to Angle's classification, transversal, vertical or anteroposterior malocclusion, even with interference or alteration of mandibular movement.

Physical tests were performed, such as the "provocation test", the "end-feel test", or the "dynamic or static test", which can indicate differences between muscle or joint disorders [3]. To formulate a correct diagnosis, other helpful supplementary investigations should be used, such as radiological examination (OPT, condylar radiography, magnetic resonance imaging of TMJ, CT) and instrumental examinations (superficial electromyography, cinematic analysis and T-SCAN). Electromyography is used as a method of investigating muscle activity at rest and during function.

Discussion and conclusions Stomatognathic system disorders may be an important factor in the aetiology or symptomatology of tension-type headache, which is often connected to psychological or pathophysiological factors of the patients, encouraging the resolution or the duration of the disorder. It is evident how the cooperation between specialists of different medical fields is essential for establishing an efficient therapy and a satisfactory remission of the disorder's symptomatology.

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CASE REPORTS I

DID MICHAEL BULGAKOV SUFFER FROM MIGRAINE?

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Michail Bulgakov (1891–1940) is considered one of the major Russian contemporary authors. He graduated in medicine but left the medical profession three years later, after the publication of his first work in a local journal. His masterpiece, “The Master and Margarita”, published posthumously, is structured in different levels, apparently disconnected, but flowing into a unique design, that sees the eternal opposition between good and evil. Part of the tale takes place in the palace of the Roman governor of Palestine, Pontius Pilate; despite a terrible headache, he has to judge a young Jew, Jeshua Hanozri, condemned to death by the Synedriion. The governor is aware of the beginning of his headache, because it starts with an intolerance to a particular odour, the smell of rose oil. Furthermore, it is possible to note the typical symptoms of the migraine attack from the behaviour of the governor during the trial: photophobia, phonophobia, aggravation with routine physical activity, instinctive manoeuvres to alleviate the pain intensity, and effort to maintain an acceptable concentration. It is possible that Bulgakov, during the years he worked as a physician, directly saw a migraine attack, and that the description of Pontius Pilate’s migraine is a consequence of his medical experience. However, some specifics should be given in such detailed manner only by a migraineur: the osmophobia (not yet inserted in the present IHS diagnostic criteria), the instinctive manoeuvres, and the incapacitating intensity of pain. The rich details that Bulgakov includes in the description of Pilate’s migraine, besides being an elegant literary description of this ailment, should be considered as evidence that he suffered from migraine.

CLINICAL OUTCOME OF HYPNIC HEADACHE

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Introduction Hypnic headache (HH) is a primary headache, which occurs exclusively during sleep. At the time of this writing, 87 patients with this disorder have been described. The natural history of HH is not well known. It is assumed that it tends to be chronic unremitting, but only 25 patients have been observed for at least 2 years. To better comprehend the outcome of HH, we have prospectively followed 7 patients for a period ranging from 2 to 6 years.

Results We diagnosed 7 patients (6 females and 1 male) with HH. *Case 1:* 76-year-old female, the headache started in 1998 and was chronic from the onset. She died in 2004, due to cerebral haemorrhage. *Case 2:* 72-year-old male with a previous history of migraine, the nocturnal headaches began in 1996 and had an episodic pattern, with two different active periods until now, each period lasting about 6 months. *Case 3:* 66-year-old female with a long history of migraine, the nocturnal attacks started in 1999 and occurred in bouts of 2–3 months with intervening spontaneous breaks of 4–5 months. *Case 4:* 74-year-old female, the headache began in 2000 and was chronic from the onset. *Case 5:* 67-year-old female with previous migraine headaches, the attacks started in 2000 and remained chronic on a nightly basis over the following years. *Case 6:* 64-year-old female, affected by chronic migraine. In 2003, she had a prolonged period lasting 8 months of nocturnal headaches fulfilling the International Headache Society (IHS) criteria for HH. During the active period of HH, she did not report migraine attacks, which recurred with the previous usual characteristics when the HH spontaneously ceased. *Case 7:* 53-year-old female, suffering from chronic migraine. In 2003, she had a protracted period of exclusively nocturnal headaches, meeting the IHS criteria for HH, with concurrent disappearance of migraine attacks. This period lasted for 4 months, then the HH attacks spontaneously disappeared and the migraine headaches relapsed with the same previous clinical features.

Discussion Four of the seven patients with HH showed an episodic pattern, with active periods followed by complete remissions; two

patients had only a single bout until now. In 5 patients, HH was strictly associated with migraine; in 3 cases, there was a history of previous migraine headaches, and in the remaining two patients, a bout of HH intervened in the course of chronic migraine, with concurrent, temporary, complete remission of migraine attacks.

MIGRALEPSY: A CASE REPORT

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Migraine and epilepsy are two paroxysmal disorders with epidemiological and clinical comorbidity. The mechanisms underlying this association are not clear; it is hypothesized that the occipital cortex in migraineurs has a low excitation threshold, which may trigger the seizures. In addition, during migraine with aura, there are changes in cerebral perfusion that could trigger subsequent seizures. Whereas migraine-type headache is not uncommon following a seizure, a seizure only rarely hits during or after a migraine attack. This phenomenon, defined as “migralepsy”, has been described in subjects affected by migraine with aura, and the diagnostic criteria have been incorporated in the ICHD-II 2004. We report a 36-year-old female patient with congenital hypoxic encephalopathy and repeated episodes of migraine with aura with associated seizures (migralepsy). The patient was the first child, born prematurely (8th month) for dystocia by forceps delivery. The first generalized convulsive seizure occurred at 3-years of age. Psycho-physical development was normal, she is married with one child, and works at a news stand. She underwent antiepileptic therapy with phenobarbital for occasional seizures until age 10 with no additional seizures. Thereafter, at age 31, she experienced a visual deficit in the left hemifield (“I saw a top spinning”), which resolved in about 20 minutes and was followed by a diffuse headache, pulsating, particularly severe, associated with nausea and vomiting, and exacerbated by physical activity. After about an hour, the patient suddenly lost consciousness and fell to the ground, with clonic spasms involving all limbs. The patient was brought to the Emergency Department where another generalized tonic-clonic seizure occurred. Routine laboratory testing, ECG, and chest X-rays were all normal. Brain-MRI revealed a picture compatible with perinatal hypoxic damage. The EEG showed modest signs of irritative alterations in the right temporal lobe. Valproate 600 mg/day was prescribed. Since then, she has presented 5 similar episodes of migraine with aura, followed by secondarily generalized seizures beginning as focal motor manifestations on the left side. Migralepsy disappeared (follow-up at 9 months) by increasing valproate to 1800 mg/day and adding levetiracetam 1000 mg/day. Migralepsy is a rare phenomenon. Two cases have been described with reversible MRI abnormalities during the crisis, which suggests an inherent overlap in the underlying pathophysiology of these events.

AMAUROSIS AND HEADACHE AS THE FIRST CLINICAL EVIDENCE OF MULTIPLE SCLEROSIS

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A 13-year-old patient presenting with amaurosis and headache was shown by neuroimaging to have demyelinating lesions in the brain. This case offers the opportunity to consider rare causes of secondary headache presenting only with clinical features of migraine with aura.

A CASE OF HEADACHE THAT HAS TO BE DEFINED

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Introduction Precise official indications exist to aid us in headache diagnosis. Despite the existence of the IHS classification, several cases often cannot be classified into precise nosological entities, either due to the variability of signs and symptoms or to therapeutic efficacy.

Case report We describe the case of an 87-year-old woman, who suffered from an intolerable headache, which was located in the left supraorbital region. During 4 months of observation, its location remained constant, but its characteristics and associated signs instead changed. The onset was unexpected and coincided with the positioning of a dental prosthesis in the left upper dental arch. Pain was preceded by cutaneous reddening, without pruritus, in the left orbital area accompanied by prominent lacrimation of the ipsilateral eye. The prickly and stabbing pain lasted about 1 or 2 minutes every day; the attacks occurred, at a set time (2 and 9 pm), with a frequency of 30 to 40 per day. After a few days of medical therapy (amitriptyline), the frequency and form of the crises changed: a 3-hour persistent, stabbing and burning pain alternated with transitory crises lasting 30 minutes without autonomic features. After medical therapy with amitriptyline had been suspended for excessive sleepiness, a week of well-being followed; afterwards, 2 crises of lancinating pain, lasting 120 minutes, occurred 4 days apart and were treated with indomethacin, prochlorperazine, and caffeine. Clinically, we noticed an ache at the epicranial emergence points of the unilateral trigeminal nerves. The patient was given a series of anaesthetic blocks of the epicranial nerves, which produced at first, the appearance of abortive crisis, followed by complete and persistent remission.

Conclusions This case is a fine example of changeable characteristics and various coexisting manifestations, which prevent us from reaching a precise diagnosis (according to the present classification). Generically, we can consider this condition a cephalalgic form, denominated short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) with pain length and autonomic features. However, current indications regard the response to indomethacin as a fundamental feature in the differential diagnosis with chronic paroxysmal hemicrania. Examining our case further, we observe that some characteristics (periodic crises during the day, fixed-sided distribution and stabbing-type pain) are pathognomic elements of cluster headache. We cannot identify an exact form, or even the existence of concomitant forms, because of the various and changeable aspects which coexist in this case. This is a further confirmation of a growing doubt: headaches represent a world that is yet to be defined. Thus, indications used to determine diagnoses are not realistic representations, apart from a few exceptions.

NEW DAILY PERSISTENT HEADACHE AND PRIMARY STABBING HEADACHE: A CASE REPORT

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New daily persistent headache (NDPH) is a new entity, included in the revised international classification of headache disorders (ICHD-II) among other primary headaches (chapter 4). The main feature of this form of headache concerns its temporal pattern, which is chronic from the onset. Data regarding epidemiology, pathophysiology, and treatment of NDPH available in the literature are quite poor. Primary stabbing headache (PSH) is a well-known form of

headache, codified in chapter 4 at the first diagnostic level, frequently experienced by migraine (40%) or cluster headache (30%) patients. We present the case of a 37-year-old woman who came to our attention complaining for four months of a dull, mild-intensity, diffuse headache without any accompanied signs or symptoms, and not exacerbated by physical activity. She referred with great precision the day of onset of her headache. From the beginning, the headache presented daily and was responsive to administration of simple analgesics. Nevertheless, the patient rarely took drugs for treating her headache, as it was not disabling. Furthermore, she referred the contemporary onset of head pain occurring as a series of stabs, in the temple and parietal areas with an alternation of side, lasting less than three seconds, recurring 2–4 times a day, and not accompanied by any other symptom or sign; the frequency of this pain was not regular. General and neurological examinations were normal. A brain MRI was performed that did not show any significant alteration. As a preventative treatment, she was prescribed amitriptyline 30 mg/day with a gradual, net improvement of headache frequency. To our knowledge, this is the first case of an association between NDPH and PSH, both forms responding to preventative treatment with low dose amitriptyline.

CASE REPORTS II

THUNDERCLAP HEADACHE BY SPONTANEOUS INTRACRANIAL HYPOTENSION

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Objective To demonstrate that thunderclap headache (TH) may be the initial manifestation of spontaneous intracranial hypotension (SIH) caused by a CSF leak [1].

Background An excruciating headache of instantaneous onset is known as TH. A subarachnoid haemorrhage is the prototypical cause, but other serious disorders may also present with TH, including cerebral venous sinus thrombosis, carotid artery dissection, and pituitary apoplexy. We report a group of patients with TH as the initial manifestation of SIH caused by CSF leak.

Design/methods We evaluated 24 patients with SIH between 1992 and 2004. Four of them (16%; 3 females and 1 male, mean age 31 years, range 25 to 43) initially experienced an excruciating headache of instantaneous onset. One patient was affected by Marfan's syndrome.

Results Excruciating pain lasted from 10 seconds to a few minutes. The pain was described as head swelling or like a hard blow to the head, followed by gravative occipital-nuchal and frontal orthostatic headache. Mild neck stiffness was present in 1 patient. Patients were studied with CT, cerebral angiography (1 patient), and MRI angiography (1 patient), all of which were unremarkable. The patients were also examined with lumbar puncture (3 patients), brain gadolinium MRI, spinal MRI and MRI myelography (3 patients), CT myelogram (1 patient), and radioisotope cisternography (1 patient). CSF pressure was low. Brain MRI showed diffuse pachymeningeal enhancement in all patients. CSF leakage was demonstrated gadolinium in only 1 patient at the cervical level. Three patients received supportive measures only (bed rest, analgesics, and hydration). The patient with cervical CSF leak underwent epidural blood patch.

Conclusions We suggest that SIH should be included in the differential diagnosis of thunderclap headache even when meningism is present.

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A CASE OF CHRONIC PAROXYSMAL HEMICRANIA WORSE- NED BY ABNORMALITIES OF STATIC CERVICAL LOAD

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We report the case of a then 50-year-old menopausal woman, who began to complain of mild, tolerable pain at the temple and in the left orbital and periorbital region, lasting 10–20 minutes and occurring 4–5 times a day. When she was 60-years-old, there was an intensification of the attacks with symptoms of conjunctival injection, lacrimation and ipsilateral rhinorrhoea, although the number and duration of the attacks did not change. At age 62, she underwent a surgical operation to correct an S-shaped scoliosis with application of a support bar along 14 vertebral (T2 to L4). Two months before the operation, while she was wearing a trunk plaster cast, she noticed that the occipital region ached during the attacks. After the operation, the plaster cast was positioned not at the base of the neck but at the base of the head. Immediately after removal of the plaster cast, the attacks got remarkably worse; using a scale from 1 to 10, pain intensity was 10, lasting always 10–20 minutes. The autonomic phenomena were more remarkable, with the number of attacks once every 2 hours during daytime, and once every 3 hours at night (10–11 a day). NSAIDs, gabapentin, and cortisone infiltrations had no effect. When she was 67-years-old, she was visited at our headache centre. The neurological examination was unremarkable with few alterations; brain CT and blood tests were not relevant; the diagnosis was chronic paroxysmal hemicrania [1]. She was prescribed indomethacin 50 mg/day and for the first time in 15 years experienced tangible improvements, with a reduction in the number of attacks to 2–4/day, mitigation of the autonomic phenomena, and reduction in the intensity of pain from 10 to 4–5. During the following years, she continued to use indomethacin at the highest dosage of 100 mg/day with positive effects. The relevant elements in this case are:

1. pain was extended to the cervical area when she wore a plaster cast before the operation;
2. lack of homogeneous distribution of attacks during daytime and nighttime [2];
3. considerable aggravation after the operation on the spinal column and after removal of the plaster cast probably in relation to alterations of the static cervical load.

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MIGRAINE SECONDARY TO SUPERIOR OBLIQUE MYOKYMIA RESPONSIVE TO GABAPENTIN: A CASE REPORT

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A case of migraine secondary to superior oblique myokymia (SOM) is reported. SOM is characterized by intermittent, small-amplitude, monocular, paroxysmal, high-frequency oscillations. These oscillations are mainly torsional in the primary gaze position and in abduction and evoke oscillopsia during paroxysms. The pathophysiology of this condition is not clear; often the patients are otherwise healthy, sometimes vascular compression of the IVth cranial nerve may be responsible, and rarely there are other neurologic diseases. A 27-year-old male with a negative clinical history, reported that four years ago he started experiencing a "tremor" of the left eye. The duration of the initial symptom

was 1 to 2 minutes, with periods of spontaneous remission during the first 2 years from onset; subsequently, the attacks occurred almost daily. The "tremor" was followed by a pulsating headache, which spread from the back of the neck to one-half of the head, almost always on the left side. The intensity was moderate-severe and receded after taking paracetamol or nimesulide orally. The frequency was about 3–4 episodes per week and was triggered mainly in those situations in which he was forced to concentrate. The headache never occurred during the night; it was associated with phonophobia, photophobia, osmophobia, and if of severe intensity, also with nausea without vomiting. The attack lasted a few hours. The eye examination was negative. The condition was so disabling that the patient interrupted his studies. During the years he underwent routine blood tests, ECG, EEG, VEP and BAERS, chest X-rays, CT of the paranasal sinuses and orbits, brain MRI with gadolinium and angio-CT, all with negative results. The Hess-Lancaster Test showed in the left eye hyperfunction of the superior oblique muscle compatible with the diagnosis of SOM. Treatment with baclofen 50 mg/day, levetiracetam 1500 mg/day, bromazepam 3 mg/day, and carbamazepine 600 mg/day for at least 2 months was unsuccessful; gabapentin was then started and progressively increased to 900 mg/day. Once this dosage was reached the myokymia receded, and the patient had no other migraine attacks. Follow-up visits at 3, 6, and 9 months were negative for myokymia and headache. The correlation between the two pathologies is substantiated by the clinical trend of the disorder and by the resolution of the attacks with an effective therapy. This case calls attention to the correlation between migraine and SOM and proposes gabapentin for treatment of this condition.

CLINICAL AND RADIOLOGICAL FINDINGS IN A CASE OF SYMPTOMATIC CLUSTER HEADACHE

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Introduction Cluster Headache (CH) is a primary disorder, defined by the International Headache Society (IHS) classification as a severe unilateral pain lasting 15–180 minutes if untreated and associated with ipsilateral autonomic dysfunction and/or agitation [1]. In recent years, several cases of cluster-like syndromes associated with intracranial pathologies have been described, usually with atypical manifestations [2]. We report a case of cluster-like headache completely fulfilling IHS diagnostic criteria at the time of presentation, with neuroimaging evidence of an organic brain lesion.

Case history A 60-year-old woman presented with a 3-week history of paroxysmal headaches occurring every night at the same hour (about 4:00 AM) and lasting 30 to 90 minutes. The pain was severe or excruciatingly severe, strictly localised in the left temporal region, and accompanied by ipsilateral lacrimation, conjunctival injection, rhinorrhoea, and occasionally, ptosis. The initial physical examination disclosed exclusively a mild left eyelid ptosis. The initial laboratory parameters and CT scan with contrast enhancement were normal. The patient was administered prednisone 50 mg daily, with rapid and complete improvement. Two weeks later, she reported intermittent diplopia and the ptosis worsened. Furthermore, a few days earlier the patient had begun suffering from low back pain. A brain MRI showed an iso/hyperintense area in the anterior aspect of the left cavernous sinus, significantly enhanced by contrast material, consistent with a possible metastatic lesion. In a few days, the ptosis became complete and low back pain worsened; the patient was subsequently admitted to the hospital. The spinal X-ray and total-body CT scan disclosed the presence of diffuse bone and liver metastases. A CT-guided liver biopsy was performed and the histological examination revealed metastasis from an undifferentiated carcinoma of unknown origin. The patient died 35 days after onset of the symptoms. An autopsy was not performed.

Discussion Increasing evidence indicates that pain and autonomic symptoms typical of CH result from activation of the trigeminal vascular and cranial parasympathetic pathways. The circadian rhythmicity of CH is thought to result from hypothalamic dysfunction, with secondary involvement of the trigeminal autonomic pathways, as demonstrated by PET studies [3]. Our case indicates that an organic lesion in the anterior aspect of the cavernous sinus presumably involving the first division of the trigeminal nerve could have triggered the trigeminal autonomic hypothalamic circuitry. CH is a well-defined primary headache syndrome with a peculiar clinical picture that allows a relatively easy diagnosis. Nevertheless, a cluster-like syndrome can be the consequence of a structural brain injury involving primarily the cavernous sinus and the trigeminal autonomic complex. The presence of even minimal unusual aspects must prompt the clinician to seek a secondary cause of CH.

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FAMILIAL TRIGEMINAL NEURALGIA: CASE REPORT

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Introduction Only 20 cases of familial trigeminal neuralgia have been described in the literature, frequently in association with glossopharyngeal neuralgia, Charcot-Marie-Tooth neuropathy, or hypertension and brachydactyly. A mechanism of autosomal dominant transmission is assumed whose relevance still remains uncertain.

Case report We describe the case of a 60-year-old man. Twenty-five years ago, he suffered from paroxysmal crises of severe, burning, lancinating pain in the right V1 and V2 divisions of the trigeminal nerve, associated with trigger points and accompanied by lacrimation. The pain was provoked by mastication and speech. The patient controlled the symptomatology by means of medical therapy (carbamazepine), progressively increasing the dosage because of its worsening, with no results as yet. After diagnostic examinations excluded a secondary cause, we decided at first to continue the medical therapy (carbamazepine+gabapentin), which initially resulted in a partial resolution of the crises in the territory of the first trigeminal branch. Subsequently, we decided to subject the patient to radiofrequency coagulation of the Gasser ganglion, which had a positive outcome. During the taking of the patient's history, we also found the presence of trigeminal neuralgia in the other two brothers. One of his brothers, 70-years-old, also had his first attack when he was approximately 30-years-old, and jolts always interested the same territory of distribution (right V1 and V2 divisions); he underwent alcohol block of the Gasser ganglion 20 years ago, with only 4 months of complete anaesthesia. Currently, he is in pharmacological therapy (carbamazepine) with good control of the symptomatology. The other brother, 64-years-old, had the first attack only 2 years ago, in the same territory of distribution of the trigeminal nerve (right V1 and V2 divisions). Pharmacological therapy (gabapentin) manages to control the symptomatology. The interesting feature is that 40-years ago, he was diagnosed with a form of multiple sclerosis, which is recognized to be one of the causes of secondary trigeminal neuralgia.

Conclusions We believe that the clinical history of the first two brothers can be considered an example of rare familial trigeminal neuralgia; conversely, the third case has to be included in a secondary form of trigeminal neuralgia (connected with multiple sclerosis). However, we

emphasize that multiple sclerosis is a genetic disease. In our opinion, this case is interesting as it can confirm a pathogenetic hypothesis of familial trigeminal neuralgia (autosomal dominant) and, moreover, it suggests the necessity of further studies on penetrance and genetic localization, in order to understand what factors determine predisposition to the development of cranial neuralgias among the same familial nucleus, without stopping at the appeared coincidence of two familial forms and a secondary one among three brothers.

UNUSUAL HEADACHE: THE ONSET SYMPTOM OF ONE CASE OF SPONTANEOUS SPINAL EPIDURAL HEMATOMA

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Spontaneous spinal epidural hematoma (SSEH) is a rare clinical entity [1] and represents a neurosurgical emergency requiring urgent investigation and prompt intervention. We describe one case of SSEH admitted to our department: a 77-year-old woman presented with an intense and incapacitating headache resembling the one attributed to subarachnoid haemorrhage immediately followed by sensory and motor dysfunction. Magnetic resonance imaging (MRI) of the cervical spine revealed a C2-C4 dorsally placed extradural lesion causing significant compression on the thecal sac. A partial C2-C4 and complete C3 hemilaminectomy on the left side was performed. No abnormal vessels were noted during surgery. The patient made an almost complete recovery of the deficits within a week. Although our case was initially suspected as cerebral stroke, a MRI of the cervical spine was performed on the spine and spinal cord in the axial and sagittal sections. SSEH should be suspected in the differential diagnosis of sudden, intense headache and neck pain with radicular radiation, accompanied by variable neurological deficits, and when confirmed by MRI, emergent surgical decompression should be performed. Early diagnosis and immediate treatment are mandatory to obtain good prognosis for patients with SSEH [2]. In most cases, such as ours, emergent surgical treatment leads to complete resolution of the symptoms.

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HEADACHE IN CHILDHOOD AND ADOLESCENCE I

PRIMARY HEADACHE AMONG ADOLESCENTS: CLINICAL CHARACTERISTICS AND PSYCHOSOCIAL CORRELATES

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Objective Headache is a common problem among children in primary school. We evaluated the prevalence of headache subtypes in adolescents, aged 14 to 15 years, in primary school, and their relationship with lifestyle and psychological aspects.

Subjects and methods The study population was screened with a multistage questionnaire between May and June 2004, in 4 primary schools of L'Aquila. Data were collected by means of a screening questionnaire, consisting of 31 items, administered to all students; a clinical interview, based on 33 questions; and the Migraine Disability Assessment Scale (MIDAS), administered to all headache sufferers.

Headache was diagnosed according to the diagnostic criteria of the International Headache Society, 2nd edition. Students without headache were used as controls.

Results Among a total of 151 students examined, 52 (34.4%; 95% CI 26.9–42.0) reported recurrent headache episodes (6 men and 46 women, mean age 15 ± 0.6 years). Migraine without aura (IHS 1.1) was the most frequent diagnosis (50%), followed by probable migraine with or without aura (IHS 1.6) (17.3%), frequent episodic tension-type headache (IHS 2.2) (13.5%), infrequent episodic tension-type headache (IHS 2.1) (7.7%), chronic tension-type headache (IHS 2.3) (3.8%), migraine with aura (IHS 1.2) (3.8%), probable tension-type headache (IHS 2.4) (1.9%), and unspecified headache (IHS 14.2) (1.9%). Emotional disorders were more frequently reported by headache sufferers compared with control subjects: anxiety feelings were mostly associated with tension-type headache (OR=12.6; 95% CI 2.3–67.4), whereas mood disorders were mainly observed among patients with migraine (OR=5.4; 95% CI 2.1–14.0). Insomnia was more frequent in subjects with migraine (OR=2.8; 95% CI 1.1–7.4). A trend towards an increased time spent watching TV was found in patients with tension-type headache (OR=4.3; 95% CI 1.2–15.2).

Conclusions Headache is frequent among adolescents and is mainly related to psychological comorbidity and lifestyle. Assessing headache among adolescents as early as possible is essential in order to plan adequate preventive strategies.

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CLINICAL STUDY AND FOLLOW-UP IN PRESCHOOL AGE CHILDREN SUFFERING FROM PRIMARY HEADACHE

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Introduction In preschool children, the prevalence of headache ranges from 3% to 6% and migraine from 3% to 7.4%; moreover, 25% of migraineurs have their first attack in the preschool period. Goals of this study were to compare two different paediatric age groups of headache sufferers and to evaluate the existence of predictive factors.

Subjects and methods Two groups of subjects were considered: the first group (G1) with early headache onset (<6 years old) and the second (G2) with late onset (12–18 years old). The diagnosis was made according to the IHS 1988 criteria (retrospective study).

Results G1 consisted of 163 subjects, mean age at first evaluation 4.9 ± 0.9 years (range 2–16) and mean age at headache onset 3.8 ± 1.0 years (range 1–5.8), and G2 consisted of 80 subjects, age at first evaluation 14.4 ± 1.4 years (range 12–18) and mean age at headache onset 13.1 ± 1.2 years (range 12–16.5). The male percentage was higher in G1 (58%) than in G2 (39%). The attacks lasted less than 1 hour in 52% of G1 and 15% of G2. Associated symptoms prevailed in G2: nausea (39% vs. 20%), photophobia (70% vs. 52%) and phonophobia (72% vs. 54%), while vomiting was similar (19% vs. 18%). In G1 compared to G2, the diagnosis of migraine (M) was made in 36% vs. 58%, tension-type headache (TTH) in 42% vs. 41%, and idiopathic stabbing headache (ISH) in 10% vs. 1%. In G1, 12% were not classifiable (0% in G2). The diagnosis of migraine disorder 1.7 prevailed in G1 (54%) vs. G2 (22%) as well as tension-type disorder 2.3 (51% vs. 39%). Family history of headache prevailed in G1 (78%) vs. G2 (59%). The mean follow-up of G1 was 3.5 ± 2.7 years (range 0.5–10). The first diagnosis remained the same for 61% of M and 46% of TTH. None of the subjects with episodic TTH became chronic, while 50% of those with chronic TTH became episodic. The prognosis was: remission (21%), improvement (46%), worsening (15%), and stability (18%). Favourable evaluation was superior in TTH and ISH compared to M. Unfavourable outcome was associated with vomiting during attacks.

Discussion This study shows different gender distribution in the two groups as reported in the literature. Our data suggest that preschool age headache has different clinical characteristics. Positive family history represents an additional risk factor for young patients, especially for M. In our follow-up, headache with preschool age onset seems to have a relatively benign prognosis.

OSMOPHOBIA IN JUVENILE PRIMARY HEADACHES

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Introduction The differential diagnosis between migraine (M) and tension-type headache (TTH) is based on ICHD-II criteria (2004), among which the associated symptoms of nausea, vomiting, photo- and phonophobia are very important. Osmophobia (O), commonly described during migraine attacks and reported in the “Appendix” of ICHD-II as a possible accompanying symptom of migraine without aura (MO), has never been studied in childhood headache. The aims of the study were: to evaluate the prevalence of O in juvenile primary headache sufferers in M versus TTH patients; to analyse which attack phase is most frequently associated with O; to verify possible correlations with gender and/or age; to identify the prevailing types of offending stimuli; and to assess whether and which odours might trigger attacks.

Patients and methods We recruited 123 consecutive outpatients referred to the Childhood and Adolescent Centre for Headaches in 2005, mean age of 11.1 years (range 6–18 years), 74 females and 49 males. According to ICHD-II criteria, M was diagnosed in 69 patients (56%; MO 60, MA 9), and TTH in 54 patients (44%; ETTH 46, CTTH 8).

Results Prevalence: during the attacks, 18.7% of headache patients reported O. Gender: O was reported by 65.2% of females and 34.8% of males. Age was uncorrelated with O. Type of headache: O was more frequent in M (21.7%) than in TTH patients (14.9%). Specifically, O was prevalent among male M sufferers (26.9% vs. 18.6%), and female TTH patients (20% vs. 5.3%). The other associated symptoms were: nausea (34.1%; M patients, 78.3% vs. TTH, 3.7%); vomiting (17.8%; M patients, 31.9%); photophobia (63.4%; M patients, 78.3% vs. TTH, 44.4%); phonophobia (61%; M patients, 68.1% vs. TTH, 51.8%). Among osmophobic patients, 74.0% reported O during the attack and 26% prior. The offending odours were perfumes (56.5%), food-related smells (47.8%), smoke (34.8%), and other odours (4.3%). The olfactory stimulus triggered the attack in 43.5% of osmophobic patients, that is, in 8.1% of the entire study population (MO, MA, TTH).

Discussion Our preliminary results indicate that O is present during headache attack also in juvenile primary headaches, particularly in migraineurs, but it seems less specific than in adults. The main offending odour is perfume.

HEADACHE RECURRENCE IN FAMILY AND CLINICAL CHARACTERISTICS: A CLINICAL STUDY ON 200 CHILDREN AND ADOLESCENTS

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Introduction Migraine is a complex disease, where genetics and biology interact with environmental factors, determining a polygenic multifactorial etiology.

Objective The aim of this study was to analyse whether the clinical characteristics of migraine change according to headache familial recurrence compared with other Headache subtypes (oHs).

Subjects and methods Two hundred children (92 M; 108 F; range 4.6–17.9 years) and their parents were enrolled in the study. To record headache history and symptomatology, a semistructured interview (ICHD-II criteria 2004) was carried out. Data were collected on the occurrence of headache in first and (indirectly) second-degree relatives. Chi-square was computed to analyse contingency tables.

Results Cross-checking data on the family history of migraine and oHs, we found that 138 patients (69%) were positive for migraine. Thirty-eight children had no positive family history of either migraine or oHs (19%), whereas 93 children had one parent diagnosed with either migraine or oHs (46.5%) and 69 children had both parents diagnosed with either migraine or oHs (34.5%). Prevalence of headache of any kind in parents was 81%, with a predominance in the family of migraineurs. Twenty-two patients did not have any parents with headache (11% vs. 8% oHs); 42 had only the mother (21% vs. 8% oHs); 25 only the father (12.5% vs. 5% oHs); and 49 had both parents (24.5% vs. 10% oHs). The clinical characteristics and age at onset of migraine were not influenced by the presence of headache in parents, but considering second-degree relatives (double familial loading), differences in headache characteristics were found: aura and photophobia ($p < 0.05$).

Discussion The recurrence of headache in family members strongly suggests a genetic transmission of headache. However, this kind of transmission was studied extensively in migraineurs, even though one study [1] showed a 3.1-fold increased risk of chronic tension-type headache among first-degree relatives of probands with chronic tension-type headache. Our findings underscore the importance of genetic factors (mostly in the maternal line) in migraine, but less for tension-type headache. No difference in clinical phenotype exists in migraine according to familial occurrence, except for aura and photophobia, if double familial loading was considered.

Conclusions Children with migraine have more often first and second-degree relatives with migraine (mainly in the maternal line). Only the symptoms of photophobia and aura seem to show the effect of a likely genetic-related transmission.

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THE COLD PRESSOR TEST: COMPARISON BETWEEN CHILDREN WITH HEADACHE AND THEIR HEALTHY PEERS

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Introduction Few studies have investigated experimentally-induced pain perception in children with chronic painful symptoms, especially psychophysiological reactivity. This type of research may elucidate certain mechanisms occurring in chronically painful conditions [1, 2]. The aim of this study was to assess reactivity to pain induced with the cold pressor test - turning to subjective, behavioural and physiological parameters - in a group of headache children compared with healthy children.

Patients and methods Thirty-two patients affected by recurrent primary headache (15 M, 17 F) (18 with migraine without aura (MO); 14 with chronic tension-type headache (CTTH)) (mean age 10.6 years; SD 1.6), for over 6 months, were compared with the sample of 141 healthy children (77 M, 64 F) (mean age 10.1 years; SD 1.24). In this study a new instrument, validated in a previous research, was used to induce cold pressor pain.

Procedure The child was asked to immerse the arm in water at ambient temperature (Baseline) and a Visual Analogue Scale and Face Scale were administered. After 2 minutes, the child was asked to put the arm into the tank containing cold water at 10°C (Start) and to report the first

pain sensation (Threshold) and intolerable pain (Tolerance). Between these two stages, at 10-second intervals, the child assessed the pain on a scale of 0-10. At the end of pain induction (max 3 minutes), the child again placed the arm in the first tank and repeated the subjective scales (Recovery). During the test, the cardiovascular indexes were recorded continuously and the pressor indexes were measured three times.

Results The mean age of headache children was slightly higher than that of healthy children. The latency times for the pain threshold were comparable in the two groups, whereas the pain tolerance was higher in the headache sufferers. The sensorial and affective assessments, like the trend of the pain, were comparable in the groups. During the painful stimulation, an increase in all the cardiovascular indexes - with the exception of the resistances which diminished - was observed. Although no statistically significant differences emerged, the mean stroke volume values and peripheral resistances tended to be higher in the headache sufferers. The headache characteristics did not influence the children's pain perception.

Conclusions Apart from a greater pain tolerance, reactivity to pain in patients with recurrent headache seems to be much the same as in healthy children. Physiological indicators follow the same trend in the two groups, although minor differences might suggest a hyperfunctioning of the sympathetic nervous system in the headache sufferers.

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HEADACHE IN CHILDHOOD AND ADOLESCENCE II

THE IMPACT OF LIFE EVENTS ON PRIMARY HEADACHE IN CHILDREN AND ADOLESCENTS

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Introduction The relevance of psychological factors as triggers of headache disorders has been extensively outlined, but often without making clear distinction between the occurrence of life events, psychiatric comorbidity, or psychosocial factors. The association between different headache subtypes and the direction of influence between psychological factors and headache is a matter of debate. The aim of this study was to analyse the occurrence of major life events in different headache sub-types.

Subjects and methods To record headache history and symptomatology, we used a semistructured questionnaire with a section on history of life events (e.g. divorce, moving, serious illnesses, etc). This questionnaire was administered to parents to collect data on 187 children and adolescents (range 4.6-17.9 years; 89 M; 98 F) with migraine without aura (MO), migraine with aura (MA), and episodic and chronic tension-type headache (ETTH) (CTTH). Headaches were diagnosed according to ICDH-II criteria (2004). Chi-squares were computed in order to analyse contingency tables.

Results Of 138 migraineurs, 30 (22%) subjects showed significant life events (MO=23; MA=7), and of 49 tension-type headache patients, 15 (30.6%) showed the same condition (CTTH=13; ETTH=2), whereas 40.6% (13/32) of CTTH, 28% (7/25) of MA, 20.3% (23/113) of MO and 11.7% (2/17) of ETTH patients showed significant life events ($p < 0.05$).

Discussion Major life events (divorced, widowed, separated) have been related to headache chronicity in adults [1]. Karwautz et al. [2] showed that migraine was not related to psychosocial factors, whereas

TTH was associated with a higher rate of divorced parents and fewer peer relations. Our findings confirmed the recurrence of life events both in CTTH and MA (the severest headache sub-types for recurrence and intensity rates), independently from likely genetic factors (more related to MA).

Conclusions This study shows an important link between major life events and headaches, which points toward the relationship between headache and psychological factors.

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PSYCHIATRIC COMORBIDITY AND PRIMARY HEADACHE IN CHILDREN AND ADOLESCENTS: A CLINICAL STUDY ON FAMILIAL RECURRENCE

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Introduction The relevance of psychiatric comorbidity (Psi-co) in headache raises questions on the likelihood of a common etiological mechanism and direction of influence.

Objective Our aim was to analyse the relationship between familial recurrence of headache and psychiatric disorders by estimating the prevalence of mood, sleep and anxiety disorders in children compared with their parents' Psi-co and headache.

Patients and methods Headache history and symptomatology were collected in a clinical sample of 200 patients and their families, using a semistructured questionnaire (ICHD-II criteria, 2004). The questionnaire was composed of different sections in which we assessed Psi-co in parents, according to DSM-IV criteria. Chi-square was calculated to analyse contingency tables.

Results One hundred and twenty-three patients (61.5%) referred psychiatric disorders: 77 (38.5%) sleep disorders, 89 (44.5%) anxiety disorders, and 6 (3%) mood disorders (multiple disorders co-occurred in 23% of patients). Comparing psychiatric comorbidity and different diagnosis: 71 (62.8%) migraine without aura (MO) and 16 (64%) migraine with aura (MA) children had psychiatric disorders, versus 20 (62.5%) chronic tension-type headache (CTTH), and 10 (58.8%) episodic tension-type headache (ETTH) patients (n.s.). Analysis of Psi-co showed that 94 mothers (47%) and 51 fathers (25.5%) had at least one psychiatric disorder (mainly mood and anxiety disorders), while analysis of headache diagnoses in children (migraine) revealed a significantly statistical relation when comparing migraineurs versus non-migraineurs: parents of children with migraine showed higher levels of maternal Psi-co, ($p < 0.05$). It is worthy to note, that patients of mothers with Psi-co showed higher recurrence of psychiatric disorders than children whose mothers had no history of psychiatric disorders: 65 (69.1%) vs. 29 (30.9%) ($p < 0.05$), without differences across headache subtypes. Children suffering from multiple psychiatric disorders had more often mothers with psychiatric disorders than those children whose mothers had no history of psychiatric disorders ($\text{Chi}^2 = 4.382$; $\text{gdl} = 1$; $p = 0.036$). By considering anxiety disorders, we found that 36 of 57 children (63%) had mothers with anxiety disorders, while of 111 children who did not suffer from this disorder, 41 (37%) had mothers with psychiatric disorders (mother: $\text{chi}^2 = 5.534$; $p = 0.019$; father: $\text{chi}^2 = 0.277$, n.s.).

Discussion Not only migraine, but also psychiatric disorders run in families. This finding needs to be further studied to understand the influence and likelihood of a co-transmission of headache and psychiatric disorders.

Conclusions The occurrence of psychiatric disorders is high not only in children with headaches but also in their parents and is common to all headache subtypes, even though it is greater in migraine than in other headache subtypes. It may be due to a genetic mechanism, but the role of a shared familial environment needs exploration.

HEADACHE COMORBIDITY IN CHILDHOOD

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Introduction Headache comorbidity has been studied more in adults than in children and adolescents. Comorbidity is very important and in recent years has influenced diagnostic procedures and therapy.

Aim The aim of the present study was to evaluate retrospectively the comorbidity in children to verify any differences among patients presenting headache with and without comorbidity.

Patients and methods The sample consisted of 120 children, 49 males and 61 females, who presented to the Paediatric Headache Clinic of the University of L'Aquila in the last year (2004). Each patient completed a questionnaire with information about the headache and personal history. The age range was 3-14 years. The children were divided into 3 groups according to age: Group 1, 25 children, aged 3-5 years; Group 2, 70 children, aged 6-10 years; and Group 3, 15 children, aged 10-14 years.

Results Fifty-four patients suffered from tension-type headache (TTH) and 55 from migraine with and without aura (M). Comorbidity was found in 71% of the sample and there were differences among the 3 groups: 60% in Group 1, 84% in Group 2, and 93% in Group 3 ($p < 0.01$). The prevalent comorbidities were: sleep disorders (22%), thinness (14%), epilepsy (12%), obesity (10%), fainting (6%), allergies (12%), and psychiatric disorders (8%). There was no difference between males and females. Epilepsy, thinness, and allergies were prevalent in migraine patients, whereas obesity and psychiatric disorders were prevalent in TTH patients ($p < 0.05$).

Conclusions We underline the high percentage of comorbidity in adolescence (Group 3). Epilepsy and obesity are factors that have an influence on the therapy of children examined.

HOW THE LOSS OF EITHER PARENT AFFECTS A CHILD'S HEADACHE

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An event with strong emotional impact, such as the loss of a family member, has often been indicated as a trigger for headache. The purpose of this study was to compare the headache characteristics of a group of patients without either parent. In 6 months, 320 patients were evaluated, of whom 51 (15.9%) without either parent (separation, 68.8%; divorce, 23.5%; death, 7.8%). These were compared with young headache sufferers (HS) having both parents. Headache characteristics and psychiatric comorbidity were evaluated. Group I: $n = 51$ (25 M, 26 F), age range 3-18 years; mean 11.4 ± 2.9 years. Group II: $n = 51$ (24 M, 27 F), age range 3-18 years; mean 9.9 ± 2.9 years. Episodic tension-type headache (ETTH) and migraine without aura (MO) were reviewed. Migraine with aura (MA) (Group I: $n = 29$ (17 F, 12 M), M.I.(DxI) 8 ± 2.4 ; Group II: $n = 25$ (14 F, 11 M), M.I. 3.7 ± 3.4 , $p < 0.0001$). ETTH (Group I: $n = 12$ (7 F, 5 M), M.I. 6 ± 2.6 ; Group II: $n = 22$ (9 M, 13 F), M.I. 3.5 ± 3.8 , $p < 0.0001$). In only 10% of Group I did the onset of headache coincide with the loss of either parent (3 MA, 1 ETTH). In Group I, anxiety was higher in ETTH patients, and depression in those with MA. Headache is more evident in HS who have lost a family figure, but is not a trigger. The high levels of anxiety and depression show greater involvement of HS. More attention to the child's environment is per se a therapeutic intervention.

MIGRAINE AND TENSION-TYPE HEADACHE IN CHILDHOOD AND ADOLESCENCE: IS THE PSYCHOTHERAPEUTIC APPROACH MORE OR LESS EFFECTIVE THAN TRADITIONAL OUTPATIENT TREATMENT? A CONTROLLED TRIAL

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Introduction The management of child and adolescent idiopathic headache currently involves psychological interventions in association with pharmacotherapy. Despite the fact that psychological therapies are nowadays widely used in clinical practice, yet there is a paucity of research on their efficacy. The present study is a randomised controlled trial evaluating the effectiveness of brief psychodynamic therapy (BPT) in the treatment of child and adolescent idiopathic headache.

Subjects and methods Subjects aged from 6 to 18 years referring to our outpatient service for newly diagnosed idiopathic headache were randomly assigned to either an experimental group or a control group. Within the experimental group, patients received a time-limited (8–10 sessions) psychodynamic therapy, held in individual or family sessions, every two weeks. In contrast, the control group performed the standard outpatient treatment, which entailed a follow-up visit every two months after the first consultation. The two groups were evaluated at baseline (T0) and at a 6-month follow-up after the beginning of the study (T1). Measures of effectiveness were reduction of attack frequency, duration and intensity and improvement in patients' quality of life and global functioning, as reported by EuroQoL, CBCL and CGI scores. Given the small sample size, statistical analyses were performed with a 1% level of significance.

Results Thirty-three subjects completed the study: 17 patients (9 males, 8 females; mean age 9.18 years; SD±2.07) were assigned to the experimental group and 16 subjects (4 males, 12 females; mean age 10.20; SD±2.72) were allocated to the control group. Comparing the two treatment groups at T0, there were no significant differences in the main demographic and clinical data. At T1 the experimental group exhibited a statistically significant reduction in the duration of headache attacks ($p=0.005$) and improvement in the patients' quality of life, as reported by EuroQoL ($p<0.001$). Furthermore, T0/T1 comparison showed a statistically significant improvement in the CBCL Psychosomatic Complaints scale score ($p=0.01$) in the experimental group. Individual and family psychotherapeutic approaches seemed to be equally effective.

Discussion Compared to the usual outpatient treatment, BPT was more effective in the treatment of idiopathic headache, both at the clinical and psychopathological level.

Conclusions The relation between headache and psychopathology is controversial; yet the present study provides some evidence of the effectiveness of brief individual or family psychodynamic therapy in the treatment of idiopathic headache in childhood and adolescence. Indeed, a better mental elaboration of intrapsychic conflicts may have a protective role in the development of psychosomatic diseases.

HEADACHE IN CHILDHOOD AND ADOLESCENCE III

THE PREVALENCE OF PRE- AND PERINATAL COMPLICATIONS IN CHILDREN WITH HEADACHE: A STUDY OF 200 PATIENTS AND THEIR MOTHERS

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Introduction Genetic and environmental factors are hypothesized to be involved in the pathogenesis of migraine to a similar degree. Twin data showed that the genetic liability to migraine is about 40%–60%, and the contribution of non-shared environmental factors ranges from 35% to 55% [1–4]. The study of environmental factors is compelling, as well as genetic studies, in order to search for factors differentiating primary headache. The aim of this study was to analyse the risk of migraine according to the influence of complications during the pre/perinatal period.

Patients and methods In a sample of 200 patients diagnosed with headache and their mothers (ICHD-II criteria, 2004), we analysed patients histories using a semistructured interview administered to the mothers. Chi-square was computed to analyse contingency tables.

Results Sixty-four percent of the patients showed at least one pre/perinatal problem: 35.5% (71/200) reported prenatal problems and 28.5% (57/200) perinatal problems. There was no difference between the occurrence of migraine or tension-type headache in patients. Analysing the headache subtypes of mothers, migraineurs had children with more pre/perinatal problems (45.9%, 28/61), than mothers who did not suffer from headache (23.3%, 17/73) ($p<0.05$).

Discussion The explanation may be only speculative, but the occurrence of such a prevalence of pre/perinatal problems needs further studies, because of the likely implication in the pathogenesis of migraine and non-migrainous headache. It is noteworthy that migrainous mothers of migraine children showed a higher risk during pregnancy or delivery: it may be speculated that migraine is a risk factor for pregnancy and delivery, whereas pregnancy is a protective factor for migraine attacks in most women. Aromaa et al. (1996) [5] showed that women with prepregnant headache had more pregnancy symptoms, as well as poor emotional health and higher stress scores than controls. It is noteworthy that migrainous mothers of migraine children showed the highest risk during pregnancy and delivery.

Conclusions Headache patients show a very high prevalence of pre/perinatal problems compared to data from the general population (10%–15%) [6]. Moreover, migraine in mothers is a risk factor both for developing migraine in children and the occurrence of pre/perinatal complications. The data has important aetiological and pathophysiological implications.

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RECURRENT ABDOMINAL PAIN AND HEADACHE ARE RELATED TO INTERNALISING DISORDERS: A CONTROLLED STUDY BY CBCL

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Introduction Recurrent abdominal pain (RAP) and headache are among the most common reason for paediatric consultation. Both disorders affect daily life and activities: school absence, eating and sleeping prob-

lems, incapacity to meet friends, and interruption of sports. Few studies have been realized comparing the two disorders, even though similarities characterize these disorders since the youngest age: recurrent, paroxysmal, painful symptoms, and high familial recurrence, with comparable psychological pattern (mainly anxiety disorders). Headache and RAP sufferers show anxiety (e.g. generalized anxiety, school and social phobia) and mood disorders [1, 2]. However, very few studies on common psychological characteristics have been realised.

Patients and methods We compared the occurrence of Internalising and Externalising Disorders in headache, RAP and control group with the meaning of Children Behavior Checklist (CBCL) [3]. The CBCL was administered to the accompanying parent of 25 headache patients, 25 RAP and 25 control subjects (range age 4–17.9). The headache patients (12 migraine without aura, 5 migraine with aura, 5 episodic tension-type headache, 3 chronic tension-type headache) were recruited at the Child and Adolescent Headache Centre of the University La Sapienza. Headache diagnosis were made according to IHS criteria (ICHD-II, 2004). Children with RAP (without organic cause) ($n=25$) were recruited from the Department of Paediatric Gastroenterology of the University La Sapienza. RAP diagnosis respected Apley and Naish's criteria [4]. The control group matched sample was recruited in different schools. For statistic analysis, Mann-Whitney test was used.

Results Forty-eight percent of headache children and 64% of children with RAP showed statistically significant scores for Internalising Scale compared to the control group (only 4%) ($p<0.0001$). None of the scores for Externalising Scale Disorders was significant in all the three groups. No difference according to gender and age of patients was found.

Discussion The headache and RAP groups showed a very similar trend in the association with Internalising Disorders (anxiety and mood disorders), outlining the role of psychological factors. Headache and RAP patients showed a similar psychopathological liability (anxiety/mood disorders), related to somatization disorders.

Conclusions From the youngest age, with the assessment and intervention on psychopathology it is critical to manage headache and RAP and prevent somatization.

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PET THERAPY AS BEHAVIOURAL TREATMENT IN CHILDHOOD MIGRAINE

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Introduction Pet Therapy (PT) was born accidentally for the treatment of autism [1]. Studies have ascertained that this therapy positively modifies several physical parameters (AP, ECG, EEG, etc.). In PT, the animal, with the help of expert personnel, acts as an emotional mediator in thus helping the patient to overcome several psychic, psychosocial, and also psychomotor problems. In the genesis of headache, both psychiatric comorbidities and social discomfort have considerable weight. In the past, we published data, that indicated the positive effect of this therapy for young headache sufferers [2, 3].

Patients and methods Forty-eight young patients (YP) were included in the study (25 F; 23 M; 41 MO, 7 MA, range 6/16 years), in whom the triggering cause was mainly linked to psycho-social discomfort (in the family, at school or in the peer group) and who had high levels of anxiety and/or depression. The therapeutic scheme consisted of 15 weekly

sessions lasting 1 hour each. PT takes place in a 1000 sq.m. garden with trees, animals (dogs, cats, rabbits, birds, sheep), psychotherapists and 3 groups of YP aged 5–8, 9–11 and 12–17. The data controlled at T0 and T30 weeks for headache: duration and frequency with Migraine Index (M.I.); for the psychological aspect: drawing of the family, CDI, Culture-Free Self-Esteem Inventory (CFSI), FAB-C, ability to deal with a situation of discomfort, and semistructured questionnaire for parents.

Results Headache showed a >40% reduction (M.I. 13.3+/-8, 6.8+/-3.3; $p<0.005$). The psychological characteristics greatly changed both in the values of the tests CDI (13.3+/-3.6, 9.6+/-3.1; $p<0.003$), CFSI (24.5+/-6.2, 28.7+/-5.9, $p<0.05$), FAB-C (12.4+/-2.9, 10.5+/-2.9, $p<0.05$), but above all, in how situations of discomfort were dealt with.

Conclusions Undoubtedly, how pet therapy works is complex, since three factors must be evaluated: the relationship with the animal world, the psychotherapists, and finally, the therapeutic group. We think that PT works as a result of taking care of the animal, through which the child learns to abide by rules, socializes in handling animals, and acquires greater confidence. Thus, we believe that this intervention may be very useful in childhood migraine.

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QUALITY OF LIFE AND HEADACHE EVOLUTION IN A CHILD AND ADOLESCENT COHORT

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Introduction This study examined the changes in the clinical picture during the different phases of childhood with regard to the quality of life, headache treatment and diagnoses following the ICHD-II criteria.

Subjects and methods The study included 67 subjects with age ranging between 7 and 13 years visited at the Modena Headache Centre between January 2002 and December 2003. The diagnosis according to IHS criteria (ICHD-II) were migraine with (MA) and/or without aura (MO), chronic and episodic tension-type headache. All diagnoses were re-evaluated following the ICHD-II criteria. The present data are referred to one third of the group (21 cases). The quality of life was calculated by using the Ped-MIDAS questionnaire and the Child Depression Inventory (CDI). We checked headache frequency, intensity, drug use and the presence of other treatment at the control visit.

Results At the moment, all the first diagnoses were confirmed after one-year (12±6 months) follow-up (9.5% MA, 57% MO, 28% episodic tension-type headache (ETTH), 5.5% chronic tension-type headache (CTTH)). The clinical evolution was favourable in all patients and the mean number of days with headache was 2/30; the intensity of pain was unchanged. Eighty percent of examined subjects showed a Ped-MIDAS score <10, which means no or mild disability, and only 20% reached a moderate score of disability (>40). The CDI scores ranged from 0 to 15, which is considered within the normal range (0–19). In 4 items there were more "pathologic responses" than normal responses: item 2 "desperation", 60%; item 14 "negative body image", 52%; item 24 "self devaluation", 70%; and item 26 "disobey", 53%. Only one half of patients underwent prophylactic treatment lasting two months, (30% with calcium antagonists and 70% with tryptophan compounds). The drug most used for the treatment of attacks was paracetamol (60%) and only 2 patients used ketoprofen or sumatriptan spray. None underwent psychological treatments in this first series.

Discussion Data revealed the constancy of the diagnoses, which could be related to the short follow-up period we examined, and the clinical improvement of these subjects, even if only 20% of the subjects underwent a real prophylactic short-term treatment. The CDI test showed that patients had a bad perception of themselves with low self-esteem and often feelings of desperation. These emotional states were connected to disobedience and a negative body perception, which were confirmed by clinical experience.

Conclusions The data are only preliminary and do not allow correct statistical analysis which was avoided, but we plan to complete the examination of all cohorts within two months.

THERAPEUTICAL CHOICES: THE STATE OF THE ART AND FUTURE DEVELOPMENTS

A SIX MONTH OPEN-LABEL STUDY TO TEST EFFICACY AND TOLERABILITY OF LEVETIRACETAM AS PROPHYLACTIC TREATMENT OF MIGRAINE WITH AURA

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Introduction Migraine with aura with high frequency of attacks could represent a very demanding therapeutic problem. D'Andrea et al. [1] reported efficacy of the antiepileptic drug lamotrigine in this form of migraine. Levetiracetam is a new antiepileptic drug with an excellent tolerability profile. Mechanisms of action of this drug remain largely unknown, but recently, levetiracetam has been shown to exert inhibitory effects on N-type calcium channels. The aim of this study was to evaluate the efficacy of levetiracetam as prophylactic treatment for migraine with aura with high frequency of attacks.

Methods We performed a small open-label trial treating 16 patients affected by migraine with aura with high frequency of attacks. After a 1-month run-in period, patients were treated with levetiracetam at the dosage of 1000 mg/day for 6 months.

Results Attack number per month was significantly reduced during the first month (vs. run-in: $p < 0.001$), and it further lowered during the second month (2nd vs. 1st month: $p < 0.001$) and the third month (3rd vs. 2nd month: $p < 0.001$) of the treatment. This improvement persisted unchanged during the remaining three months of treatment. In 7 of 16 patients (44%), the attacks were completely abolished after 3 months of treatment. Severity and duration of headache and duration of aura were also significantly reduced at the 3rd and 6th months ($p < 0.001$). Levetiracetam was well tolerated (only 3 patients complained of light dizziness and somnolence).

Conclusions Levetiracetam was proven effective and safe in the treatment of migraine with aura. Controlled trials are needed to confirm the observed results.

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ACUPUNCTURE EFFICACY IN THE PREVENTIVE THERAPY OF MIGRAINE PATIENTS WITH OCCIPITAL PAIN LOCALIZATION: PRELIMINARY RESULTS OF A PILOT STUDY

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Background The potential role of acupuncture for the treatment of chronic neck pain as well as for the prevention of migraine has been demonstrated. Recently, it has been suggested that the trigeminocervical complex plays a crucial role in the pathophysiology of neck discomfort which accompanies the migraine attack. The aim of this study was to evaluate the efficacy of acupuncture treatment in the prevention of migraine with occipital pain localization.

Patients and methods A sample of migraine patients suffering from "back" pain was consecutively recruited according to ICHD-II criteria (2004). All patients underwent neurological examination, tenderness examination of craniomandibular muscles and physical examination of the cervical spine. The Beck Depression Inventory (BDI) and the State and Trait Anxiety Inventory (STAI 1-2) were also administered to each patient. To evaluate migraine disability, Headache Impact Test 6 items (HIT-6) and Migraine Disability assessment (MIDAS) were administered. The acupuncture treatment consisted of a combination of body acupuncture and ear acupressure. Point selections was carried out, according to the literature, considering each acupoint to have a positive effect on chronic pain in the neck regions. Each subject received two treatments per week and a total of 16 treatments over an 8-week period. **Preliminary results** Of the 26 patients recruited (mean age \pm SD = 42 ± 10 years; 24 females and 2 males), 24 patients had completed the study (mean age \pm SD = 44 ± 8 years), and 2 female patients dropped out. After the acupuncture treatment period, we observed a significant reduction of the scores in the clinical and psychometric variables in all migraine patients ($p < 0.05$).

Conclusions Our data confirm that adequate acupuncture treatment may reduce the frequency and intensity of pain as well as migraine disability also in patients with severe and refractory migraine. The therapeutic efficacy of acupuncture in migraine treatment has been observed also in the reduction of depressive and anxiety states. We hypothesized that an accurate and multidisciplinary evaluation of migraine patients performed by both the acupuncturist and neurologist may be important to specifically select the acupoints in a heterogeneous pathology such as migraine. It may be important to pick out these clinical features in migraine, not only for the therapeutic implications but also for understanding the pathophysiological link between cervical spine and pain features of migraine attack as well as for understanding the therapeutic "mechanisms of action" of acupuncture in migraine prophylaxis.

AN EXPERIENCE OF HATA YOGA AS A SIDE THERAPY FOR HEADACHE SUFFERERS

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Introduction Since chronic headache often produces generalized pain and is often accompanied by depression and/or anxiety, we thought that self-help groups could be of therapeutic benefit.

Patients and methods Twenty-five patients suffering from chronic daily headaches (80% with analgesic overuse, as stated by the ICHD-II classification), 15 women and 7 men aged 35–63 years (mean age 52) participated freely in this study. A trained Yoga master led the group in Hata Yoga and a questionnaire was used to evaluate the results of this approach. Each session lasted one and one-half hours once a week in the period November 2004–March 2005.

Results Although patients were often in pain, worked and had a family to take care of, the attendance was always quite high. From the questionnaire, 90% of participants reported that they had learned to relax, by reaching an inner calm, and freeing their minds when "the whole body was wreathing with pain". Their opinion regarding this experience was excellent and 80% referred a significant improvement in their quality of life.

Conclusions The patients discovered that they needed to learn to listen to their body and breathing despite the frantic type of life they led. They also discovered the pleasure and the importance of taking care of themselves

as a whole rather than following a purely rational, drug-based approach to their disorder. Also, being together with other people who understood each other when they tried to explain their pain proved extremely encouraging and reassuring. The caring and sharing has been a highly helpful aspect of the yoga activities.

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HYPNIC HEADACHE: TREATMENT AND REPORT OF FOUR CASES

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Hypnic headache (HH) is a rare syndrome first described by Raskin in 1988 [1]. Until 2003, over 70 cases had been reported in the literature [2]. The pathophysiology of hypnic headache is unknown, but the hypothesis of a chronobiological disturbance is also supported by the efficacy of lithium in disorders such as cluster headache [2]. The four clinical cases consisted of two men aged 58 and 70 years, and two women aged 79 and 71 years, who fulfilled the criteria of the International Headache Society classification (ICHD-II) [3]. Magnetic resonance imaging, electroencephalography and twenty-four hour blood pressure monitoring were normal. Polysomnographic findings in a male patient also demonstrated sleep apnoea syndrome. The prophylactic treatment with caffeine and melatonin, administered together before bedtime, reduced in over fifty percent of the patients the frequency and intensity of headache. Some studies suggested that HH may be a REM sleep disorder related to disturbances of the brainstem [4], but the attacks can occur also in some patients during non-REM sleep [5]. In older patients, the function of the hypothalamic-pineal axis is reduced, thus impairing melatonin secretion. Lithium increased melatonin levels. We suggest caffeine and melatonin as possible first line prophylactic treatment in these patients.

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AUTOLOGOUS EPIDURAL BLOOD PATCH IN THE TREATMENT OF HEADACHE CAUSED BY SPONTANEOUS CSF LEAK

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Objective To evaluate the efficacy of epidural blood patch (EBP) in the treatment of headache by spontaneous CSF leakage (SCSFL) [1].

Background Spontaneous intracranial hypotension (SIH) generally results from spontaneous spinal CSF leakage. EBP has emerged as the most important nonsurgical treatment for SCSFL. We have attempted to determine the efficacy of EBP in the treatment of headache by SCSFL.

Patients and methods We observed 24 patients with SCSFL between 1992 and 2004. In 6 patients (4 women and 2 men; age range 31–66 years, mean age 44) we performed EBP treatment. Follow-up ranged from 6 months to 2 years. All patients had received EBP in the lumbar

region, using 15 to 30 ml (mean 23ml) of autologous blood.

Results All patients had orthostatic headache. Other manifestations were nausea, vomiting, mild neck stiffness, tinnitus, blurred vision, diplopia, and bilateral upper limb numbness. Spinal taps were performed in 4 patients. The level of the leak was determined in 4 patients. All 6 patients failed an initial conservative treatment, which consisted of bed rest and hydration, (over a period of 2 to 13 months). The first 5 EBP patients (83%) became asymptomatic; one patient responded only to a third EBP. In 3 patients the EBP was given at the lumbar level where we found the leak, instead 1 patient with cervical CSF leak received EBP at a different level from the leak. “Blind” lumbar EBP was performed in 2 patients. All patients after injection remained in the Trendelenburg position at approximately 30° for 24 hours. Headache relief was obtained immediately.

Conclusions Our data confirm the efficacy of EBP and also suggest the efficacy of “blind” lumbar EBP and especially the importance of a prolonged Trendelenburg position in SCSFL.

Reference

1. Ferrante E, Savino A, Sances G, Nappi G (2004) Spontaneous intracranial hypotension syndrome: report of twelve cases. *Headache* 44:615–622

HEADACHE BY SPONTANEOUS CERVICAL CSF LEAK TREATED WITH LUMBAR EPIDURAL BLOOD PATCH

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Objective To evaluate the efficacy of lumbar epidural blood patch (EBP) in the treatment of spontaneous cervical CSF leakage (SCCSFL) [1].

Background Spontaneous intracranial hypotension (SIH) generally results from spontaneous spinal CSF leakage. Treatment is usually conservative, consisting of bed rest. Sometimes an autologous EBP at the site of CSF leakage may be necessary. When CSF fistula occurs at the level of the cervical spine, EBP is difficult to perform.

Design/methods We report one case of SCCSFL (among the 24 with this condition evaluated between 1992 and the present).

Results A 31-year-old woman presented sudden, intense nuchal pain, lasting for about 10 s, followed by gravative occipito-nuchal and frontal orthostatic headache. Additional clinical symptoms included nausea, vomiting, tinnitus and hearing impairment, mild neck stiffness, and bilateral upper limb numbness. All symptoms worsened with the orthostatic position. Neurological examination, routine blood tests, and brain CT scan were normal. A brain MRI showed diffuse pachymeningeal enhancement and mild subdural fluid collections. Angio-MRI was unremarkable. After two months of bed rest, orthostatic headache and tinnitus were still present. At this time, spinal MRI and MRI myelography were negative, whereas CT myelography showed left-sided contrast extravasation (C2–C3 level). CSF pressure was not measurable. The patient was treated with autologous EBP (20 ml) at the level of L1–L2. After injection, she remained in the Trendelenburg position at approximately 30° for 24 hours. She was asymptomatic within 24 hours after EBP. At 6-month follow-up she was in good health.

Discussion and conclusions In this case we hypothesize that recovery is due to the fact that EBP, even though injected at the level of the lumbar spine (i.e., far from the site of CSF leakage), may move upward reaching the cervical segments. This is possibly favoured by a prolonged Trendelenburg position. Alternatively, EBP may determine an increase in intracranial pressure, which would favour the closure of the everted borders of the dural hole. Thus, extradural injection of autologous blood at the level of the cervical spine, where the procedure is difficult to attempt, may not be necessary.

Reference

1. Ferrante E, Savino A, Sances G, Nappi G (2004) Spontaneous intracranial hypotension syndrome: report of twelve cases. *Headache* 44:615–622

TREATMENT OF TENSION-TYPE HEADACHE

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Introduction The “tension-type headache” often represents the symptomatologic manifestation of temporomandibular disorders. It is frequently associated with an occlusal alteration able to produce a muscular-articular overload [1].

Patients and methods Limitation of the functional mandible’s movements, teeth abrasions, or hypertrophy of the mandibular elevator muscles often represent the associated symptoms of myogenous pain regarding “tension-type headache” [2]. The dentist’s aim should be to diagnose and to treat adequately muscular problems originating from the stomatognathic system. To obtain this goal, a Michigan splint treatment was performed. It is a resin device applied on the maxillary dental arch, and is realized by an irreversible hydrocolloid impression of both dental arches of the patient and by a “construction wax-bite”, which indicates the maxillary-mandibular relationship [3].

The wax-bite’s height was defined to obtain the most relaxed muscular position, and the minimal, symmetric muscular activation was checked by a clinical palpation examination at the established position. Fifty patients (30 women and 20 men; aged between 18–60 years) were selected for this study. Inclusive criteria were: (1) diagnosis of muscular disorders, and (2) alteration of occlusion or of mandibular movements. Clinical parameters (maximal opening, degree of masticatory muscle tension, degree of pain during mandibular movements), and surface electromyography (sEMG) were recorded on days 0, 20, and 60. The electromyography test was performed using surface electrodes placed on the skin corresponding to the maximum projection of the muscle points. The skin was previously cleaned with ethyl alcohol to remove any greasy residues. Electrical performance recordings were obtained from both pairs of masseter, anterior temporalis, sternocleidomastoid, and anterior digastric muscles, both at rest and during function. Therapy should resolve problems of hyperactivity or disequilibrium between the different muscles and restore muscular balance [4]. All the patients were instructed in proper dental hygienic, and the correct use of the splint.

Results A remarkable reduction in the clinical parameters recorded at each follow-up was observed in all patients. The sEMG recordings showed a significant decrease in hyperactivity and a favourable muscular balance was restored at each session.

Discussion and conclusions The “Michigan splint” seems to be an efficient device to lessen or eliminate muscular tension related to the “cranio-cervico-mandibular” disorders. “Michigan splint” therapy should be part of a multidisciplinary treatment of tension-type headache.

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CHRONIC HEADACHE PREVENTION

SUPERFICIAL EMG IN CHRONIC TENSION-TYPE HEADACHE: FOLLOW-UP

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Our study, began in 2004, and continues to follow 10 patients (6 women and 4 men) with chronic tension-type headache (CTTH) and temporomandibular joint disease. All patients underwent superficial EMG of the jaw muscles and neurological examination. Patients were divided into 3 groups for different treatments: Group 1 was treated with BITE and muscle relaxants for 1 month; Group 2 with muscular stretching, psychotherapy and muscle relaxants for 1 month; and Group 3 with muscle relaxant for 2 months. Group 1 showed 70% reduction of the symptomatology, Group 2 45% reduction of the symptomatology, and Group 3 25% reduction of the symptomatology.

Conclusions Superficial EMG study of jaw muscles is very important in CTTH with temporomandibular joint disease.

TREATMENT OF 20 CASES OF CHRONIC TENSION-TYPE HEADACHE WITH ACUPUNCTURE

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Introduction Several studies on the treatment of chronic tension-type headache (CTTH) with traditional Chinese acupuncture have been published, but further studies need to be carried out to verify the validity. The peculiarity of this study was the use of International Headache Society (IHS) diagnostic criteria in the recruitment of patients.

Patients and methods The study was conducted on a total of 20 patients (mean age 32 years: 8 males and 12 women) fulfilling IHS criteria for CTTH. Two parameters were considered: (1) number of days of headache/month; (2) number of nonsteroidal anti-inflammatory drugs (NSAIDs) taken (oral medication)/month. The patients were asked to keep a daily diary for headache and oral NSAIDs one month before treatment, during the treatment period and one month after the treatment ended. The patients underwent a total of twelve sessions of 20 minutes each. The first eight sessions were weekly, whereas the last four sessions were bi-weekly. The treatment required a period of four months.

Results The diaries before and after treatment were compared: three of the 20 patients achieved complete remission of symptomatology and no longer took NSAIDs; four patients experienced a 70%–80% reduction in headache frequency and the number of times they used NSAIDs/month; six patients had a 40%–60% reduction in headache attacks; four patients had a 20%–30% reduction; and three patients had no changes.

Conclusions We believe that the treatment of CTTH should be dealt with in a multidisciplinary manner in further studies, i.e., acupuncture, as well as other different techniques (i.e., relaxation training, biofeedback, etc.), are reasonable alternatives to pharmacological therapy.

EFFECTS OF AMITRIPTYLINE AND INTRA-ORAL DEVICE IN CHRONIC TENSION-TYPE HEADACHE: A CLINICAL AND LASER-EVOKED POTENTIALS STUDY

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Introduction We reported that laser-evoked potentials (LEPs), recorded at the vertex, were increased in amplitude in chronic tension-type headache (CTTH) patients when pericranial sites were stimulated; the amplitude increase was significantly associated with the Total Tenderness Score (TTS) [1]. These findings suggested that pericranial tenderness may be a primary phenomenon that precedes headache and is mediated by a greater cortical, pain-specific hypervigilance. In the present study, we examined clinical and LEP features in two groups of CTTH patients treated with two different approaches: application of an intra-oral prosthesis, aimed at reducing muscular tenderness, and administration of amitriptyline, acting at the central level.

Patients and methods Eighteen patients suffering from CTTH (ICDH-II, 2004), participated in the study. We performed baseline evaluation of the clinical features and LEPs in all patients (T0) vs. 12 age- and sex- matched controls; subsequently, patients were randomly assigned to a two-month treatment with amitriptyline or an intra-oral prosthesis. All subjects underwent a recording session with 23 scalp electrodes, placed according to the 10–20 International System. The stimulus was a laser pulse generated by CO₂ laser; the dorsum of the hand and the cutaneous zones corresponding to pericranial muscles were stimulated. Clinical and LEP evaluations were performed after treatment (T1).

Results The late LEPs, especially the P2 component, were significantly increased in amplitude in the CTTH group; the P2 amplitude was correlated with TTS and anxiety levels. Both the intra-oral prosthesis and amitriptyline significantly reduced headache frequency. TTS was significantly different between the two groups; in fact, it was reduced in the prosthesis-treated group. The amplitude of the P2 response elicited by stimulation of the pericranial zones showed reduction after amitriptyline treatment.

Discussion and conclusions Overall, the results of this study support pericranial tenderness as a primary phenomenon in chronic tension-type headache: it may initiate a self-outstanding circuit, favoured by central sensitization at the level of the spinal dorsal horn/trigeminal nucleus and cortical nociceptive areas devoted to the attentive and emotive components of pain. Interventions at both the peripheral and central level may interrupt this reverberating circuit, improving headache outcome.

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BOTULINUM TOXIN: A PLACEBO CONTROLLED TRIAL

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Our study began in 2004, and continues to follow a group of 20 patients: 10 treated with Botulinum Toxin Type A (BTX-A) and 10 treated with sodium chloride 0.9%. Patients had previously tried many prophylactic therapies (Ca-agonists, Beta-blockers, antiepileptics) without having any significant improvement. The treatments were based on injection of 25 units of BTX-A or 0.5 cc of sodium chloride 0.9%: into the four frontalis sites; into the two temporalis sites; into superficial sites; and into the glabellar sites. The treatments were performed every 3 months for a year. After 12 months, 75% of patients treated with BTX-A showed a significant reduction in the frequency and severity of migraine attacks. We observed no reduction of the symptomatology in the patients treated with sodium chloride. Practically all patients treated with BTX-A continued the injections every 3 months and none of them had secondary effects either on muscles or in general. All the patients treated with sodium chloride 0.9% had no secondary effects but they did not continue treatment.

Conclusions Therapy with botulinum toxin is increasingly used in the prophylaxis of migraine with or without aura. Generally, it does not have secondary effects.

CHRONIC DAILY HEADACHE AND MEDICATION OVERUSE: COMPARISON BETWEEN IN- AND OUTPATIENT MANAGEMENT

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Introduction Chronic daily headache (CDH) is an invalidating pathology affecting 4%–5% of the population. The majority of patients with CDH also overuse acute medication. Medication overuse is thought to play an important role in the transformation of episodic headache into chronic headache. Furthermore, until the abused medication is withdrawn, prophylactic medication may be ineffective in reducing the headache frequency.

Objective To compare the efficacy of a detoxification scheme in two groups of patients: the first group was hospitalized for a ten-day period, while the second group was admitted to Day Hospital daily.

Patients and methods We studied two groups of 10 patients each, affected by CDH with medication overuse, (>15 simple analgesics or >10 triptans/combination medication intake per month for at least three months) without psychiatric comorbidity or opioid/barbiturate overuse. Patients underwent a 10-day treatment scheme consisting of: withdrawal of the overused drugs and administration of dexamethasone (4mg/day iv) and amitriptyline (75 mg/day). Subsequently, these drugs were tapered and prophylactic treatment, chosen on the basis of the patients' characteristics, was begun. Outcome measures were: number of days with headache during treatment, headache index (number of days with headache/total number of days) at 1 and 3 months and analgesic intake in the 3 months following detoxification.

Results Headache index and analgesic intake were significantly lower at follow-up as compared to the month before treatment. There was no other significant difference regarding all evaluated parameters between the two groups.

Conclusions Although the sample population is small, our results suggest that an outpatient management of CDH with medication overuse is a valid therapeutic option in the absence of conditions requiring hospitalization (psychiatric or medical comorbidities, opioid/barbiturate overuse, dehydration). Hospitalization, which represents a stressful event for patients, can thus be avoided and management costs reduced.

ADVICE ALONE VERSUS STRUCTURED DETOXIFICATION PROGRAMMES FOR MEDICATION OVERUSE HEADACHE (MOH): A PROSPECTIVE, RANDOMIZED, OPEN-LABEL TRIAL IN TRANSFORMED MIGRAINE PATIENTS WITH REDUCED MEDICAL NEEDS

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Introduction The effectiveness in MOH of doctor's advice alone, without adjunctive pharmacotherapy, has not yet been defined.

Aim To compare the effectiveness of intensive advice to withdraw the overused medication with the effectiveness of two different structured strategies for patient detoxification.

Patients and methods One hundred and eight patients diagnosed with probable MOH plus migraine participated in the study. Exclusion criteria were: previous detoxification experiences, co-existent, significant and complicating medical indications, major depression, overuse of opioids, benzodiazepines, and barbiturate-containing agents. The patients were randomized in equal numbers into three different treatment groups. Group A received only intensive advice to withdraw the overused medication, group B underwent a standard outpatient detoxification programme, and group C underwent a standard in-patient withdrawal programme. Withdrawal therapy was considered successful if, after 2 months, the patient had reverted to an episodic pattern of headache and was taking fewer than 10 doses of medication per month.

Results Three patients were excluded because they showed no improvement following withdrawal. Sixteen patients dropped out of the study (group A, $n=5$, group B, $n=6$, group C, $n=5$, $p>0.05$). Of the 89 subjects who completed the study, the success rates were: group A, 90%; group B 80%; and group C, 86.3% ($p>0.05$). In patients with transformed migraine with reduced medical needs and no previous detoxification experience, effective drug withdrawal may be obtained through the giving of advice alone.

APPLICATION OF THE ICHD-II DIAGNOSTIC CRITERIA FOR PAEDIATRIC HEADACHE USING A COMPUTERIZED STRUCTURED RECORD. PRELIMINARY RESULTS

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The actual application, by a computerized structured record, of the current International Headache Society (IHS) diagnostic criteria in clinical practice has been investigated in adults while data in children are lacking. We tested the computerized record, based on the ICHD-II criteria, by entering and analyzing data reported on the case sheets of 183 consecutive children (range 6–18 years) attending our paediatric headache centre. The diagnoses reported by the clinician were: migraine without aura (MO) in 108 patients; probable migraine with-

out aura (PMO) in 33; chronic migraine (CM) in 13; migraine with aura (MA) in 4; episodic tension-type headache (ETTH) in 10; chronic tension-type headache (CTTH) in 8; probable episodic tension type headache in 6; and non classifiable headache in 1. Concordance between the clinical and the computerized diagnoses was found in 131 of 183 cases examined (71.58%). There was absolute agreement in the diagnosis (100%) in subjects with CM and MA and almost complete agreement in those with MO (99.1%). In the episodic tension-type headache group the concordance was reached in 50% of the cases and only 9% was reached in the probable migraine group. In the remaining types of headache the computerized record showed, other than the diagnosis provided by the clinician, further probable alternatives. The computerized structured record could be, in selected cases, an improvement for the specialist. Further studies are needed to improve the software in order to increase the diagnosis concordance.