

ORAL PRESENTATIONS

Published online: 11 August 2006

KEY LECTURES

GENETICS OF TENSION-TYPE HEADACHE

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Objective To analyze the importance of genetic and environmental factors in tension-type headache.

Subjects and methods Review of literature.

Results A family study of chronic tension-type headache suggested that genetic factors are important due to a 3-fold significantly increased risk of chronic tension-type headache among first degree relatives compared to the general population. A twin study suggested that tension-type headache is caused by 81% non-shared environmental effects and of 19% additive genetic effects. Another twin study suggests that no and frequent episodic tension-type headache is partly inherited due to a significant higher concordance rate among monozygotic than dizygotic twin pairs, while infrequent episodic tension-type headache is caused by environmental factors. Data for chronic tension-type headache were inconclusive.

Discussion The first twin study was based on twin pairs with co-occurrence of tension-type headache and migraine. This probably biased the result, since migraine increases the risk and frequency of tension-type headache. The family study of chronic tension-type headache was a clinic population and some of the probands had co-occurrence of migraine and tension-type headache, which may have caused overestimation of the family risk.

Conclusions Genetic factors are likely to play a role in no and frequent episodic tension-type headache. Infrequent episodic tension-type headache is caused primarily by environmental factors. Chronic tension-type headache may be inherited but the data are too limited to allow firm conclusions.

THE ROLE OF PLACEBO IN HEADACHE RESEARCH

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For a long time it has been known that almost any treatment or procedure used in headache patients will lead to an improvement. This is true for the treatment of headache attacks and the prevention of headache. The concept of controlled randomised trials revealed that placebos have a profound effect in headache patients. The consequence was that most modern trials in the treatment of headache use placebo groups. The responder rate to placebo depends on the endpoint and is around 20%–30% for improvement of headache in trials treating acute headache events and around 30% in prevention trials. Originally, it was assumed that the placebo effect would decrease over time. Long-term studies with topiramate or botulinum toxin, however, showed that the effect of placebo lasts over 6 or 9 months. Subcutaneous placebo is more effective than oral placebo. In the U.S.A. and in Southern Europe the placebo response is higher than in Northern Europe. Children and adolescents have a much higher placebo response than adults. Expectation will play a major role, when the randomisation ratio between placebo and verum is known. The quality of a trial has no influence on the placebo responder rate. Placebos can lead to side

effects. In trials treating anxiety, placebo resulted in headache in 20% of the patients. Information about possible weight gain in a migraine prevention trial resulted in profound increase in body weight in the placebo run-in phase. Placebo might have a similar mode of action as “real” drugs. PET and functional MRI studies indicate that placebo will activate similar brain structures as opioids.

ICHD-2 AND ITS REVISION

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ICHD-2 features many improvements over the first edition of The International Headache Classification. Perhaps the single most important change is the introduction of the entity medication-overuse headache (MOH). The strengthening of the causal relations under secondary headaches, the changes regarding migraine with aura and the introduction of a number of new entities are also important. Subsequently, the introduction of chronic migraine was criticised because it was extremely demanding and very few patients would fit into these criteria. In order to include a reasonable number of patients with frequent migraine and headache on 15 days or more per month, new appendix criteria for chronic migraine were published. Also the criteria for MOH were changed. It is now a default rule that, if patients have a medication-overuse and a primary headache they must receive the diagnosis of medication-overuse headache.

A last major remaining problem is the Classification of secondary headaches, where improvement or disappearance of headache is requested after removal of the causative disorder. This means that patients cannot actually receive the diagnosis while they still have the headache.

This latter problem and other problems will be dealt with subsequently by the Classification Committee and revised appendix criteria will be printed in Cephalgia. It is the hope that these appendix criteria will subsequently be tested and that results will justify the changes so that they can be included in a future revised version of the ICHD-2.

MIGRAINE HEADACHES: FROM MODELS TO MECHANISM

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

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

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

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

NEUROGENIC INFLAMMATION: FURTHER THERAPEUTIC PERSPECTIVES

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

lation promoted by CGRP released from perivascular endings of trigeminal sensory neurons significantly contributes to the migraine mechanism. Inhibition of CGRP release by triptans or blockade of the CGRP receptor are different strategies that successfully target a similar pathogenic mechanism.

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GENETICS OF PRIMARY HEADACHES

NEURONAL CALCIUM CHANNELS AND MIGRAINE

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Mutations in CACNA1A, the gene encoding the pore-forming subunit of Cav2.1 (P/Q-type) calcium channels, cause a group of dominantly inherited human neurological disorders, including familial hemiplegic migraine type-1 (FHM-1), a rare autosomal dominant subtype of migraine with aura. P/Q-type calcium channels are expressed in all brain structures that have been implicated in the pathogenesis of migraine and play a prominent role in controlling neurotransmitter release. Functional studies into FHM-1 may provide unique insight into the molecular and cellular mechanisms of migraine. We have investigated the functional consequences of eight FHM-1 mutations by expressing recombinant human Cav2.1 channel subunits in HEK293 cells and in cerebellar granule cells from *cacna1a*^{-/-} mice lacking Cav2.1 channels. A consistent effect of FHM-1 mutations was to increase Ca^{2+} influx through single human Cav2.1 channels in a broad voltage range, as a consequence of an increased channel open probability mainly due to a shift to lower voltages of channel activation [1]. Recently, the generation of knockin (KI) mice carrying the R192Q [2] and S218L FHM-1 mutations allowed us to analyze for the first time mutant Cav2.1 channels expressed at their endogenous level in neurons, and evaluate the consequences of FHM-1 mutations on neurotransmission and cortical spreading depression (CSD, the phenomenon underlying migraine aura). Compared to wild-type mice, KI mice showed: 1) an increased P/Q-type Ca^{2+} current density in cerebellar granule cells in primary culture and dissociated cortical pyramidal cells in a broad voltage range and similar current densities at higher voltages; 2) an increased susceptibility to CSD as revealed by a lower threshold for induction and a higher velocity of CSD propagation *in vivo*. S218L KI mice also showed a higher incidence of recurrent waves of CSD after stimulation. Moreover, facilitation of CSD propagation was strikingly larger in S218L than in R192Q KI mice, in correlation with the more severe clinical phenotype of the S218L mutation. The gain-of-function effects on both P/Q-type Ca^{2+} current and CSD were about twice as large in homozygous as compared to heterozygous mice, revealing an allele-dose effect consistent with dominance of the mutation in FHM-1. Our data show an important role of Cav2.1 channels in the initiation and spread of CSD, and point to cortical hyperexcitability as the basis for increased susceptibility to CSD in migraine. The FHM-1 KI mice are promising animal models to study migraine mechanisms and treatments.

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GENETIC MUTATIONS AND POLYMORPHISMS IN MIGRAINE

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

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

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

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

MOLECULAR GENETICS OF CLUSTER HEADACHE: A REVIEW

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Introduction In the past, cluster headache (CH) was not thought to be an inherited disorder. Recent studies have suggested that genetic factors play a role in the disease [1]. Genetic epidemiological surveys have clearly shown that first-degree relatives of CH patients are more likely to have CH than the general population. In addition, CH has been reported in some concordant monozygotic twin pairs. Recently,

we have reported in an Italian population a significant association between the *HCRT2* gene and the disease. This association was confirmed in a German study. The purpose of this review is to describe recent advances in the molecular genetics of CH.

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

Results Several studies reported lack of association between different candidate genes and CH. Excluded genes were: *CACNA1A*, *NOS*, *HFE*, *Clock* and elusive amine receptors (*TAR 1*, *TAR 3*, *TAR 4*, *TAR 5*, *PNR*, *GPR58*) genes. We reported a significant association between the 1246 G>A polymorphism of the gene encoding for the hypocretin receptor 2 (*HCRT2*) and CH [2]. Patients homozygous for the G allele, in comparison with the remaining genotypes, have a five-fold higher risk of developing the disease. This association was confirmed in a large sample of 226 patients with CH from Germany.

Discussion At present, the type and the number of genes involved in cluster headache are still unclear. A significant association between the *HCRT2* gene and the disease was found. This gene, however, is not a major gene but rather a disease-modifying gene. These findings suggest that the hypocretin/orexin system may be involved in the pathogenesis of CH. Hypocretins influence a wide range of physiological and behavioural processes like appetite regulation, sleep-wake cycle, neuroendocrine and sympathetic functions. Moreover, recent findings suggested that hypocretins modulate pain threshold and nociceptive transmission. Additional studies are needed to elucidate the role of the *HCRT2* gene in the pathogenesis of CH and to search for major genes in this rare but severe headache disorder.

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

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

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

Materials and methods Fifty-seven unrelated MOH patients were recruited and the diagnosis confirmed after 2 months of drug discontinuation. All patients were interviewed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), to obtain a categorical psychiatric diagnosis, and completed the TPQ. After obtaining written informed consent from the patients, their genotype with respect to a 120 bp "tandem duplication" in the 5'-untranslated region of the DRD4 gene was determined. Two types of polymorphism-lengths occurred: long (L), the commonest, and short (S), which have been correlated with high NS scores and substance dependence.

To find predictors of the monthly amount of drug consumption, in the statistical analysis we considered as independent variables: years of disease duration, type of analgesic drug, genotype, and the subscales of TPQ in the statistical analysis.

Results Twenty-eight patients were homozygous carriers for the L form (L/L), 26 were heterozygous (L/S) and 3 were homozygous for the S form (S/S).

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

Discussion As with disorders characterized by substance dependence, in MOH the S allele is related to NS. Moreover, the S allele seems to also be a predictor of increased drug consumption so that it can be regarded as an aggravating factor for this disease.

Conclusions In MOH patients the DRD4 polymorphism is linked to behavioural components like NS and is correlated with the extent of the drug overuse.

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

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Introduction Several studies suggested that iron metabolism may be involved in the pathogenesis of migraine. Iron concentrations in the periaqueductal gray matter of migraine patients are significantly increased. A large population-based study showed a high migraine prevalence in women with hemochromatosis (HH), a disease associated with progressive iron overload in several organs. The hemochromatosis gene (*HFE*) is located in 6p21.3 and encodes for a HLA class I-like molecule involved in iron metabolism. Two principal polymorphisms in the *HFE* gene, C282Y and H63D, have been identified as the cause of HH. Using a case-control design, we performed an association study in a cohort of Italian migraine patients to evaluate whether a particular allele or genotype of the *HFE* gene would modify the occurrence and the clinical features of the disease.

Methods A total of 256 consecutive unrelated migraine patients (98 men, 158 women; mean age \pm SD=40.3 \pm 9.4 years) were involved in the study. The diagnosis of migraine was made according to the International Classification of Headache Disorders (ICHD-II) criteria. Two hundred and twenty-five patients fulfilled the diagnostic criteria for migraine without aura (MO) and 31 for migraine with aura (MA). A group of 237 sex-, age- and geographically (Northern Italy) matched healthy subjects (95 men, 142 women, mean age \pm SD=41.5 \pm 13.3 years) were used as controls. Patients and controls were genotyped for the C282Y and H63D polymorphisms of the *HFE* gene.

Results Phenotype and allele frequencies of both polymorphisms were similarly distributed in migraine patients and controls. The patients carrying the DD genotype of the H63D polymorphism showed a later age at onset of the disease and an increased number of migraine attacks.

Discussion Our data suggests that the *HFE* gene is not a major disease gene for migraine. However, the H63D polymorphism of the *HFE* gene may be considered a modifying genetic factor in migraine.

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

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Currently available treatments for primary headaches have a limited efficacy, due in part to the wide variation in individual responses. Variability in individual response to headache treatment may be due to several factors, including a patient's compliance with treatment, severity and type of headache and intercurrent illnesses, drug interaction with other medications taken concurrently, diet, and individual biological characteristics such as age, nutritional status, hepatic and renal functions. Hereditary differences may therefore be only one of the causes of the variable effect of pharmacotherapy in primary headache. However, genetic factors may underlie much of such variability.

Most drugs are subjected to more or less extensive metabolism. Only a few of the cytochrome P (CYP) 450 family enzymes are responsible for the majority of metabolic reactions involving drugs. They include the isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Several of the drug metabolizing enzymes are polymorphic, having more than one variant of the gene. This polymorphism is responsible for interindividual differences in the efficacy of drug treatment, side effects of drugs, and drug toxicity. Genetic polymorphisms with clinical implications have been described for 2D6, 2C19, 2C9, 1A2, and 3A4. Genetic polymorphism of CYP450 enzymes characterizes the general population into three groups: poor metabolizers, extensive metabolizers, and ultraextensive metabolizers. There are three ways to gain information on metabolizing enzyme activities: to study the genes that code for the enzyme, to study the level of enzyme expression in a certain tissue, and to assess the actual enzyme activity using an enzyme specific probe (phenotyping). Genotyping is a more simple procedure compared to phenotyping. Phenotyping might be helpful in detecting interethnic differences, or in studies aimed at detecting enzyme induction or inhibition. Probe substrates that may be used to assess the activity of specific cytochromes P450 *in vivo* are: caffeine for CYP 1A2, dextromethorphan for CYP 2D6, and midazolam for CYP 3A4.

Polymorphism of CYP450 enzymes may or may not have a clear clinical significance for the affected medications, depending on the importance of the enzyme for the overall metabolism of a medication, the expression of the other drug metabolizing enzymes in the patient, the therapeutic index of the drug, the presence of concurrent medications or illnesses, and other polygenic factors that impact drug response.

PATHOGENETIC ASPECTS OF HEADACHES: FROM THE EXPERIMENTAL MODEL TO MAN

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

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Introduction Activation of trigeminal ganglion (TG) nociceptors and consequent neurotransmitter release are centrally involved in the development of migraine headache. Calcitonin gene-related peptide (CGRP) is one of the most important vasoactive neurotransmitters in migraine. Major lines of evidence are: *i*) CGRP is found in human jugular venous during migraine attacks; *ii*) the administration of the antimigraine agent sumatriptan relieves headache and re-establishes normal CGRP levels; and *iii*) intravenous administration of CGRP induces headache and migraine in migraineurs. Elucidation of the release mechanism for CGRP in TG neurons may thus be critical in the understanding of migraine pathology [1, 2]. In dorsal root ganglia (DRG) neurons it has been recently shown that a significant component of exocytotic release and even a greater fraction of depolarization-induced CGRP release do not require Ca^{2+} influx. We then set out to assess the Ca^{2+} dependence of exocytosis and of CGRP release in TG neuron of mice. This investigation was carried out considering that a subtype of migraine with aura, familial hemiplegic migraine type 1 (FHM1), is caused by mutations of $\text{CaV}2.1$ channels, abundantly expressed in TG neurons [2].

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

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

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

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

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Background Hypocretin-1 and -2 (Hcr1 and Hcr2), also referred to as orexin-A and -B, are two neuropeptides, which are considered critical components for maintaining and regulating the stability of arousal to mediate the hypothalamic response to stress. Experimental evidence suggests that corticotrophin-releasing factor (CRF) activates the hypocretin system, which relays orexin-A to brainstem nuclei as well as to the extended amygdala, a structure involved in the negative motivational state that drives addiction [1, 2].

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

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

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

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

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

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

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

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

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

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

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

ture medium was changed within 24 h from seeding. Plating medium was enriched with 50 ng/mL of 2.5 S murine nerve growth factor. Cytosine arabinoside 10 μ M was added to arrest non-neuronal cell growth. All experiments were performed from 3 to 6 days after dissection. In this model, we developed a radioimmunoassay (RIA) method to measure calcitonin gene-related peptide (CGRP) released in the incubation medium; this parameter can be taken both as an index of neuronal function as well as a pivotal mediator of migraine pathology. We found that CGRP was released in sizable amounts after 10–60 minutes experiments. Basal CGRP release was increased in a significant manner by depolarizing solutions (i.e., incubation media containing 56 mM KCl). Release was also increased by the Na⁺-channel activator, veratridine, with significant increases from 10⁻⁸ M onward. Apart from non-specific depolarizing agents, CGRP release was also increased in a concentration-dependent manner by the vanilloid receptor agonist capsaicin, with an estimated EC₅₀ of 0.3 μ M.

Preliminary findings show the opioid-related peptide nociceptin, also referred to as orphanin, reduces basal CGRP release from cultured neurons. We are currently investigating the effects of nociceptin over specific (capsaicin) and non-specific (KCl and veratridine)-stimulated CGRP release.

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

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Introduction Migraine is considered a frequent, primary headache disorder due to transient abnormal brain function. According to the current classification of the International Headache Society, structural brain lesions are absent in primary headaches. However, recent studies with voxel-based morphometry (VBM) demonstrated selective brain alterations in both cluster headache (bilateral increase of gray matter in postero-lateral hypothalamus) and chronic tension-type headache (gray matter decrease in orbitofrontal cortex, insula, and anterior cingulate cortex). The purpose of this study was to investigate the presence of structural abnormalities in patients with migraine using the optimized voxel-based morphometry method, a highly sensitive technique to detect focal gray and white brain matter abnormalities.

Methods A group of 27 right-handed migraine patients, diagnosed according to ICHD-II criteria, and 27 right-handed healthy controls underwent high resolution structural magnetic resonance imaging (MRI). Data was analyzed using MATLAB 6.5 and Statistical Parametric Mapping 2 (SPM2). Covariance analysis was used to detect local gray matter changes in migraine patients and between episodic and chronic migraine. Regression analysis was performed to search for a relationship between local gray matter changes with the clinical characteristics of migraine.

Results Significant gray matter volume reduction was found in the right superior temporal gyrus, right parietal operculum, right inferior frontal gyrus, left angular gyrus, left inferior parietal lobule and left precentral gyrus of migraine patients. In comparison with episodic migraine, patients with chronic migraine showed a significant bilateral reduction of gray matter concentration in the anterior cingulate cortex (AAC), right angular gyrus and right inferior frontal gyrus. Finally, we found a significant correlation between the frequency of migraine attacks and the reduction of gray matter concentration in AAC of migraine patients.

Discussion Our study shows a significant gray matter reduction in migraine patients of several cortical areas involved in pain processing and a selective alteration of AAC related to frequency of migraine attacks. Functional neuroimaging shows that several brain regions are activated by pain, including frontal and pre-frontal cortices, operculo-insular cortex, primary and secondary somatosensory cortices, AAC, thalamus and regions within the parietal and temporal cortices. In addition,

AAC plays a key role in the affective and attentive processing of pain sensations. Our data supports the results of previous studies suggesting that migraine may be considered a progressive brain disorder and highlights the importance of prophylactic antimigraine therapy in order to avoid the progression of the disease.

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

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Background It has been postulated that chronic exposure to antimigraine and/or analgesic treatment may interfere with the pain control system, leading to a central sensitization phenomenon responsible for chronic headache.

Diffuse noxious inhibitory controls (DNICs) are part of a central pain modulatory system that relies on spinal and supraspinal mechanisms. It has been postulated that chronic or frequent exposure to antimigraine and/or analgesic treatment may lead to a downregulation of specific receptors and may subsequently change central inhibitory (anti-nociceptive) pathways such as DNICs, leading to central sensitization phenomena responsible for chronic headache pain. Our previous study [1] showed that the temporal summation threshold (TST) of the nociceptive flexion reflex (RIII) represents a useful tool to evaluate both the central sensitization of pain pathways and the functional activity of DNICs.

Objective The present study investigated the TST of the RIII reflex in medication-overuse headache (MOH) patients before and after withdrawal therapy.

Methods Twenty-four MOH patients before and after withdrawal treatment and 25 age- and sex-matched controls were evaluated. TST of the RIII reflex and the subjective painful sensation were measured before, during and after activation of the DNICs by the cold pressor test (CPT), which involved immersing the hand in cold water (2–4°C). After 7–10 days of withdrawal treatment all patients were re-evaluated.

Results Significantly ($p < 0.01$) lower RIII threshold and TST were found in patients versus controls. In patients, the CPT induced a significantly ($p < 0.01$) lower TST increase with respect to controls. After the withdrawal therapy we found an improvement of the evaluated parameters, and a highly significant increase ($p < 0.01$) in the TST during CPT.

Conclusions These data confirm the hypothesis of a lack of function of the DNICs and of a central sensitization phenomenon in MOH patients. The improvement after withdrawal treatment suggests that medication overexposure could interfere with inhibitory central pain mechanisms.

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EFFECT OF PREGABALIN IN A STRESS AND NITROGLYCERIN-INDUCED MODEL OF HYPERALGESIA IN THE RAT

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Introduction Nitroglycerin activates spinal and brain nociceptive structures via nitric oxide (NO) and plays an important role in the initiation and maintenance of pain. Chronic stress affects both pain threshold and behaviour, and unavoidable stress paradigms such as immobilization are used to study nociception. We have recently reported that chronic stress enhances the hyperalgesia induced by nitroglycerin in the rat. This may be particularly relevant to migraine, since nitroglycerin triggers spontaneous-like attacks in humans, and an unfavourable migraine outcome (transformation into a chronic daily headache) is associated with chronic stress and comorbid depression. Pregabalin is an antiepileptic and analgesic drug with significant effects on thermal allodynia and mechanical hyperalgesia; we therefore investigated the effect of pregabalin in this experimental model of chronic migraine.

Materials and methods Pain perception was measured using the latency of response to a tail flick test (hot stimulus). Measures were made 1, 2 and 4 hours following nitroglycerin (10 mg/kg i.p.) in rats immobilized for 7 days using dedicated plexiglass restraining cages, and treated with pregabalin at the dose of 60 mg/kg per os or with vehicle.

Results Chronic stress caused hyperalgesia, which was further enhanced by nitroglycerin after 2 and 4 hours ($p < 0.05$). By contrast, chronic stress-induced pain perception decreased in pregabalin treated animals ($p < 0.05$); in the same group, the hyperalgesic effect of nitroglycerin was also found to be significantly dampened ($p < 0.05$).

Discussion and conclusions These preliminary data suggest that pregabalin acts as an antinociceptive drug by affecting the mechanisms leading to hyperalgesia in the rat. Pregabalin may thus represent a novel therapeutic option in the management of chronic migraine in humans.

CEREBRAL EXCITABILITY IN MIGRAINE

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

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

Abnormal cortical information processing, probably based on the phenomenon of altered neuronal synchronization, may be a basic feature in migraine; the brainstem, particularly the zones corresponding to the PAG, may consequently change its ascending firing to the cortex and its descending control on the nociceptive afferents, with a self-maintaining circuit prone to the generation and the persistence of headache.

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CORTICAL EXCITABILITY AND HABITUATION MECHANISMS IN MIGRAINE

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Controversy has arisen about the excitability status of the cerebral cortex in migraineurs between attacks. Intuitively, some clinical features of migraine such as hypersensitivity to environmental light or noise, and the aura symptoms suggest hyperexcitability of the cerebral cortices. In the physiological sense, however, hyperexcitability would mean that the brain responds to a subliminal stimulus with an increased amplitude. This abnormality has never been precisely demonstrated studying cortical excitability in migraine patients.

Increased cortical excitability or decreased intracortical inhibition, as well as hypoexcitability or normal function of inhibitory cortical interneurons have been observed in migraine by using transcranial magnetic stimulation (TMS), thus providing ambiguous results.

It has been hypothesized that the finding of an interictal deficit of habituation of cortical evoked responses is probably not due to hyperexcitability or to underactivity of intracortical inhibition, but to a reduced preactivation excitability level of the sensory cortices, stated by activity in thalamo-cortical loops and aminergic projections from the upper brainstem. This low preactivation level, in conjunction with the cortical "ceiling theory", could indeed explain the low amplitudes found in the first blocks of several types of evoked responses and the lack of habituation in subsequent blocks, since it would offer a larger range for suprathreshold cortical activation before reaching the "ceiling".

Interestingly, this dishabituation phenomenon is reversible, since it normalizes just before and during an attack. It remains to be determined if activation of the dorsal rostral brainstem and of thalamo-cortical projections may contribute to ictal normalization of the cortical preactivation level.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN MIGRAINE: RECENT EVIDENCE

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Transcranial Magnetic Stimulation (TMS) has been employed to study the pathophysiology of migraine. All studies reported abnormal cortical activation in migraineurs during the interictal phase; the findings however were controversial, some authors describing hypo- and others hyper- excitability of the migraine visual cortex.

Repetitive TMS (rTMS) is able to modulate cortical excitability, with low frequency (≤ 1 Hz) decreasing while high frequency (> 1 Hz) increasing activation of stimulated cortices.

A few rTMS studies have been conducted in migraine. We showed that low-frequency rTMS has paradoxical facilitatory effects on striatal and extra-striatal cortex in migraine and interpreted this result as due to reduced efficiency of cortical inhibitory circuits, unable to be up-regulated by rTMS. According to this hypothesis, we found dysfunction of inhibitory circuits also in the motor cortex of migraineurs. Through paired pulse TMS we showed that migraineurs present reduced intracortical inhibition at baseline. After 1 Hz stimulation, paradoxical potentiation of intracortical facilitation (ICF) occurs, opposite to the suppression of ICF induced by the same trains in healthy controls.

In contrast, Bohotin et al. [1] in a rTMS experiment found that the facilitatory frequency 10 Hz favours the recovery of habituation of visual evoked potentials that is reduced in migraine. The authors speculated that migraineurs have a reduced cortical activation that can be reversed by facilitatory rTMS. Moreover, in the authors' view, the relationship between reduced-activation and deficient-habituation is also confirmed by the results of 1 Hz rTMS application in healthy subjects; in this group, in fact, reducing activation through 1 Hz rTMS that normally exerts an inhibitory effect gives similar habituation impairment compared with migraine.

However, the effects of rTMS greatly depend on the basal excitability state of stimulated cortex. In fact, in a recent paper [2] we found that during visual deprivation, a condition known to increase visual cortical excitability, rTMS can exert opposite effects, with low frequencies increasing while high frequencies decreasing excitability of the occipital cortex. This means that rTMS should be interpreted cautiously when investigating cortical excitability, to avoid a circular reasoning, i.e., the same rTMS effects are conditioned by the basal excitability state of the stimulated cortex.

rTMS if given in repeated stimulation sessions is also able to induce persistent plastic changes of the stimulated cortex, and this is the rationale for its use in experimental treatment of various neurological and psychiatric diseases.

Recent findings about this rTMS application seem to open interesting therapeutic perspectives in migraine.

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VISUAL EVOKED GAMMA BAND RESPONSES IN SUBGROUPS OF MIGRAINE WITH AURA

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Background Visual stimuli evoke high frequency oscillations in the gamma band range (GBOs, 20–35 Hz) generated both by pre- (early GBOs) and post-synaptic (late GBOs) mechanisms. Recently, Sandor et al. [1], with MR-lactate spectroscopy, observed that a pattern of dishabituation, as previously found with evoked potentials, was present in a subgroup of migraine patients with associated paraesthesia, paresis or dysphasia as aura (MAplus), while in the subgroup with high resting lactate, the aura seems to be limited to the visual cortex.

Taking into account that a close relationship was observed between oscillatory response and metabolic cortical demand [2], we searched for pathophysiological differences in the clinically distinct subgroups of migraine with aura (MA) exploring visual evoked GBOs during the interictal period.

Materials and methods Eighteen patients affected by migraine with typical aura (ICHD-II code 1.2.1, 2004) were enrolled in this study: 8 with pure visual aura (MA) and 10 with visual aura associated with paraesthesia or dysphasia (MAplus). Migraineur groups were compared to 15 healthy volunteers (HV).

We extrapolated the GBOs from the broad-band visual evoked potentials (VEPs), with an off-line band pass digital filter (20–35 Hz). We analyzed peak-to-peak amplitude and habituation (the amplitude change (%) between the 1st and 6th block of 100 sequential averaged responses) of the conventional broad-band N1-P1 and of each of 6 peaks of GBO burst evoked by the checkerboard pattern. We considered as early GBOs the first 3 oscillatory peaks, and as late GBOs the last 3.

Results The conventional broad-band VEPs showed the well-known pattern of dishabituation in both MA ($p=0.038$) and MAplus ($p=0.001$) patients when compared to HV.

After digital filtration, there was a significant habituation deficit of the later two, but not of the earlier GBO peaks in MAplus patients compared to HV (respectively $p=0.035$ and $p=0.032$). In contrast, the MA group with pure visual aura showed an increased early oscillatory peak activity compared to HV (2nd $p=0.024$ and 3rd $p=0.013$), without habituation deficit of the later GBO peaks.

Discussion We found different patterns of visual oscillation responses in two subgroups of MA patients, which seem to mimic those observed with MR-lactate spectroscopy in patients with the same diagnosis. We hypothesized that an abnormal metabolic demand due to repetition of visual stimulus leads to dishabituation, which exists in MAplus patients, and to a predominant energetic metabolism dysfunction in MA patients.

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HYPEREXCITABILITY OF THE SOMATOSENSORY SYSTEM IN CHILDREN WITH MIGRAINE

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Introduction Although migraine represents the most common primary headache in childhood, its pathophysiology is poorly understood. In spite of the bulk of studies dealing with this problem in adults, the pathophysiological base of paediatric migraine has been only rarely investigated. As in adults, children with migraine show a reduced habituation to repetitive sensory stimuli [1, 2]. Although this characteristic neurophysiological phenomenon suggests an abnormal excitability of the cerebral cortex in this disease, whether cortical excitability in migraine is reduced or increased is still far from demonstrated.

Materials and methods We investigated cerebral cortex excitability in 15 children (mean age 11.7 ± 1.6 years, 5 males, 10 females) affected by migraine without aura (MO) and in 10 age-matched control subjects (CS) (mean age 10.9 ± 2.1 years, 6 males, 4 females). We calculated the somatosensory evoked potential (SSEP) latency and amplitude modifications after paired electrical stimuli at 5, 20 and 40 ms interstimulus intervals (ISIs), comparing it with a single stimulus condition taken as baseline.

Results In MO patients, the amplitudes of the cervical N13 and of the cortical N20, P24 and N30 responses at 20 and 40 ms ISIs showed a higher recovery than in CS (two-way ANOVA, $p<0.05$).

Discussion Since the SSEP recovery cycle depends on inhibitory interneuron function, our findings suggest that a somatosensory system disinhibition occurs in migraine. This is a generalized phenomenon, not limited to the cerebral cortex, but involving also the cervical grey matter.

Conclusions The shortened SSEP recovery cycle in migraine children, besides showing that the somatosensory system is hyperexcitable in

this disease, might represent a useful marker to control the effect of prophylactic pharmacological treatments.

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

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

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

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

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

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

ICHD-II: RE-EVALUATION AND INSTRUMENTS OF APPLICATION

REVISION OF THE ICHD-II CRITERIA FOR CHRONIC MIGRAINE

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

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

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

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

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

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

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The classification of “Medication-Overuse Headache” (MOH) in chapter 8.2 of ICHD-II [1], although recently simplified to a list of drugs producing medication-overuse headache if overused [2], is still ambiguous as far as combination analgesic-overuse headaches are

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

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

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

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OSMOPHOBIA IN SECONDARY HEADACHES

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

Materials and methods The clinical study was conducted on a series of consecutive patients from the Neurological Clinic, the Operative Unit of Neurosurgery and the Neurotraumatological Clinic of the University of Padua, bearing pathological conditions potentially able to cause headache. Through a semistructured questionnaire we selected all patients suffering from secondary headache; the presence of a primary form of headache was also investigated (ICHD-II, 2004). A

part of the questionnaire concerned the possible presence of osmophobia in the course of headache attack both in primary and secondary headaches. All the patients who presented alterations of their state of consciousness, who for any reason could not give reliable answers or who presented anatomic and/or functional alterations of olfactory function, were excluded.

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

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

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

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

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

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

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

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

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Introduction Prior research shows that around 10% of women and 5% of men reported headache at the age of 70. However, the primary headaches (PHs) in the elderly are still poorly studied. To date, no studies that have used the International Classification of Headaches, 2nd edn (ICHD-2) to classify PHs in the elderly over 70 years old have been reported in the literature. This study had the objectives to classify the PHs in a USA and Italian elderly population (≥ 70 years old) according to the ICHD-2.

Methods Our cohort consisted of 426 elderly subjects without dementia (53% female, age range 70 to 94, mean=78.6 years). To assess the prevalence of PHs in this population we used a standardized questionnaire to prospectively survey participants of the Einstein Aging Study (EAS) and of the Rummo Aging Study (RAS). The EAS and RAS are a multidisciplinary project that follows a representative sample of seniors focusing on the description of cognitive pathways in the elderly. The questionnaire assessed current headache diagnoses (prior year), as well as prior headache diagnoses, according to the ICHD-2. All subjects participating in the EAS and RAS underwent neurologic examination, and most had neuroimaging. Consistently, we could confidently exclude secondary headache disorders.

Results One-year prevalence was 7.6% for migraine (migraine without aura 1.6%; migraine with aura 1.7%; probable migraine without aura 2.1%; probable migraine with aura 2.2%), 6.1% for episodic tension-type headache (ETTH) and 1.4% for chronic migraine. For those without headache in the past year a history of CDH was present in 3.1% of patients, a history of migraine in 4.7% and a history of ETTH in 6.9% of the sample. A remission of headache before age 50 was present in 50% while before age 65 in 81.2%. Around 15% of our sample had recurrent PHs in the past year, and 7.6% met ICHD-2 criteria for migraine. Most fulfilled a probable diagnosis rather than the full criteria.

Conclusions While 4.8% of patients had more than 15 days of headache per month at some point in their life, just 1.1% had it now. Headache remission prior to age 65 is common.

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

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The actual application, by a computerized structured record, of the current International Headache Society (IHS) diagnostic criteria in clinical practice has been investigated in adults, while data in children are lacking. We tested the computerized record, based on ICHD-II criteria, by entering and analyzing data reported on the case sheets of 800 children (range 6–18 years) attending our paediatric headache centre.

Concordance between the clinical and computerized diagnoses was found in 70% of the cases examined. There was an absolute agreement of diagnosis (100%) in the subjects with chronic migraine (CM) and migraine with aura (MA) and almost complete in those with migraine without aura (MO) (99.1%). In episodic tension-type headache, concordance was reached in 50% of the cases and only in 9% with probable migraine. In the remaining types of headache, the computerized record showed, other than the diagnosis provided by the clinician, further probable alternatives.

In the types of headache with a large amount of information and typical accompanying symptoms, concordance was 100% and there were no diagnostic problems. In contrast, when we have headache types with intermediate characteristics and/or lack of accompanying symptoms, the software elaborates different diagnoses according to ICHD-II criteria.

The computerized structured record could be, in selected cases, an improvement for the specialist to orient the diagnosis. The clinician must make the diagnosis and consider the clinical and family history, the presence of trigger factors, and the psychological aspects in a holistic vision of the patient. Further studies are needed to improve the software in order to increase the diagnostic concordance.

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

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Migraine and tension-type headache represent the most common forms of primary headaches. In the absence of biological markers, the diagnosis of these forms of headache depends entirely on the information obtained from clinical interviews as well as from physical examination. Headache diaries make it possible to record prospectively the characteristics of every attack, and this may reduce the recall bias and increase accuracy in the description.

The advent of the International Classification of Headache in 1988, with its recent revision (2004), has greatly contributed to the definition of precise criteria for the diagnosis of migraine and tension-type headache across the world. Nonetheless, support is needed to facilitate the adoption of these criteria, especially in the non-specialized clinical settings. We have recently developed a basic version of a diagnostic headache diary for migraine and tension-type headache. Our objective was to devise a tool for assisting the diagnosis of these two types of headache in headache centres, as well as in non-specialized practice. The diary had to satisfy two important requisites: 1) simplicity, and 2) completeness for ICHD-II based diagnosis.

A pilot study was performed in order to test the diary in the Headache Centres of Pavia and Copenhagen. The data obtained were presented and discussed in a Consensus meeting held in Valencia during the last European Headache Federation Congress (April 2006). The findings obtained showed that the use of the diary is suitable for naive (*de novo*) patients and provides complete information for diagnosis in a very high percentage of subjects. Comparison of the diagnoses based on history and physical examination (gold standard) with those obtained from the diary showed a satisfactory degree of concordance. Furthermore, the use of the basic headache diary allowed a more detailed diagnostic definition.

A second version of the diary, aimed at a more precise detection of aura symptoms, is under preparation and will be tested in several European countries in the near future. Hopefully, this process will lead to the

availability of a validated tool – common but at the same time country-specific – for the proper and homogeneous diagnosis of migraine and tension-type headache across Europe.

Future steps include: 1) the preparation of an electronic version with a software-assisted diagnostic process; and 2) the elaboration of targeted diaries (i.e., for menstrual related attacks, for cluster headache, for children, etc.).

CLINICAL ASPECTS OF HEADACHES I

SYNCOPE IN MIGRAINE

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Introduction Migraine is an episodic, multifactorial neurovascular disorder characterized by recurrent attacks of disabling headache and autonomic nervous system (ANS) dysfunction. Syncope is a paroxysmal symptom consisting of a brief, self-limiting transient loss of consciousness due to global cerebral hypoperfusion. Several reports suggest that there is comorbidity between the two conditions.

Case report We describe the case of a 53-year-old woman suffering from migraine without aura since the age of 20. The attacks were constantly characterized by severe intensity and remarkable autonomic disturbances, in particular, nausea, vomiting and photophobia. In association with the most disabling attacks, usually once a year, she suffered from typical syncopes, which never occurred outside the migraine attacks. The patient was otherwise healthy and did not need any pharmacologic treatment, other than the symptomatic drugs for migraine. After age 40, the syncopes occurred more frequently, on average 2–3 times a year, with the intensity and frequency of migraine remaining unchanged. The patient consequently underwent a cardiac electrophysiologic study that was normal. At the age of 51 she had an extremely severe migraine attack with prominent autonomic disturbances; she developed multiple brief syncopes and was thus referred to the Emergency Department. Immediately after her admission, she had a protracted loss of consciousness, and the ECG-monitoring showed a complete sinus arrest lasting 20 seconds and resolved by the precordial thump procedure. After sinus rhythm was restored, further brief episodes of sinus arrest were documented. It was therefore established, considering the previous history of frequent and recurring syncopes, to implant a permanent pacemaker. The cardiologic tests were normal, in particular, possible coronary heart disease was ruled out by performing a treadmill test and a myocardial scintiscan. The tilt table testing was positive for induced syncope. After her discharge, she was regularly followed-up for 2 years and no further syncope recurred, despite the persistency of severe migraine attacks.

Discussion A higher lifetime prevalence of syncope among migraineurs was reported in some studies and an autonomic dysregulation was suggested to be involved in the pathophysiologic mechanisms of migraine. A dysfunctional or unstable ANS might render an individual more susceptible to migraine by reacting to triggers at a lower threshold.

Conclusions Migraineurs with disabling attacks seem to be more prone to ANS dysfunction. To our knowledge, we report the first patient suffering from strictly and exclusively migraine-associated syncopes who required the implant of a permanent pacemaker.

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

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Introduction Migraine is characterized by a complex biochemical dysfunction attributed to a disorder of the trigeminal and hypothalamic pathways. Impairment of glucose metabolism has been reported in migraine, but data are scarce and inconsistent [1].

Objective The main aim was to verify if migraineurs present alterations in glucose and insulin metabolism.

Patients and methods The study population included three groups of subjects: 1. Migraineurs (M) consecutively seen at the headache centre of our hospital; 2. Patients affected by headache other than migraine (O), consecutively seen at our headache centre; 3. Healthy volunteers (HV), recruited among colleagues, nurses and technicians from our hospital. All the recruited people underwent a general blood test and a standard oral glucose tolerance test after a 12-hour fasting period, measuring levels of glucose and insulin.

Results In a 6-month period we recruited 84 migraineurs (73 women, 11 men), 25 patients with non-migraine headache (20 women, 5 men), and 26 healthy controls (24 women, 2 men). Both headache groups presented blood glucose levels (mg/dL) higher than the healthy control group (fasting: M 96, O 98, HV 83, $p=0.000$; at 30 minutes: M 142, O 143, HV 114, $p=0.001$; at 60 minutes: M 122, O 117, HV 95, $p=0.008$; at 120 minutes: M 102, O 93, HV 93, $p=0.139$). Compared to the other groups, migraineurs presented significantly higher insulin levels at any time of the test, both fasting and after glucose loading (fasting: M 10, O 7, HV 6, $p=0.001$; at 30 minutes: M 86, O 47, HV 48, $p=0.000$; at 60 minutes: M 79, O 43, HV 35, $p=0.000$; at 120 minutes: M 51, O 28, HV 29, $p=0.001$).

Conclusions High blood glucose levels can be recorded in headache patients, but do not seem to be specific to migraineurs. High insulin levels are recorded in migraineurs, and these data seem to be specific to this group of patients [2]. These findings are in keeping with recent reports on the effects of insulin on brain functions and lend support to the possible involvement of insulin in the pathogenesis of migraine.

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CLINICAL PICTURE OF CLUSTER HEADACHE IS NOT RELATED TO SEVERITY OF PATENT FORAMEN OVALE

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Introduction Patent foramen ovale (PFO) recently has been implicated in several diseases such as cryptogenic stroke, Obstructive Sleep Apnea Syndrome (OSAS) and migraine with aura. The nature of the relationship between PFO and migraine has not been completely understood. Although migraine and cluster headache (CH) are separate entities, pathophysiology and treatment partially overlap between them; also, in CH some studies have documented that the prevalence of PFO is higher than in the general population [1]. No correlation has been found between the clinical picture of migraine and severity of PFO [2] and no data are available for CH.

Material and methods We studied 18 patients (15 males and 3 females) with episodic CH, according to ICHD-II criteria (2004), who resulted positive for the presence of PFO to evaluate a correlation between the entity of PFO and clinical picture (duration, daytime recur-

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

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MYOFASCIAL TRIGGER POINTS IN MIGRAINE PATIENTS

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Introduction Previous studies have shown that migraine patients often present myofascial trigger points (TrPs) in the cervical muscles whose target areas coincide with the site of migraine pain and that TrP treatment (repeated injections) over two months significantly improves migraine symptoms during the same period.

Objective The aim of the present study was to evaluate, in this type of patients, the long-term effects of TrP treatment, and in particular, to assess if TrP extinction results in stable, beneficial effects on migraine symptoms.

Methods Thirty-five patients (30 women, 5 men, aged 23–47 years), affected with frontal and/or temporal migraine and TrPs in the sternocleidomastoid, splenius cervicis or semispinalis cervicis muscles (targets located in the same sites as the migraine attacks) were examined. All underwent measurement of electrical pain thresholds in skin, subcutis and muscle at TrP and target level at baseline, and after 60, 120 and 180 days. TrP infiltration with local anesthetic was performed on days 1, 3, 10, 30 and 60. Number and maximal intensity (VAS scale) of migraine attacks were recorded for 60 days before and 180 days after the start of treatment. All patients were free from any other pain medication during the study.

Results At baseline, pain thresholds of all three tissues at TrP and target level were significantly lower than those recorded in 20 healthy controls of comparable age, testifying to the state of hyperalgesia ($p < 0.001$). After 60 days of treatment:– all thresholds were significantly increased in both TrP and target (ANOVA: $p < 0.002$); number and intensity of migraine attacks decreased significantly compared to pre-treatment ($p < 0.001$). The threshold increase correlated significantly with the reduction of migraine pain ($p < 0.01$). At 120 and 180 days, all thresholds did not change significantly with respect to day 60. Number and intensity of migraine attacks relative to the periods: days 60–120 and days 120–180 did not differ significantly from those of the period days 0–60 of treatment.

Conclusions Extinction of myofascial TrPs, whose targets coincide with the site of migraine pain, has beneficial effects on migraine symptoms, which go far beyond the treatment period. This procedure is therefore recommended as an integral part of migraine treatment in these cases.

STATIC AND DYNAMIC POSTURE OF HEAD AND NECK IN MIGRAINE PATIENTS

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Background Migraine attacks may be accompanied by tension headache-like symptoms, such as neck and shoulder pain with muscle contraction. Headache due to cervical dystonia has been recently recognised by the new IHS classification of headache disorders.

Objective The aim of this study was to assess the head-neck static posture and the range of head-neck motion in migraine patients without any disorders of the cervical spine or soft tissues of the neck.

Methods We studied the head-neck static posture and the range of head-neck motion in 70 headache-free migraine patients and 70 controls. Static posture was assessed with a photographic method. Dynamic posture was assessed with a specific computerized device that evaluated the following head-neck movements: right/left rotation, flexion/extension and right/left sidebending (while the patients were in the sitting position). The results were expressed as angles (in degrees).

Results Head-neck static posture was normal in migraine patients and controls. In motion testing, head rotation was decreased on one side and extension was less marked than flexion in migraine patients. Statistically significant differences between right versus left-side head rotation ($p < 0.001$) and head flexion versus extension ($p < 0.01$) were found in migraine patients, but not in controls.

Conclusions The results of this study suggest that, although the head-neck static posture was normal, head-neck motility may be abnormal in migraine patients. Muscle tenderness and contraction, as a possible consequence of pain, may be responsible for these abnormalities. Alternatively, more complex central mechanisms, such as sensitisation, may be evoked in the interpretation of our results.

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

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Introduction Headache is one of the most frequent complaints in the population referring to an emergency department (ED): in previous studies it accounted for 1%–4% of all presenting symptoms. In Italian studies this percentage varied from 0.6% to 1.2%. Moreover, headache represents one of the most frequent reasons for neurological consultation (NC).

Methods By means of a computerized database, we retrospectively examined all clinical records of patients presenting to our ED during 2005, complaining of headache as the only or prevalent symptom.

Results A total of 69 441 patients were admitted to the ED during 2005. Among these, 1 009 (1.45%) complained of headache; 390 were males, 619 were females; mean age was 39.5 years (41.4 years for males, 37.6 years for females). In this period 2 437 NC were done in the ED (3.51% of all consultations) and 40.8% of them were requested because of headache. Two hundred and fifty-one (24.8%) headaches were diagnosed as primary headaches (PH) (belonging to the first 4 groups of the IHS classification) and 439 (43.5%) as secondary headaches (SH). Four hundred and thirty-two (42.8%) patients were coded as "headache not otherwise specified" (NOS) (code 784.0 of the International Classification of Diseases system (ICD)). As regards to diagnosis, 1 037 consults were requested; 418 (40.3%) were NC, followed by 50 (4.8%) neurosurgical, and 31 (3.0%) neuropaediatric visits. CT scan was performed in 341 patients (82.6%) requested mostly by the ED physician. Moreover, 5 perfusional SPECT (in migraine with aura), 3 lumbar punctures and 2 MRI were carried out. Four hundred and eighty-four

(47.9%) patients received post-discharge advice. Among these, 191 (39.4%) were referred to our headache centre, but only 48 (25.1%) attended it.

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

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

HANDEDNESS AND UNILATERAL HEADACHE IN MIGRAINE

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

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

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

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

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

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

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

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

Surprisingly, in the right-handed patients (74.76%) (209) with recurrent pain on the same side, it was referred to the right side, and only

25.36% (71) referred pain to the left side. In contrast, 55.56% (15/27) of the left-handed patients identified headache on the right side, and 44.44% (12/27) referred headache to the left side.

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

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

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CLINICAL ASPECTS OF HEADACHES II

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

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

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

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

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

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

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

Results In group A, 13 patients (35.1%) were positive and 24 (64.9%) negative to the infection; in group B, 20 (37%) were positive and 34 (63%) were negative to the infection; finally, in group C, 2 (15.4%) were positive and 11 (84.6%) were negative to the infection (*p*=ns).

Discussion and conclusions On the basis of these data the presence of chronic gastric *H. pylori* infection does not seem to be related to gastrointestinal features during attacks, even though patients with gastrointestinal symptoms have a higher percentage infection than those without (36.3% vs 15.4%).

This observation could suggest the opportunity to ascertain the presence of infection particularly in this group of patients.

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HEADACHE PICTURES DURING THE COURSE OF CEREBRAL VENOUS THROMBOSIS

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Aim Description and classification of headache symptoms during the course of Cerebral Venous Thrombosis (CVT) in the acute-subacute phase (group A) and among headache patients with angiographic abnormalities suggesting previous CVT (group B).

Methods Headache classified according to ICHD-II; neurological deficits and outcome by National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS); seizures, intracranial hypertension, subacute encephalopathy and other syndromes by standard descriptive criteria. Neuroimaging: MRI and/or CT intracranial angiography and digital subtraction angiography (DSA). Clinical and neuroimaging follow-up: mean 19 months.

Patients Consecutive cases of acute CVT: $n=40$ (group A), 32 F (80%), mean age at onset 37.4 years; main risk factors: thrombophilic conditions in 28 patients (70%), oral contraceptives in 19 subjects (47.5%), overweight (BMI ≥ 30) in 30%. Site of thrombosis: transverse sinuses (70%), superior sagittal (60%) and others (cortical veins/jugular/others) isolated or in combination (55%). Clinical pictures (acute-postacute phases): headache as presenting symptom in 25/40 (62.5%), during the entire course, 85%, isolated – as the only symptom – in 5/40 (12.5%); sensorimotor deficits 37.5%; seizures 30%; intracranial hypertension with or without papilledema 17.5%; other neurological syndromes 50%. Most frequent complications during follow-up: epilepsy (42%) and headaches (33%); neuroimaging evidence of partial or complete recanalization occurred in over 85% at different time intervals from the acute event.

A smaller group of headache patients – $n=17$ (group B) with disabling symptoms (either episodic or more or less continuous), poor response to treatments, with neuroimaging signs suggesting a previous/remote CVT: 12 F, 5 M, 39.2 years at observation and with concomitant neurological focal abnormalities (clinical/EEG, CT/MR) in 36%.

Results Headache (any new/sudden-onset) is confirmed as being the most frequent symptom during the acute phase of CVT (present in 85% of cases) and also the most frequent and significant inaugural symptom. Headaches attributed to CVT are more frequently characterized by hyperacute disabling symptoms mimicking primary thunderclap headache and headache during the course of CSF hypotension or subarachnoid haemorrhage – as underscored by ICHD-II. Less frequently, migraine-like attacks, cervicogenic headache and other headaches with less specific characteristics may be observed.

Migraine-like headaches and clinical pictures fitting the criteria for one of the complications of migraine are more often observed during the long-term follow-up of CVT as well as among those headache patients showing chronically recurring disabling symptoms coupled

with evidence of possible-probable previous/remote CVT. Also for these cases, even in the absence of a close temporal relationship to the thrombotic event, the inclusion in the 6.6 diagnostic subgroup should be considered.

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

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Introduction The differential diagnosis between migraine (M) and tension-type headaches (TTH) is based on ICHD-II criteria (2004) including photophobia, phonophobia, nausea and vomiting as significantly associated symptoms. Osmophobia (O), i.e., altered odor perception, is reported in point D of the Appendix of this classification as a possible accompanying symptom of migraine without aura (MO); recently O has been found to be specific for the diagnosis of adult migraine [1]. In a pilot study we found that O was frequent in juvenile M, but it seems less specific than in adults [2].

Materials and methods Two hundred and seventy-five consecutive patients, referred to our Centre in 2005, were affected by M or TTH, according to ICHD-II criteria. Mean age was 11.4 ± 3.0 (6–17 years), 158 females (57.5%) and 117 males (42.5%). One hundred and sixty-seven (60.8%) suffered from M (144 (52.4%) MO and 23 (8.4%) migraine with aura (MA)), and the remaining 108 (39.2%) from TTH (88 (32%) frequent TTH and 20 (7.2%) chronic TTH).

Results The prevalence of O during attacks in the study population was 18.5%, higher in M patients (25.1%) compared to those with TTH (8.3%). In particular, O was found in 27.1% of MO, 13% of MA, 8% of episodic TTH and 10% of chronic TTH. There was no correlation between O and age or gender. O was usually described as a very early onset symptom (mean age at the onset of O: 8.1 ± 3.3 years and of headache: 8.1 ± 2.7 years). The offending odors were perfumes (63%), food-related smells (53%) and tobacco smoke (30%). The olfactory stimulus triggered the attack in 37.3% of osmophobic patients (26.2% with M).

In the differential diagnosis between MO and episodic TTH, O was a poorly sensitive symptom (27.1%) but rather specific (91.7%), and its specificity was greater than photophobia (61.4%) and phonophobia (45.5%). Regarding the positive predictive value, O had a greater value (82.3%) when compared to photophobia (74.1%) or phonophobia (65.5%), occupying third place after nausea (95.3%) and vomiting (100%).

Discussion In this sample of patients with juvenile primary headache, during M attacks, O was present in a smaller proportion (25.1%) than in adults reported in the literature (24.7–47.7%), and was observed less frequently in TTH. However, O represents a more specific factor for the diagnosis of migraine than photophobia and phonophobia.

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HEADACHE IN CHILDREN YOUNGER THAN 6 YEARS OF AGE

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

Methods We included in the study children who were evaluated during a period of five years (from 2001 to 2005), and were under 6 years of age at first observation. All the patients underwent a clinical evaluation/history and, if necessary, laboratory tests, radiological and other instrumental investigations. The headaches were classified according to the second edition of the International Classification of Headache Disorders (ICHD-II, 2004).

Results Of a total of 2 935 patients examined in the study period, 115 children (3.9%) were younger than 6 years, with a male/female distribution=68/47 (59.1% vs. 40.9%); mean age was 4.5 years, age range from 1.10–5.11 years. One hundred subjects (87%) had a positive family history for headache.

Thirty patients performed imaging tests: in 5 cases neuroimaging abnormalities were identified and led to the diagnosis: Arnold Chiari type 1 malformation in 1 case, sinusitis in 3 cases, and low CSF pressure in ventriculoperitoneal shunt in 1 case.

According to ICHD-II, 2004, we found 96 children at first observation with primary headaches (83.5%): 11 cases with migraine without aura (MO) (9.6%), 1 case with migraine with aura (MA) (0.86%), 2 cases with cyclical vomiting (1.7%), 6 cases with benign paroxysmal vertigo of childhood (5.2%), 69 cases with probable migraine (60%), 3 cases with infrequent tension-type headache (2.6%), 3 cases with probable tension-type headache (2.6%). Sixteen subjects had secondary headache (13.9%) (particularly systemic viral or bacterial infections and sinusitis); three children reported a mixed pattern.

A follow-up evaluation was possible in 57/115 cases (49.6%), 34 males (59.6%) and 23 females (40.4%); mean age of 4.5 years. Eighteen children (31.5%) were in "remission" and 39 patients (68.5%) showed recurrent symptoms: 12 cases with MO (21%), 1 case with cyclical vomiting (1.8%), 1 case with MO and cyclical vomiting (1.8%), 2 cases with benign paroxysmal vertigo of childhood (3.5%), 21 cases with probable migraine (36.8%), 2 cases with infrequent tension-type headache (13.5%). At follow-up only primary headaches were present.

Conclusions Our study shows male gender prevalence in pre-school age (male/female=1.44/1). Primary headaches were more frequent than secondary and post-traumatic headache; chronic daily headache and idiopathic stabbing headache were absent. Further follow-up studies are necessary to improve knowledge, treatment and outcome of headache in children younger than 6 years of age.

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

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Thunderclap headache, defined by IHS classification as a severe head pain of sudden onset, may raise the question of whether a subarachnoid hemorrhage has occurred.

We report two very unusual cases of thunderclap headache complicating minimally invasive medical procedures.

In the first case, headache developed as the consequence of a pneumocephalus caused by an inadvertent intrathecal puncture during oxygen-ozone therapy for lumbar disk herniation.

The headache of the second case was due to intracranial hypotension, caused by the persistence of the needle used for epidural anesthesia, which then penetrated into the subarachnoid space.

TREATMENT OF NONTRAUMATIC HEADACHE IN THE EMERGENCY DEPARTMENT

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Introduction Nontraumatic headache (NTH) is a common complaint in the Emergency Department (ED), accounting for 0.6%–4.5% of all visits. Guidelines for therapy of headache in the ED setting are lacking.

Objective The aim of the study was to analyse the therapies employed in patients presenting to the ED with a chief complaint of headache in order to provide therapeutic guidelines to ED physicians and improve the cost-to-benefit management of such patients.

Patients and methods A retrospective analysis of the records of all patients presenting in a six-month period (January 1, 2004 to June 30, 2004) with nontraumatic headache (NTH) to the ED of the University Hospital of Trieste was performed. Demographic and clinical information, therapies administered, and time spent in the ED were obtained. Data were analysed using the Statistical Package for the Social Sciences (SPSS 12.0).

Results We screened 300 NTH patients (0.8% of all ED visits), 61% F and 39% M with a mean age of 45 [SD 19] years. Diagnosis at discharge was secondary headache (41.3%), primary headache (24.3%), and headache "not otherwise specified" (NOS) (34.4%). One hundred and seventy patients (56.6%) were treated with mono- (86 patients, 50.6%) or poly-therapy (84 patients, 49.4%): 56.7% with NSAIDs, 13.4% with benzodiazepines, 10.7% with antiemetics, 6.2% with antihypertensives, 1.5% with triptans, and 11.5% with other drugs. Forty out of 50 patients with migraine received pharmacologic treatment, 90% with NSAIDs and 10% with triptans. The mean time spent in the ED was 225 [SD 285] minutes, with no differences between primary, secondary and NOS headaches ($p=NS$). The length of stay in the ED was similar in patients with primary headache treated with mono- (119 [SD 121] minutes) or poly-therapy (114 [SD 60] minutes) ($p=NS$). A significant difference in the length of stay in the ED between migraineurs who were administered triptans (112 minutes [SD 25]) and migraineurs treated with NSAIDs (265 minutes [SD 282], $p=0.02$) was found.

Conclusions Most used drugs were NSAIDs, first of all ketorolac and indomethacin. Patients with primary headache had the same outcome in terms of time spent in the ED when treated with mono- or poly-therapy. Only 10% of migraineurs received triptans, despite the recommendation to use triptans as first-line drugs for moderate and severe migraine attacks. The administration of triptans in patients with migraine significantly reduced the length of stay in the ED. Patients in whom triptans were used did not need other drugs. Therapeutic guidelines to ED physicians are needed to improve the cost-to-benefit management of such patients.

CHRONIC HEADACHES: NEW ACQUISITIONS

THE ROLE OF SENSITIZATION MECHANISMS IN CHRONIC HEADACHES

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

evidence that early triptan treatment blocks the migraine attack and cutaneous allodynia in allodynic patients. It is reasonable that an activity-independent central sensitization can develop in patients with frequent attacks and long-lasting disease, leading to a chronic form of headache. This hypothesis could explain the high extracephalic sensitivity to electrical stimuli in chronic migraine with overuse of symptomatic drugs, to thermal and mechanical stimuli, observed in patients with migraine attacks and transformed migraine as well as the close association between chronic migraine and other chronic painful syndromes such as fibromyalgia, in which both a widespread central sensitization and a defective functioning of the supraspinal antinociceptive system, has been hypothesized.

Functional imaging studies in chronic headaches emphasized the involvement of modulatory nociceptive and antinociceptive brainstem and cortical structures. Such structures may contribute to the pathological changes in the physiological properties of trigeminal neurons and could explain the subsequent sensitization of the nociceptive pathways at several levels of the central nervous system during migraine attack. In this view, both an activity-dependent (sensitization of peripheral nociceptors) and an activity-independent (probably driven by a permanent dysfunction of descending modulatory pathways) central sensitization, may account not only for the transformation of episodic to chronic pain condition but also for a widespread abnormal nociceptive processing along the cephalic and extracephalic pain pathways, inducing a spreading process of central sensitization.

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

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The treatment of Chronic Daily Headache (CDH) is still inadequate. Effective, well-tolerated prevention represents the last goal for a complete rehabilitation of CDH patients. Medication-overuse headache (MOH) often overlaps CDH, causing the re-prophylaxis phase schedule after detoxification to be inadequate and providing only short-term relief. We presently reviewed studies concerning the efficacy of Botulinum Toxin Type A (BoNT-A) as preventative treatment for CDH. The 2004 IHS classification of CDH includes all chronic headaches lasting more than 15 days per month, for a period longer than 90 days. The clinical forms mentioned in this term are the following: Chronic Tension-Type Headache (CTTH), Chronic Migraine (CM), Transformed Migraine (TM), Hemicrania Continua (HC), and New Daily-Persistent Headache (NDPH). This large group of chronic headaches needs to be definitively recognized in the next revision of the IHS Classification.

The therapeutic armamentarium of CDH is based on old drugs, antidepressants (tricyclics) and NSAIDs. There is an evident paucity of evidence-based medicine current treatments used in the prevention of CDH. Both topiramate and BoNT-A seem to represent – in terms of efficacy – the most convincing options in the operational therapeutic scenario of CDH. Nevertheless, the presence of adverse events (AEs) should always be considered in the therapeutic choice of these chronic disorders.

A retrospective analysis of both open and double-blind studies on the efficacy of BoNT-A in CDH, with or without MOH, showed conflicting results. Some authors explained these results with a selection of CDH patients with and without MOH in the trials. BoNT-A prevention mechanisms for CDH are not completely known, and are probably not just based on acetylcholine inhibition of the neuromuscular junction. BoNT-A may have a distinct antinociceptive mechanism or inhibit calcitonin gene-related peptide release, substance P and other neuropeptides at the trigeminal level, as suggested by studies in animal models. Further larger studies are needed to confirm the efficacy of BoNT-A and therefore to provide a new effective, safe and widely accepted therapeutic option for CDH.

THE CHRONIC PATIENT AND DRUG ABUSE

MEDICATION-OVERUSE HEADACHE: FROM THEORY TO PRACTICE

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Medication-overuse headache (MOH) is a secondary headache coded in section 8.2 of the revised International Classification of Headache Disorders (ICHD-II) [1]; the diagnostic criteria for MOH defines the substance overused (ergotamines, triptans, analgesics, opioids, combinations), the duration of overuse (at least 3 months), and the days of intake per month. According to ICHD-II, the diagnosis of MOH can be assigned when, within two months of discontinuation of the overused medication, the following conditions are met: reversion of headache from a chronic to episodic pattern (<15 headache days/month) and discontinuation of overuse (<10–15 days/month).

MOH is a considerable health problem, reported by up to 10% of European Specialty Headache Clinics. The clear pathogenesis of MOH is unknown. Is the overuse a causative, aggravating or facilitating factor? Does the overuse depend on the drug type, the duration of exposure, or the habits of the patient? There is general agreement that the only treatment for MOH is withdrawal of the overused drug, but there are no guidelines or consensus recommendations on the management of this condition. There are some indications on withdrawal as outpatients or in-patients but very few prospective studies have investigated the course and outcome of MOH after withdrawal.

The main problem in the management of MOH is relapse into overuse after withdrawal. The management of these patients must therefore include, in addition to detoxification and drug therapies, an integrated programme of care covering the needs of the patient and family members, lifestyle indications, non-pharmacological therapy, interaction between patients (support groups), and planning for discharge.

In our Headache Centre a course of care (CARE) has been developed for the management of MOH patients [2]. In this prospective study inpatient detoxification was followed by scheduled visits for two years after discharge. Each subject underwent a baseline standard interview and a Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). After discharge the subjects returned for five scheduled visits (three in the first and two in the second year). We also conducted telephone follow-ups between visits. The management of these patients needs more than pharmacological treatment and must include non-pharmacological modalities and patient education. CARE is a model for the management of a chronic condition and it allows monitoring of the course of MOH with regard to relapses and predictors of outcome.

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

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

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

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

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

MEDICATION-OVERUSE HEADACHE: CLINICAL ASPECTS AND PATHOPHYSIOLOGICAL IMPLICATIONS

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

A linear relationship between analgesic use and headache frequency has been found. The disorder affects either adolescents or adults of various ages. MOH has been frequently associated with psychiatry comor-

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

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

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

Patients and methods A total of 120 patients, 82 females (68.3%) and 38 males (31.6%), mean age 48.6±10.4 years, affected by probable chronic migraine (PCM) and probable medication-overuse (PMOH) according to ICHD-II diagnostic criteria were admitted to the study. Patients were treated in an outpatient regimen with abrupt discontinuation of the medication-overused, intravenous hydration and ademetionine, metoclopramide if necessary, and oral or intravenous administration of benzodiazepines for 7–10 days. Analgesics or triptans were used under medical supervision only in cases of severe rebound headache. Prophylactic medication was started immediately after admission.

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

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

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

frequency of headache of 71.7% in group A and only 10.1% in group B ($p<0.001$). Similarly, the duration of head pain was reduced by 61.2% in group A and 15.6% in group B ($p<0.0002$). The headache score after one year was 17.7 in group A and 52.0 in group B ($p<0.0001$).

A total of 51 (42.5%) successfully detoxified subjects in group A returned to an episodic pattern of migraine, compared to 10 (8.3%) in group B ($p<0.003$).

The mean LDQ total score was higher in group B (11.10 ± 6.35) than in group A (9.27 ± 5.51) at baseline. Group B had the highest scores in item 9 ($Z=-5.27$, $p<0.001$) addressing the need for the continued administration of the drug to maintain well-being, and in item 3 ($Z=-2.39$, $p<0.05$), exploring compulsion to start the use of the drug. A significant reduction of LDQ scores was found at the one-year follow-up in group A (5.21 ± 2.78) compared with group B (10.20 ± 5.23) ($p<0.001$).

Discussion The results of the present study suggest that the abrupt withdrawal and detoxification regimen leads 56.7% of patients to discontinue the overused drugs and the majority of them within one year to return to a pattern of episodic migraine. The remaining patients did not discontinue the abused drugs and retained a chronic pattern of headache. They showed a behaviour of drug dependence similar to that found in the drug-addicted group. Patients who positively responded to the drug detoxification regimen had, in contrast, a drug dependence behaviour, which seemed to originate essentially from the necessity for the analgesic to cope with everyday life [2].

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ADVICE ALONE VERSUS STRUCTURED DETOXIFICATION PROGRAMMES FOR MEDICATION-OVERUSE HEADACHE: A 1-YEAR PROSPECTIVE, RANDOMIZED, OPEN-LABEL TRIAL IN TRANSFORMED MIGRAINE PATIENTS WITH LOW MEDICAL NEEDS

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

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

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Introduction Chronic migraine (CM) with medication-overuse headache (MOH) is a very disabling condition, frequently associated with psychiatric comorbidity. At present, clear guidelines for the withdrawal of the overused drug and detoxification are lacking. In this regard, a role for psychological support has been hypothesized.

Objective We studied the efficacy of an integrated pharmacological and brief analytic psychotherapeutic approach in these patients.

Patients and methods We enrolled patients affected by probable CM and MOH (ICHD-II). They underwent a standardized neurological and psychiatric evaluation before and 6 months after medication withdrawal. Patients were randomly assigned to pharmacological treatment alone (group A), or associated with a brief analytic psychotherapy (group B). We applied the technique of Gillieron (1989), based on the principles of brief psychodynamic psychotherapy and mainly oriented toward assisting the patients with clarification and understanding of their disorder [1].

Results Twenty-one consecutive patients (M/F: 1/20, mean age 46 ± 10 years) with probable CM and MOH were included. Headache frequency was 27.9 ± 5.4 days/month, with a mean drug intake of 60.3 ± 35.2 tablets (25.5% triptans, 13.1% ergotamine, 2.2% codeine, 32.4% NSAIDs, and 26.9% combined analgesics). The mean age of first attack was 19.6 ± 7.8 years and mean duration of MOH was 7.6 ± 9.4 years. Eleven patients were randomly assigned to group A and 10 to group B. About 70% of patients presented with psychiatric comorbidity, in particular, anxiety (42%) and depressive disturbances (32%). To date, 15 patients had completed the 6-month follow-up (A, 6; B, 9), showing a clinical improvement (headache frequency 16.7 ± 11.4 days/month, drug intake 12.9 ± 11.0 tablets/month). With respect to baseline, patients treated with the integrated approach showed a greater decrease of headache frequency (days/month: -48% vs. -32%) and drug intake (tablets/month: -87% vs. -68%, $p<0.04$) than those only treated pharmacologically. In particular, they showed a lower relapse rate (10% vs. 36.4%).

Conclusions The integrated approach improved treatment efficacy in MOH patients, particularly decreasing drug overuse. This practical form of brief psychological support is effective and may help the patients in a shorter time and at a lower cost than long-term psychotherapeutic treatments.

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ALEXITHYMIC FEATURES AND PERCEIVED STRESS IN CHRONIC TENSION-TYPE HEADACHE AND MEDICATION-OVERUSE HEADACHE PATIENTS

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Introduction The definition of a personality profile in headache patients is no longer considered an attainable goal for empiric research, which has focused on specific psychological variables including coping mechanisms, emotional distress and alexithymia, conceived as difficulty in identifying and communicating emotions. Recent studies have found alexithymic features connected with anxiety and depression in headache patients [1, 2].

Objective The study intended to investigate the relationships between alexithymia and perceived stress in primary headaches, exploring pos-

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

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

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

Conclusions Findings supported the association between alexithymia and perceived stress as an index of psychological maladjustment. CTTH and MOH patients showed some distinctive features that require further research.

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PSYCHOPATHOLOGICAL FACTORS IN HEADACHES

SLEEP, SLEEPINESS AND FATIGUE IN MIGRAINE

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Introduction Several lines of evidence support the association between migraine on the one hand and sleep and sleep disorders on the other. Even though several pathogenic hypotheses have been postulated, the exact nature of this relationship remains enigmatic. Recently, interictal daily activities and functions were also examined in migraine sufferers. Low levels of realizable activity and of vigour were, indeed, documented, which could be conceptualised as the consequence of a migraine specific CNS functioning or alternatively as an acquired habit to anticipate and/or avoid a migraine attack. Moreover, limited data have suggested that daytime vigilance levels are impaired and that the complaint of chronic fatigue is greater in chronic migraine than in controls. The aim of this study was to verify sleep quality and daytime functioning parameters, such as sleepiness and fatigue, in episodic migraine.

Materials and methods One hundred patients diagnosed with migraine without aura, according to the second edition of the International Classification of Headaches (2004), were enrolled. Pittsburgh sleep quality index and Epworth Sleepiness Scale (ESS) were applied to all patients to evaluate sleep quality and “habitual” daytime sleepiness. In sixty patients, the Stanford Sleepiness Scale (SSS) was also administered in the prodromal phase (–24, –12 and –2 hours before attack onset) and during migraine attack, at onset and 1, 2, 4, 12 and 24 hours later to evaluate “critical” sleepiness. Patients were instructed to treat migraine attack with triptans in the early phase.

Results A total of 62% of migraineurs reported poor sleep quality and complained of chronic fatigue, while only 12% showed intercritical excessive daytime sleepiness according to ESS.

Evaluation of the time course of sleepiness by means of SSS confirmed significant impairment of vigilance levels in the prodromal phase, respectively, at –12 and –2 hours from the beginning of the episode. Significant differences in SSS scores were also documented at attack onset and 1 and 2 hours later compared with interictal values.

At four hours, mean SSS scores did not differ from their interictal values in the whole group and in patient responders to the treatment (pain free at 2 hours from drug intake), whereas non responders were sleepier than in intercritical conditions.

Discussion These data confirm the occurrence of sleepiness in the prodromal phase, possibly related to hypothalamic involvement and orexin neurotransmission impairment. The evidence that drowsiness, evident at the start of the attack, is resolved after migraine specific treatment, when efficacious, suggests that critical sleepiness might also be related to pathogenic mechanisms of migraine, whereas the role of triptans might be absent or minimal.

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

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In clinical practice and in the literature the co-occurrence of sleep disorders and headache is well known. Conversely, the intimate mechanisms of this association are not quite known. Surely, in the so-called sleep-related headaches, a causal and/or temporal relationship is admitted and both the International Classification of Headache Disorders, 2nd Edition (ICHD-II) [1] and the International Classification of Sleep Disorders, 2nd Edition (ICSD-2) [2] provide diagnostic criteria for these cases.

The ICHD-II includes two provisions for sleep-related headaches. Sleep apnea headache is a subclassification of headaches attributed to hypoxia and/or hypercapnia under the major code heading 10; it had the same code 10.1.3 in the previous classification but the diagnostic criteria are well defined only in this edition. According to the comment, it is unclear whether the mechanism of the headache is related to hypoxia, hypercapnia, or the disturbance in sleep. Hypnic headache is a new entry in the classification of headaches and is coded 4.5 within “Other primary headaches”: it is characterized by attacks of dull pain that may be unilateral or bilateral and always occurs after falling asleep with no autonomic symptoms. No pathophysiological mechanisms are purposed.

In the first edition of ICSD, sleep-related headaches were included in the secondary sleep disorders, within those due to neurologic disorders. In ICSD-2, the secondary sleep disorders are not included: “following ICD rules, as soon as the underlying disorder is diagnosed, it becomes the primary diagnosis, and the previous sleep-related diagnosis is usually dropped because it is seen as a symptom of the underlying disorder”. Thus, the sleep-related disorders are listed in Appendix A within the sleep disorders associated with conditions classifiable elsewhere.

The group includes "a heterogeneous group of different headache entities with the common feature of occurrence during sleep" (during REM sleep or 3–4 non-REM sleep) or upon awakening.

A singular sleep disorder, listed under "Other Parasomnias", is the Exploding Head Syndrome, which consists of the perception of a sudden sense of explosion in the head either at the wake-sleep transition or upon waking during the night followed by sudden arousal with a sense of fright. Although this experience is typically painless, the possible simultaneous occurrence of a stabbing pain raises the problem of a differential diagnosis from sudden-onset headache syndromes.

Knowledge of the diagnostic criteria of sleep-related headaches allows the headache specialist to better recognize the co-occurrence of the two disorders, resulting in a clear advantage for the management of the patient.

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

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Introduction Headache and epilepsy are disabling conditions affecting the life of the patients and their families.

Studies showed a high rate of anxiety and mood disorders in both conditions, but we do not know the direction of influence and the aetiological mechanisms. We know that both disorders may run in families, as psychiatric disorders do.

The main aim of this study was to examine the psychiatric situations of the mothers of headache or epileptic patients, compared to the mothers of healthy children.

Material and methods Sixty-five (37%) (mean age 39.05 years) mothers of headache sufferers, 50 (29%) of epileptic children (mean age 38.8 years) and 60 (34%) mothers of healthy children (mean age 40.07 years) were interviewed using the MINI to make diagnoses according to DSM-IV criteria. The ICHD-II (2004) was used to make the headache diagnoses and the classification of the International League against Epilepsy (1989) to classify seizures. All statistical analyses were carried out using the χ^2 test.

Results Comparing data with the healthy sample, both headache and epileptic samples showed higher numbers of psychiatric disorders than controls ($p < 0.05$). Among the 65 mothers of headache patients, 25 (38.4%) had at least one anxiety and/or mood disorder, of the 50 mothers of epileptic children, 28 (56%) had at least one anxiety and/or mood disorder ($p = n.s.$).

In the group of 65 mothers of children with headache, a subgroup exists from the 38.4% of mothers who showed at least one anxiety or mood disorder with 9 (13.85%) showing mood comorbid with an anxiety disorder.

In this sample of 25 mothers with a psychiatric disorder, we found that mothers with an anxiety disorder have a higher percentage of migrainous vs non migrainous children (24% vs 16%); mothers with mood disorders have children who suffer from tension-type headaches, mainly the episodic type (12%); mothers with an anxiety disorder comorbid with a mood disorder have the same number of children with migraine without aura (3) and chronic tension-type headache (3).

Discussion and conclusions Very few studies have investigated the psychiatric situation of the mothers of children with epilepsy or headache, while there are many concerning the psychological profile of children or adolescents with these disorders. Mothers of epileptic children showed a greater number of psychological disorders compared to mothers of headache sufferers, even without a statistical difference. The meaning of the high prevalence of psychiatric disorders needs further study to understand the direction of influence, the etiological mechanisms and the diagnostic implications.

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

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Objective Our purpose was to examine the effects of a cognitive and exercise instruction programme on frequency of headache, neck and shoulder pain in a working community.

Materials and methods Three hundred and forty-three employees of the city of Turin, whose working activities involved public contact (registry and tax office), were distributed into two groups: study group ($n=169$) and controls ($n=175$). In all subjects data were collected on headache, and facial, neck and shoulder pain, if present. They were then given a diary in which to record, on a daily basis, frequency, severity and duration of the headache and facial, neck and shoulder pain episodes from March to October 2005. At month 3, an instruction programme was administered to the study group: it consisted of brief shoulder and neck exercises to be performed several times a day, a relaxation exercise and instructions on how to reduce hyperfunction of the craniofacial and cervical muscles during the day. Both groups kept the diary for a further six months (months 3–8). For each subject, the difference in symptom frequency between each month and months 1–2 (baseline) was calculated, and the mean differences between the two groups compared with parametric and nonparametric tests.

Results The monthly frequency of headache significantly decreased over time in the study group compared to controls; the same pattern was observed for the frequency of facial pain, neck and shoulder pain ($p < 0.001$ at month 8). Moreover, the monthly frequency of drug intake significantly decreased in the study group ($p < 0.05$ at month 8). The data were confirmed in a multiple regression analysis adjusted for gender and age. The relative benefit at month 8 was: 35% for headache frequency, 38% for frequency of neck and shoulder pain and 35% for drug usage.

Discussion To the best of our knowledge, this is the first, longitudinal controlled study of this kind, carried out on a relatively extensive working community. The results demonstrate that the administration of a simple instruction programme can significantly decrease the prevalence of headache, facial and cervical pain in large population samples.

Conclusions The intervention programme employed in this trial is a powerful and economical instrument to reduce head and cervical pain, along with drug intake, in an extensive working community.

ANXIETY, DEPRESSION AND HEADACHE: CLINICAL AND THERAPEUTIC ADVANCES

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Introduction Several studies on the general population and in the clinical setting have confirmed the clinical impression that depressive and

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

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

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

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

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

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STRATEGIES IN TRIPTAN USE

TRIPTANOGENOMICS

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

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

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

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

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

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

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

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

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

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

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

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

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RESPONDERS AND NON-RESPONDERS TO TRIPTANS: BIOLOGICAL CORRELATES

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

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

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

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

nificantly reduced one hour after administration in the 5 patients with autonomic signs. After rizatriptan administration, CGRP and NKA levels in non-responder patients showed less significant variations at all time points compared with rizatriptan responders.

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

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

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ALLODYNIA AND EARLY TREATMENT OF MIGRAINE ATTACKS WITH TRIPTANS

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

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

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

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

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

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

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

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

Patients and methods The presence of severe autonomic symptoms during migraine attacks was carefully evaluated in 76 consecutive subjects (M/F 27/49; mean age 36.2 ± 6.4 years) with history of MO by both a structured interview and telethermographic investigation. Based on these findings, the entire group was dichotomized into a subgroup with severe autonomic symptoms (42 patients, migraine with aura

(MA)) and a subgroup without (34 patients, MO). The two subgroups were comparable for demographic characteristics and other clinical variables, including pain severity. Clinical response to triptans (eletriptan 40-mg tablets) during 3 consecutive migraine attacks was recorded in each subject. End points were pain-relief and pain-free response at 1 and 2 hours.

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

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

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

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

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

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

Discussion In our evaluation we found that 0.55% of the residents in our district received at least one prescription of a triptan in one year.

Assuming that the migraine prevalence in Italy is reported to be 12%, only 6% of our patients received specific triptan antimigraine drugs. About 60% received only one prescription in one year, supporting a very low utilization of triptans. Oddly, we found that 14% of the prescriptions were filled for subjects over 65 years old, a population with higher risk of hypertension and cardiovascular diseases. Oral formulations accounted for the most prescribed route (94%), probably reflecting patients' and/or physicians' preferences for the oral route of administration and better compliance. At least 3.2% of patients could be triptan abusers (>10 dosage units/month).

Conclusions This study shows a very low triptan utilization in the studied population. These data may imply that most migraine patients do not achieve adequate relief because of undertreatment and have need of more effective strategies. Another point to mention regards the considerable amount of prescriptions in the elderly and the high dosages utilized by a small cohort of subjects (triptan abusers).

PERSPECTIVES ON PROPHYLAXIS IN HEADACHES

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

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Objective To analyze the efficacy of botulinum toxin type A (BTX-A) preventive treatment of chronic tension-type headache (CTTH) and the impact on headache pharmaceutical utilization and cost.

Design/Methods A retrospective chart review of the efficacy of BTX-A preventive treatment of 100 CTTH patients, diagnosed according to International Headache Society criteria, was followed by a one-year prospective analysis of headache pharmaceutical utilization and costs before and after BTX-A treatment. A direct survey of per patient pharmaceutical consumption was obtained through appropriate questionnaires [1]. Pharmaceutical average cost and incremental (additional) average cost criteria were utilized for the periods before and after BTX-A treatment.

Results The retrospective chart review revealed that BTX-A treatment resulted in 26 patients reporting a total absence of pain and substantial reduction in pharmaceutical use; 37 patients reported significant pain reduction and significant reduction in pharmaceutical use; 22 patients reported some pain reduction and a slight reduction in pharmaceutical use; 15 patients reported no effect or "possible" worsening of pain and no reduction in pharmaceutical use. The one-year prospective analysis revealed that after BTX-A treatment, there was a 45% of reduction in the use of analgesics/antimigraine drugs, a 35% reduction of nonsteroidal anti-inflammatory drugs and a 100% reduction in the use of calcium channel blockers. The average cost of pharmaceuticals was reduced from € 853,43 before BTX-A treatment to € 450,47 after BTX-A treatment.

Conclusions BTX-A was an effective preventive treatment of CTTH resulting in a substantial reduction of headache medication utilization and cost as emerged by previous studies by our group [2].

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PREGABALIN: BEYOND NEUROPATHIC PAIN

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Objective This was an open label study aimed at evaluating the efficacy of pregabalin in reducing the number of days with headache and the amount of acute medication taken monthly in patients with chronic headache with medication overuse.

Methods The studied sample consisted of 20 subjects. Pregabalin was administered at 75 mg a day for 7 days and at 75 mg in two daily administrations. The study consisted of a titration phase (1 week) and of a maintenance phase (8 weeks).

Outcome measures

- Reduction in the number of days with headache/28days
- Reduction in the amount of acute medication taken/28 days
- Number of patients who were pain-free at two hours after triptan intake and headache recurrence rate in the 22 hours following the pain-free condition
- Tolerability profile

Results The group treated with pregabalin had a significant reduction in the number of days with headache and in the mean amount of acute medication taken.

Conclusions Pregabalin proved to be well tolerated and effective in reversing chronic migraine with medication overuse to episodic migraine.

HYPOSTIMULATION OF EPICRANIAL NERVES IN THE PROPHYLACTIC TREATMENT OF MIGRAINE

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Objective A disorder in the head region can provoke pain in the areas innervated by the trigeminal and upper cervical nerves due to convergence of the afferent fibers of the three superior cervical roots on the neurones of the spinal nucleus of the trigeminal nerve. The therapeutic effectiveness of greater occipital and supraorbital nerve blockade in 262 patients with migraine (ICHD-II classification: migraine without aura, 230; migraine with aura, 19; and cervicogenic headache, 13) unresponsive to conventional therapy was investigated.

Methods and results Patients were given repeated daily anesthetic blocks (range 5-10). Perineural injections of 0.5 to 1.0 mL of 0.5% bupivacaine were given at the epicranial emergence points of the nerves in relation to the distribution of the cephalic pain only if the nerves were conspicuously pain sensitive to pressure. Clinical evaluation was based on a monthly Pain Total Index and recording of the monthly number of migraine attacks and analgesic consumption. Patients were considered responsive when the Pain Total Index decreased by $\geq 50\%$ in the first month after treatment.

Two hundred and fifteen patients (82%) responded well and maintained a favourable response over the 6-month period of observation. The treatment was considered to be of long-lasting effectiveness and without side effects. Method and evaluation criteria are exhaustively described in a previous study carried out by our group [1].

Discussion and conclusions Therapeutic blockade of the greater occipital and supraorbital nerves may have resulted in inhibition of the constant trigeminal hyperexcitability, which characterizes headache, not only by blocking the conduction of noxious stimuli but also by blocking the antidromic flow of substance P and calcitonin gene-related peptide (CGRP), mediators of the axonal reflexes that underlie perivascular neurogenic inflammation. The consequent vasodilatation and extravasation of these peptides, local reinforcing

factors of the algogenic stimulation, may have been interrupted by the anesthetic, resulting in normalization of the response threshold to the nociceptive stimuli.

Inhibition of axonal transport by local anesthetic is well documented [2]. Repeated anesthetic blocks could produce a long-lasting hypostimulation of the peripheral nociceptors, rebalancing their activation threshold and consequently arresting induction of the neuroplastic mechanism of central hypersensitization that may clinically produce chronic pain. Repeated anesthetic nerve blockade, albeit not influencing the underlying cause, would interfere in the central pathogenic mechanism of formation and transmission of trigeminal nociceptive stimulation of the migraine crisis.

The treatment appeared to be effective in these forms of unresponsive migraine and in the chronicized form with drug abuse. We hope that this clinical experience, together with a correct neurophysiological study, may prove useful in clarifying the pathogenic aspects of migraine.

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LANGUAGE DISTURBANCES AS A SIDE EFFECT OF PROPHYLACTIC TREATMENT OF MIGRAINE

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The present study was aimed at verifying the occurrence of language disturbances as a side effect of topiramate treatment for at least 3 months in 30 migraine patients (86.7% in the chronic form). Twenty migraine patients treated with other prophylactic drugs, but not antiepileptic drugs, for at least three months and 20 migraine patients without prophylactic treatment, with similar characteristics of headache and distribution of migraine subtype and subform diagnoses, were used as control groups. Language functions were explored with neuropsychological tests, including the Trail Making Test, a test of Phonemic and Semantic Verbal Fluency, and a Denomination test. Language disturbances were referred by 26.7% ($n=8$) of patients under topiramate treatment but by none of the patients of the two control groups. The majority of patients were accompanied by other side effects. In only one case they were moderate in intensity, but mild in the other cases.

Regarding neuropsychological testing, a significant difference between the topiramate group and the two control groups emerged for the TMT-B subtest of TMT and two of the three categories of semantic verbal fluency (flowers and cities) with the worst scores for the topiramate group. When patients with referred language disturbances in the topiramate patient group were compared with those without, the former had scores indicative of a worse performance for all neuropsychological test variables, and a statistically significant difference was reached for TMT-A, TMT-B and denomination test. Patients without referred language disturbances in the topiramate group showed, in all cases, a worse performance on all tests compared to patients in other prophylactic treatments or untreated migraine patients.

It can be hypothesized that a disorder such as migraine, which involves numerous cortical and subcortical circuits implicated in pain processing as well as behavioural and emotional processing of pain, represents a facilitated substrate for the occurrence of language disturbances due to topiramate [1, 2]. This can be the expression of a more generalized impairment of cognitive processing. These aspects should be investigated in prospective studies involving larger migraine patient samples, and research should not be limited to topiramate prophylactic treatment but should also extend to prophylactic treatment with other antiepileptic drugs.

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TOPIRAMATE VS. AMITRIPTYLINE IN THE THERAPY OF CHRONIC PRIMARY HEADACHE

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Background and aims The revised edition of the International Headache Classification (ICHD-II) seems to have resolved most of the diagnostic controversy concerning chronic headaches: migraine is considered chronic if attacks occur at least 15 days a month for at least 3 months as well as the criteria already stated for tension-type headache [1]. Amitriptyline has been extensively studied and can be considered as the gold standard in the preventive treatment of chronic headache. Contemporary concepts of headache pathogenesis provide an account for the use of antiepileptic drugs as preventive drugs [2]. Therapeutic indication for topiramate is limited to migraine preventive therapy. The aim of this study was to compare amitriptyline and topiramate in the preventive therapy of chronic headache.

Methods A sample of 110 adult subjects consecutively referred to the Headache Disorder Centre, Department of Neurological and Psychiatric Sciences, University of Bari were included. All of them were affected by chronic migraine or tension-type headache according to ICHD-II criteria. The Symptom Check List 90R was administered to all of them for possible psychopathological disorders. Patients were randomly assigned a therapy of amitriptyline, 20 mg or topiramate 50 mg. The two groups were age- and sex-matched. Drug efficacy and tolerability were assessed after a three-month therapy period.

Results A $\geq 50\%$ decrease in attack frequency was shown in 63% of cases after topiramate and in 65% after amitriptyline treatment, without significant difference between drugs. No significant difference was found between amitriptyline and topiramate efficacy both in the sample of chronic tension-type headache and in the sample of chronic migraine. No difference was found between the two drugs in patients with and without symptomatic abuse. Patients with anxiety and depressive symptoms showed a greater improvement when treated with amitriptyline. Both drugs were well tolerated.

Discussion and conclusions These results suggest that topiramate as well as amitriptyline can be effective and tolerated in chronic headache. Although the exact mechanism of action of this drug in headache prevention is still unclear, it might act by means of the modulation of the nociceptive system preventing both peripheral and central sensitization, which predisposes to attack recurrence [2]. Amitriptyline should be the first choice drug in the case of headache comorbidity with psychopathological symptoms.

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EFFECTS OF PHOSPHODIESTERASE INHIBITORS ON MIGRAINE AND CLUSTER HEADACHE

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Introduction In the 2nd edition of the International Classification of Headache Disorders [1] we find at chapter 8.1.2 the “Phosphodiesterase (PDE) inhibitor – induced headache”. The diagnostic criteria are A) Headache with at least one of the following characteristics and fulfilling criteria C and D: 1 bilateral, 2 frontotemporal location, 3 pulsating quality, 4 aggravated by physical activity; B) A single dose of a phosphodiesterase inhibitor has been given; C) Headache develops within 5 hours of PDE inhibitor intake; D) Headache resolves within 72 hours. PDEs are a large family of enzymes (11 types) that break down cAMP and cGMP; the inhibition of PDEs raises intracellular levels of cAMP and cGMP. Sildenafil, the most widely known PDE-5 inhibitor, seems to determine headache through other mechanisms in addition to arterial dilatation, such as stimulation of perivascular pain sensitive fibers or central neurons of pain-pathways. We report on the effect of PDE-5 inhibitors in four patients (suffering from impotence), three affected by migraine and one by cluster headache.

Materials and methods Of three migraine patients (mean age 39 years) suffering from impotence, two were treated with vardenafil 10 mg, one with sildenafil 50 mg. One patient, affected by cluster headache (CH), was treated with sildenafil 50 mg. All patients were asked to refer the possible effect of PDE inhibition on their headache.

Results and discussion Two of the three migraine patients, one treated with vardenafil and one with sildenafil, referred headache similar to their usual migraine attacks within 5 hours from ingestion of the drug. The third patient, referred within 5 hours from taking vardenafil 10 mg a “cluster-like” attack, of less than one hour duration. The CH patient, after taking sildenafil 50 mg, referred headache similar to his usual cluster attacks.

Conclusions Whereas in two of three migraineurs the headache that followed consumption of a PDE inhibitor was like their usual headache, the symptoms of the third migraine patient were novel, in that he developed a “cluster-like” headache. Also remarkable was the headache of the patient affected by CH, who referred after taking the drug, a typical cluster attack. Thus both migraineurs [2] and CH patients should be informed of PDE-5 inhibitor-induced headache.

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PLACEBO AS A PROBLEM OR A RESOURCE?

PLACEBO AND ANALGESIA: FROM THE LABORATORY TO CLINICAL PRACTICE

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The placebo effect has long been a source of debate in order to identify its nature and real power. The effect that follows the administration of an inert treatment, pharmacological or not, is the consequence of several endogenous mechanisms, including conditioning and expectation of clinical benefit.

Electrophysiological studies in humans have highlighted the role of opioids and non-opioid systems in placebo analgesia. Several studies

show that placebo analgesia is antagonized by the opioid antagonist, naloxone, suggesting a role for the endogenous opioids, but the role of opiates is still far from clear. The use of different methodologies for exploring pain perception, including intense and prolonged stimulation (i.e., for ischaemic pain) instead of strong painful phasic electrical stimulation (i.e., nociceptive withdrawal reflex) seems to play a different role in inducing the activation of the opioids system and analgesia.

Anticipation of pain and prolonged intense stimulation seem to be necessary in producing the so-called “stress-induced analgesia”, which is typically opiate-mediated and naloxone-reversible; in contrast, the placebo effect generated by expectation of analgesia is absolutely irrelevant on the excitability of the nociceptive withdrawal reflex or plasma endogenous opioids system.

The mechanisms of the placebo response carry significant implications for clinical trial designs and thus clinical practice. The importance of the expectation of a benefit in the treatment outcome has been emphasized in several reports in recent years, and it could represent a significant limitation during placebo-controlled trials.

The utilisation of a hidden injection coupled with standard administration is known as the open-hidden paradigm, a paradigm that may provide an excellent alternative to placebo-controlled trials.

These considerations are particularly relevant in the headache field, where the placebo effect in the treatment of the attacks has been estimated to be from 6% to 47%.

Further research identifying and quantifying the factors involved in the mechanisms of the placebo response can increase the outcomes of the treatment and enhance our knowledge of the mind-brain-body interaction.

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

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Introduction Placebo and nocebo responses have not been adequately investigated in patients with primary headaches. In randomized clinical trials of analgesic, approximately 30% of the patients with migraine showed a placebo effect. However, a tremendous variation among the different studies was observed. The purpose of this study was to evaluate the prevalence of placebo and nocebo responses in a large group of patients with migraine or tension-type headache recruited from a university-based Headache Centre.

Methods A total of 726 consecutive patients (208 men, 518 women; mean age±SD=41.9±16.0 years), attending the Headache Centre of the University of Turin (Italy), were involved in the study. The diagnosis of migraine was made according to ICHD-II criteria. The patients underwent an extensive physical and neurological examination. Psychological evaluation was performed using the BDI, the STAI X-1 and STAI X-2 tests. A standardized record of all the clinical and psychological characteristics of headache was obtained. Patients were divided into three groups: A) migraine (with and without aura): 258 patients; B) tension-type headache (episodic and chronic): 137 patients, and C) mixed headaches (migraine and tension-type headache): 331 patients. Patients received a tablet containing talcum powder and were told, according to the presence or absence of pain, that the pill was able to produce a pain decrease or increase (extinction or induction of pain). Three hundred and twenty-five patients performed the placebo test and 401 the nocebo test. Patients recorded on the headache diary the presence or absence of headache in the 4 hours following the test.

Results A placebo response was observed in 31.1% of migraine patients, in 38.7% of patients with tension-type headache and in 34.0% of patients with mixed headache. A nocebo effect was reported

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

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

LESSONS FROM PLACEBO EFFECTS IN MIGRAINE TREATMENT

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

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THE "PLACEBO" EFFECT IN CHILDREN AND ADOLESCENTS

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

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SOCIO-ECONOMIC ASPECTS OF HEADACHES

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

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

orders. This general goal can be achieved by providing the technological platform of a suitable set of functionalities that are able to:

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

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

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

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Introduction Migraine disorders are, despite the heavy burden they impose on individuals and society in general, largely unrecognised and untreated. In general practice, few patients consult a physician for headache. In this view, we investigated the impact of a sensitization campaign on migraine in a large cohort of patients, living in a district of Rome. **Objectives** The aim of the present study was to evaluate the long-term effects on migraineurs of this sensitization campaign. Three-years later, patients were re-investigated by means of a semi-structured telephone interview.

Patients and methods The initial study had involved the "Cooperativa dei Medici per il Territorio" (10 general practitioners (GPs)) and a population of about 12 000 people, who had been contacted by mail and posters located in the clinics of the GPs. The study recruited 195 patients, of whom 92% ($n=179$) were migraineurs, according to the IHS criteria (1988). A total of 73% of the patients were diagnosed for the first time.

Results Out of 179 migraineurs, 90% (162 cases, mean age 40.7 ± 15 years, 139 females) underwent follow-up study. Migraine with aura was present in 25% ($n=41$) of the cases. At follow-up, a significant improvement was observed in the mean pain intensity (on a scale 0–10) (8.6 ± 1.5 vs. 7.4 ± 2.1 ; $p < 0.0001$), the mean headache duration (37.1 ± 24.9 vs. 33.7 ± 24.5 hours; $p < 0.006$) and the mean HIT-6 score (61.3 ± 7.6 vs. 57.4 ± 10.9 ; $p < 0.0001$). About 70% of the patients considered the sensitization campaign useful and 58% reported an improvement of their clinical status. Comparison between improved versus worsened or unchanged migraineurs showed a significant decrease in the mean pain intensity (-33%; $p < 0.0001$), mean headache duration (-24%; $p < 0.001$), mean days of headache per month (-72%; $p < 0.0001$), and mean HIT-6 score (-14%; $p < 0.0001$).

Conclusions Our data indicate that a simple awareness campaign is likely to identify a high percentage of previously undiagnosed migraineurs, who could thus receive more appropriate acute care and prophylactic treatment than that offered by uncontrolled self-medication. This positive effect persists for a long time after the sensitization campaign and stresses the crucial role of patient education to medical and non-medical management of migraine. This study further supports

the need for development of new interventions or educational strategies aimed at reducing the burden of migraine.

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

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Despite the prevalence, disability and burden of migraine, many patients (30%–70%) have never seen a doctor and only 4% of headache sufferers are referred to a pain specialist for their problem [1]. Possible causes may be unsatisfactory patient - physician relationships, lack of information and the insufficient ability to recognize migraine in primary care. Last year we held free meetings for a week in a Headache Centre: "The Headache Week Project" (La Settimana delle Cefalee) to understand patients' requests about their headache. This initiative was very useful for enlightening migraineurs who do not refer to physicians for their headache ("invisible migraineurs") and pointing to the lack of patient information about headache. Of the 180 participating subjects, with severe headache, 78% had never visited a headache centre nor a specialist and had never taken preventive drugs and their major request was which headache centre or pain specialist to refer to to improve their headache [2]. These results highlighted the need to extend and give continuity to initiatives for patient information, by increasing the number of sites (more headache centres) and their overall period of activity. To favour the participation of as many headache centres as possible, we have now reduced the duration of activity of each information site to one or two days, calling the initiative "The Headache Days" (Le Giornate delle Cefalee).

Nine headache centres are now scheduled to participate in the "The Headache Days Project" in the city and province of Palermo, covering a period of about two months (May - June 2006). The initiative has been advertised in local newspapers and television programmes and the list of centres involved can be found on the national website www.cefalea.it.

Participating patients will receive informative material about headache (including headache diaries and a list of the headache centres in the city and province of Palermo); moreover, they will complete a questionnaire concerning their headache, physician and specialists visited, knowledge and usage of symptomatic (triptans) and preventive treatments; they will also undergo the ID Migraine questionnaire to screen for migraine.

We hope that this will increase patients' knowledge about headache, and also provide more insight about "invisible migraineurs" with the final goal (through more appropriate diagnosis and treatment) to reduce the disability and burden of migraine.

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HEALTHCARE RESOURCES AND MANAGEMENT OF HEADACHE IN PATIENTS REFERRED TO A REGIONAL HEADACHE CENTRE

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Objectives Primary headaches are a public health problem with socio-economic burden and related disability. Despite impairing quality of life, headaches remain underdiagnosed and undertreated with a low healthcare utilization rate. We investigated the use of healthcare resources and the management of headache in patients referred to a headache centre.

Methods All consecutive patients referred for a first visit to our Headache Centre in 2000 and 2005 were considered. We investigated the primary headaches classified according to the International Classification of Headache Disorders, the management of the headache pain before access to the Headache Centre, and causes of delay in seeking a specialist medical referral.

Results We enrolled 533 patients (316 women and 217 men; mean age 45 ± 31 years) from 2000 and 624 patients (423 women and 201 men; mean age 42 ± 28 years) from 2005. Patients with migraine were 336 (63%) in 2000 and 443 (71%) in 2005 ($p < 0.05$); those with tension-type headache were 192 (36%) and 175 (28%) ($p < 0.05$); while those with cluster headache were 5 (1%) and 6 (1%) ($p = 0.79$), respectively. Before referring to the Headache Centre, patients who had never consulted a physician were 320 (60%) in 2000 and 281 (45%) in 2005 ($p < 0.005$); patients who consulted a general practitioner were 160 (30%) and 237 (38%) ($p < 0.005$); patients who asked for a neurologist were 53 (10%) and 106 (17%) ($p < 0.05$). Reasons discouraging patients from referring to a headache centre were: lack of information about specialist centres in 53 (10%) patients in 2000 and in 38 (6%) in 2005 ($p < 0.05$); self-management of pain with over-the-counter medication in 160 (30%) and in 243 (39%) ($p < 0.05$); and the attempt to live with the pain in 320 (60%) and in 343 (55%) ($p < 0.05$), respectively.

Conclusions In 2005, the diagnosis of migraine was more frequent than that of tension-type headache in 2000 showing a trend in patients with more severe headaches to search for a specialist consultation. The increased proportion of patients consulting a neurologist in 2005 and the reduced proportion of those who did not refer to a headache centre because of a lack of information suggests that a better understanding of the opportunity to refer to a headache centre represents the proper approach in headache management. These results were achieved by improving communication between general practitioners and neurologists, and explaining to patients that a specific approach to headache may improve their quality of life, and reduce the frequency and severity of the headaches.

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

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Introduction Most people with headache in the Calabria Region are treated at the primary care level. General practitioners (GPs) play a substantial role in the detection and management of headache and it is of primary importance to investigate their clinical practice.

Materials and methods A random sample of 500 GPs from the list of GPs in Calabria, received a questionnaire by mail. The questionnaire consisted of four sections focusing on: demographic and practice characteristics; knowledge about the role of studies aimed at testing effectiveness and cost-effectiveness of alternative treatments of headache;

and sources of information for headache management and educational needs perceived in this field.

Results A total of 453 (91%) completed and returned the questionnaire. Data from the questionnaire were collected, analysed and produced in tabular form. The study of almost 450 headache patients consulting their primary care physician indicated that only 9% were referred to a neurologist as part of their migraine management. In the study, the pattern of referral was not dissimilar, despite the notable differences between these healthcare systems, with only 15% of migraine patients being referred to a neurologist and only 2% seen by a headache specialist.

Discussion This pattern reflects three important and persistent barriers to improved migraine care: failure to consult, failure to diagnosis, and failure to appreciate disease severity, by not recognizing and assessing the impact of migraine on the sufferers' quality of life. Approximately 50% of people with migraine consult a physician about their headaches. Of these patients, only 21% continue under a physician's care with the majority of patients who do consult quitting after just a single consultation. The quality of migraine diagnostic skills at the primary care level may be compared with other conditions such as asthma, which has a similar occurrence, and like migraine, is managed almost exclusively at the primary care level. Physicians may be overly concerned with excluding secondary headache, at the expense of effectively managing primary headache syndromes.

Conclusions Despite the major advances achieved in migraine diagnosis and treatment, primary care physicians still face major challenges in making the correct diagnosis and selecting the most appropriate treatment for this common disabling condition.

HEADACHE AS AN EMERGENCY IN CHILDREN

HEADACHE AND CRANIAL TRAUMAS

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Children's head traumas represent one of the most widespread causes of mortality and morbidity in childhood. Cranial trauma is a functional or structural injury, which affects the central nervous system caused by physical mechanical forces. The trauma may be open or closed, in relation to the presence or not of a communication between the CSF and external spaces.

Various types of traumas may cause different types of damage: concussion, contusion, oedema, herniation, (subdural or epidural) haematoma, haemorrhages, diffuse axonal injury and cranial fractures [1].

The criteria of the ICHD-II do not focus on the characteristics of the pain but concern above all the temporal and pathogenic relationships with the traumatic event. It is possible that a trauma worsens, in terms of frequency and intensity, a pre-existing primary headache (ICHD-II, 2004).

Given the high frequency of mild cranial traumas, we shall focus our attention on these forms.

Because posttraumatic headache (PTH) follows moderate cranial trauma, the question is whether this headache is truly secondary to the trauma or is only the trigger factor. This has already been doubted by several authors, starting with Bille, Sinlappa, Raskin, Haas, Lanzi and Russell. The indications that summarize all these doubts are reviewed by Linder [2].

1. CPT may develop after light, moderate or severe trauma.
2. Often the symptoms appear more severe than the trauma itself.
3. Even though these headaches resemble migraine, they do not respond to migraine relieving/pain killing drugs.
4. It is just as important to treat comorbidity problems such as anxiety and depression.

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

In the period close to the trauma there are more anxiety manifestations, such as sleep disturbances and panic crises; this may be due to the same traumatic event as well as to possible axonal micro-damage. It is also true that after some months these disturbances diminish, due to a reassurance mechanism and also due to restoration of the axonal damage. The poor evidence of headache after moderate cranial trauma leads us to actually doubt the existence of this classifying diagnosis. It leads us, conversely, to confirm this event as a triggering moment of the headache.

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HEADACHE AND PSYCHIATRIC EMERGENCY IN CHILDREN AND ADOLESCENTS

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

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

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CLUSTER HEADACHE AND PAROXYSMAL HEMICRANIA IN CHILDHOOD

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Cluster Headache Cluster headache (CH) is infrequent and is one of the most painful primary headaches. Its prevalence in the general population is 0.1%, and it begins after the age of 20. Onset in adolescence is rare and its observation under 10 years of age is quite singular; despite the typical clinical features, it is not ever correctly diagnosed, especially in young patients. Children affected by CH have a bizarre

behaviour and frequently are excited, typical characteristics of this headache, and they are often considered affected by a psychiatric headache. According to the 2nd edition of the International Classification of Headache Disorders [1], CH crises in childhood have a short duration (15–180 minutes); they may repeat several times in a period of 10–20 days (“miniclust”) and pain has a severe intensity, strictly unilateral, in orbital, temporal or zygomatic sites. Autonomic signs, homolateral to the pain, are also present (lacrimation, conjunctival hyperemia, nasal obstruction or rhinorrhoea, miosis, eyelid oedema). In the following years, the autonomic signs increase in intensity and the cluster periods are longer (1–3 months). Scientific evidence and our personal experience suggest that clinical features of juvenile CH remain until adolescence, especially for site and type of pain.

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

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

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BRAIN TUMOURS AND HEADACHES IN CHILDREN

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

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

We report 2 cases. Case 1: 3-year-old male, suffering from a daily globular pounding headache and sleep disorders. These had begun 3 months

previously and ataxia started during the last week. MRI showed deformity, displacement and partial obstruction of the right ventricle by mass with characteristics of supratentorial primitive neuroectodermal tumours. Case 2: 11-year-old male, presenting at the hospital because of a seizure during sleep, followed by severe headache. Headache in the last year mimicked migraine. MRI showed an intracortical occipital cystic lesion (dysembryoplastic neuroepithelial tumour).

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HEADACHES IN THE PAEDIATRIC EMERGENCY DEPARTMENT

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

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

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MIGRAINE AND JUVENILE STROKE

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

Subarachnoid haemorrhage prevails in young cases and in the subgroup of patients with cerebral infarction, interatrial septum defects and inherited thrombophilic disorders seem to play an important role. Risk factors for stroke in older patients, e.g. blood hypertension, hypercholesterolemia, diabetes, smoking, can be significant also in younger patients. Moreover, in this age group the association of migraine with aura and the use of oral contraceptives seem to amplify the impact of these risk factors, especially in women younger than 45 years of age. As illustrated in a recent study of our group, the recurrence of acute cerebrovascular and cardiovascular events is higher in first degree relatives of migraine patients than controls [1]. This link could be explained considering stroke and migraine as two possible phenotypic manifestations of a common genetic background as clearly demonstrated in CADASIL and MELAS. Moreover, it is known that migraine can be characterized by stroke-like episodes and that it can also be a direct cause of ictus (i.e., migraine infarction). Finally, recent studies have hypothesized that the link between migraine and stroke could be the patent foramen ovale [2]. In children and adolescents, migraine is a frequent disorder and rarely could be the presenting symptom of stroke.

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

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

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PROS & CONS: HEADACHE PROPHYLACTIC THERAPY IN CHILDHOOD AND ADOLESCENCE

PROS: IS PROPHYLACTIC DRUG THERAPY USEFUL IN CHILDREN WITH MIGRAINE?

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Introduction The treatment of paediatric migraine requires a balance between non-pharmacological and pharmacological measures. This includes acute symptomatic treatment and more rarely a judicious use of prophylactic agents.

Acute treatment The most rigorously studied agents for symptomatic treatment of juvenile migraine are acetaminophen, ibuprofen and sumatriptan nasal spray, all of which have shown efficacy and safety in controlled trials. However, no differences in efficacy were found between oral triptans and placebo, probably because of shorter duration of attacks and migraine associated gastric stasis.

Preventive treatment Prophylactic drug therapy is indicated only for children with severe and frequent attacks (about 30%). However, the results of daily preventive medication of paediatric migraine is more controversial. Older drugs, i.e., antihypertensive agents (propranolol and clonidine), antidepressants (amitriptyline and trazodone), serotonin modulators (pizotifen and cyproheptadine), have shown insufficient or conflicting data. In the calcium channel blockers class, only flunarizine resulted effective and superior to placebo. There is not yet sufficient evidence for the emergent class of antiepileptic drugs (i.e., divalproex sodium and topiramate). Two open trials, using levetiracetam and gabapentin, have given encouraging results, even with the bias due to the open design and the small sample. Most of these drugs were well tolerated, but clinical efficacy in children and adolescents may differ from that in adults.

Two recent reviews summarized all the criticism on the present data in the literature [1, 2]. The major cause of negative results in controlled trials must be attributed to the elevated percentage of placebo-responders migrainous children both in the prophylactic (from 16% to 55%), and symptomatic (from 20% to 60%) approach.

Conclusions Future trials must take into account: a) larger multicentric sample sizes, patients recruited from primary care centres, and IHS criteria for diagnosis; b) some methodological suggestions: migraine for at least one year, three-month retrospective history, one-month prospective baseline period, randomised, double-blinded placebo-controlled trials of at least three-months' duration; c) expanded measures for efficacy of treatment: clinical improvement in headache, quality of life, lack of attendance at school, satisfaction of child and parents; d) new primary end-points incorporating both "pain" and "disability", and "migraine-free" as an important measure of efficacy; and e) new scales with a broader range of measures of pain, and lower age of children (six to twelve years).

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

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The management of paediatric migraine requires an individually tailored regimen of both pharmacologic and psychological treatment, which is based on individual and integrative approaches using symptomatic and preventive measures.

Prophylactic medication is not indicated in all cases. In published statistics, less than about 30% of children require daily preventive agents, because of high frequency and/or significant disability due to headaches. Follow-up studies demonstrated that the spontaneous outcome of headache in children is the complete remission in many cases. Moreover, we know that family and environmental interventions often reduce headache frequency. Psychiatric comorbidity and family dysfunctioning are to be evaluated in all our patients because they are often part of the clinical picture and may play a critical role in the prognosis of headache. Recently, a Cochrane review summarized the evidence about the effectiveness of different psychotherapeutic approaches for migraine and tension-type headache.

With reference to prophylactic drug treatment, there is a paucity of controlled clinical research. Older therapies (β -blockers, antidepressants, serotonin modulators and calcium channel blockers) have shown conflicting results or furnished insufficient data, and the more recent therapies (antiepileptic drugs), generally well tolerated in paediatric epilepsy, are in need of placebo controlled trials.

In conclusion, tension-type headache and migraine treatments need an integrative approach, where pharmacological therapy is to be considered only one of the different options for the care of children and adolescents.

PROS & CONS: ANTIEPILEPTICS

ANTICONVULSANT DRUGS IN MIGRAINE PROPHYLAXIS: USES AND LIMITATIONS

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

lesser extent, gabapentin, have demonstrated efficacy in randomized, placebo-controlled trials. Lamotrigine may be effective at controlling migraine aura, but has not demonstrated effectiveness at controlling migraine headache.

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ANTIEPILEPTIC DRUGS: CONS

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

ROMAN JUNIOR MEMBERS MEETING

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

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

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

Subjects and methods We elicited the nBR by stimulating the right supraorbital region with a custom-built electrode in 16 MO patients

between attacks, 15 HV and 14 HV-F. Only the responses obtained in the ipsilateral orbicularis oculi will be considered here. Habituation was measured as the % area-under-the-curve (AUC) decrease in 10 consecutive blocks of 5 averaged, rectified EMG responses.

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

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

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

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ELECTROPHYSIOLOGICAL ANALYSIS OF THE TRIGEMINAL SYSTEM IN MIGRAINE

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

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

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

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

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

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

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

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

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Background It has been shown that migraine and temporomandibular disorders (TMDs) share several epidemiological and clinical features. Nevertheless, a pathophysiological link between diseases of the craniomandibular system and cervical spine as well as between the cervical spine and migraine has been discussed.

Objective The aim of this study was: 1) to compare the clinical aspects of migraine of patients who referred to the Odontostomatological Department for their TMDs with those observed in patients who referred to our Pain Centre for migraine; 2) to perform a multidisciplinary approach in both groups of migraine patients to better understand the potential pathophysiological link between migraine, craniomandibular system and cervical spine.

Materials and methods According to IHS criteria (2004), we consecutively enrolled migraineurs with TMDs and migraineurs without TMDs with the following inclusion criteria: 1) age between 18 and 55 years; 2) patients with no preventive therapy; and 3) patients studied during the interictal phase. A control group composed of healthy subjects was also recruited. All subjects of the study underwent the following clinical evaluations: 1) a clinical investigation of pericranial muscle tenderness according to "Tenderness Total Score" (TTS); 2) a clinical investigation of the temporomandibular system according to "Cranio-mandibular Index" (CMI); and 3) physical examination of the cervical spine (PECS) by also using a chiropractic approach.

Results We enrolled 35 migraine patients with TMDs (mean age 35±10 years), 32 migraine patients without TMDs (mean age 34±11 years) and 25 healthy controls (mean age 32±12 years). All migraine patients showed significantly higher scores in TTS, CMI and PECS than healthy controls ($p<0.05$). When we considered separately the three groups of subjects, we found that those with TMDs showed higher scores in TTS, CMI and PECS scales than both those without TMDs and healthy controls ($p<0.05$). Similar differences were observed when we compared migraineurs without TMDs and healthy subjects ($p<0.05$). Duration of illness, frequency of attacks as well as MIDAS and HIT-6 scores were higher in migraineurs with TMDs than those without ($p<0.05$).

Conclusions Our data suggest that TMDs and cervical spine disorders are present in all migraineurs and that TMDs may represent a consequence of "migraine pathology" and at the same time a risk factor for high migraine disability. It may be important to pick out these clinical features in a multidisciplinary manner for therapeutic implications and to better understand the comorbidity and the pathophysiological link between migraine, masticatory system disorders and cervical spine dysfunctions.

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

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Introduction A chronic pain condition due to analgesic drug overuse is more likely developed by migrainous than other headache patients: about 10% of migrainous patients will develop as a complication of their clinical picture a chronic form of headache sustained by medication-overuse (MOH). The biological basis of this difference could be genetically determined. For instance, polymorphisms in genes regulating dopaminergic transmission were found associated with migraine, alcoholism and drug abuse. It is also well known that psychiatric comorbidity is more prevalent in MOH than migrainous patients. Many studies, with contrasting results, were conducted in the past to explore the association of MOH with the same genes known to be involved in abuse behaviour or psychiatric disorders, comparing migrainous to MOH patients. Here we propose a different approach to the problem, looking for the clinical variability in MOH related to genetic variability. If the commonly used approach is considered a categorical one (comparing two different diseases), the one we propose is a dimensional approach (observing the variation of degree of a clinical parameter).

Materials and methods Seventeen MOH patients were recruited, and diagnosis was confirmed after 2 months of drug discontinuation. All the patients, after a complete headache history, were interviewed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), to obtain a categorical psychiatric diagnosis and completed the Beck Depression Inventory (BDI), and the Cloninger's Tridimensional Personality Questionnaire (TPQ). After obtaining the patients' written informed consent, the genotype was determined for the DRD4 120bp tandem repeat polymorphism, the wolframin His611Arg polymorphism, the BDNF G196A, and the 5HTTLPR polymorphism.

Results A linear logistic regression indicated that the examined polymorphisms are predictors of a high monthly consumption of analgesic drugs. ANOVA analysis showed that the DRD4 polymorphism is related to TPQ novelty seeking (NS) and BDI score, 5HTTLPR to TPQ harm avoidance (HA) and BDI score, and wolframin His611Arg to monthly number of analgesics and BDI.

Discussion Until now, all genetic research in MOH was based on genotype-phenotype association studies, looking for genetic differences between migrainous and MOH patients. Some of these studies have not been able to verify a genetic influence in MOH. We used a different quantitative approach, preferred to the categorical one, to scan the influence of genetic variability on MOH clinical features, which yielded promising results.

Conclusions The clinical picture of MOH is influenced by the studied genes. This evidence confirms the usefulness of dimensional tools when seeking to associate biological markers with clinical disorders.

JOINT MEETING WITH THE ITALIAN ASSOCIATION OF AMBULATORIAL AND TERRITORIAL NEUROLOGISTS

TACs AND SHORT-LASTING NEURALGIAS

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Trigeminal Autonomic Cephalalgias (TACs) are a group of primary headache syndromes including cluster headache (CH), paroxysmal hemi-

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

RELATION BETWEEN PATENT FORAMEN OVALE (PFO) AND MIGRAINE

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

WARNING HEADACHES

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

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

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

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

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

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

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

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

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

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

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

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Introduction Migraine and headache have been linked, mainly in retrospective case-control studies, in general to a subsequent risk of cerebrovascular stroke. Limited data from prospective studies have evaluated the real association among various forms of headache and increased risk of cerebro- and cardiovascular pathologies.

Materials and methods The AINAT (Italian Association of Ambulatorial and Territorial Neurologists) boasts in Campania a vast network of neurologists that have been involved in the management of an epidemiological study in which the various forms of headache are compared with cerebrovascular risk factors.

They have recruited about 100 (the study is still ongoing) subjects affected by various forms of migraine. The risk factors considered were: hypertension, diabetes mellitus, smoking, atrial fibrillation, familiarity, left ventricular hypertrophy, carotid stenosis (>70%), hypercholesterolemia, hypercysteinemia, and oral contraceptives.

Results Preliminary results seem to confirm, in agreement with the limited data present in the literature, that migraine patients and, in particular, an elevated percentage of those affected by migraine with aura, show a higher association with cardiovascular risk factors.

Discussion This study confirms that patients affected by migraine, particularly with aura, have a higher cardiovascular risk compared with subjects without a history of migraine.

Conclusions Our data could offer a possible biological explanation for the increased risk of ischemic stroke among subjects affected by migraine. However, since the presence of these cardiovascular risk factors alone cannot fully explain the link between migraine and early stroke and coronary heart disease, it seems clear that other etiological factors must be involved.

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

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In the Health Programme for 2003–2005, the Minister of Health, Dr. Sirchia, introduced the so-called "devolution" plan. This has led to a more rational and economic use of the health services offered with better utilization of human resources and available funds, and has also led to the search for new models and diagnosis assistance programmes differing from those available at the national level.

One of the characteristics of the Campania Region has been to significantly increase, in recent years, its specialized assistance throughout the territory, so as to have a more capillary presence of ambulatory neurological services throughout the Region.

Based on these considerations, it has been decided, together with the Regional Coordination of the Italian Society for the Study of Headaches (SISC) of the Campania Region, to create a regional network of first level ambulatory structures dedicated to migraine and headaches, by using the neurologists working in the territory.

The first phase consisted of these specialists attending an educational course organized together with the SISC Regional Section Campania and the Italian Association of Ambulatorial and Territorial Neurologists. The course had a basic didactic scope and served to standardize current methods such as patient charts.

The second phase, which is still ongoing, foresees that every local health organization will activate an automatic system whereby each

patient requiring treatment for migraine headache will be sent to the nearest specialist adhering to this network.

The third phase, which has not yet been implemented, will have each ambulatory dedicated to the treatment of migraine headaches connected to a 2nd and 3rd level centre for further diagnostic therapeutic problems. It is worthy to note that the practical outcome of this type of organization is zero management costs, while, at the same time, guaranteeing:

- a uniform and codified diagnostic system throughout the territory;
- improvement in the diagnostic treatment offered;
- an efficient filter for the Headache Centres which will be freed from routine work that engulfs current waiting lists;
- and also the economic aspect.

HEADACHE ACCORDING TO SCIENTIFIC TRADITIONS OF THE SALERNO MEDICAL SCHOOL

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The origins of the Salerno Medical School go back to the beginning of the Medieval Age. Legend attributes its foundation to four doctors, the Hebrew Helinus, the Greek Pontus, the Arab Adela and the Latin Salernus, epitomizing that the *Ars Medica* of Salerno was born from the confluence of these four cultures.

In the scientific world of the 12th century – corresponding to the "golden period" – various personalities stand out: Masters as Bartolomeo, Ferrario, Salerno and Nicolò Salernitano wrote a series of exhaustive books on general pathology, diagnosis and pharmacological therapy widely used at the School.

Master Salerno, in his work *Catholica*, distinguishes severe headache, in which the pain is "total" from migraine, which only affects one half of the head [1].

Master Bartolomeo, in his manual *Pratica*, defines migraine as "passio capitis in media parte aut in destra aut in sinistra" [2].

Pathogenesis can always be explained by the humoral theory: various external and internal factors are quoted, which can affect and change the organic humours. The qualitative distinction of pain was given attention: acute, periodic, irregular, persistent, continuous and grave. The distinctive characteristics for the "blood headache" were: sensation of burning in the head, heaviness of the forehead, pulsation of the temples and dilatation of the veins.

The diagnosis was aided by a rich urinary semeiology.

One of the therapies for the "blood headache" was bleeding or application of blood-sucking leeches in different parts of the head. The use of purging agents, in particular, diets and remedies (such as coffee) were also advised, according to the type of headache.

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JOINT SYMPOSIUM WITH THE ITALIAN SOCIETY OF INTERNAL MEDICINE

HEADACHE IN CONNECTIVE TISSUE DISEASES

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Introduction Headache is frequently reported by patients affected by connective tissue diseases (CTDs), especially patients with Systemic

Lupus Erythematosus (SLE) or Behcet's disease (BD). Virtually all kinds of headaches ranging from migraine to tension-type are represented. Establishing whether a headache has a specific link with the underlying disease is often a difficult clinical challenge, because headache can have a number of causes other than CTDs. For instance, it may be a pre-existing condition or may be the consequence of a psychological reaction to a chronic, disabling disease.

Materials and methods Migraine of SLE patients is still a debated entity and evidence of brain impairment is controversial. SLE-migraine has been investigated as a prototype of headache complicating CTDs. Perfusion SPECT was performed to investigate brain impairment in SLE patients with migraine-like headache either since diagnosis or later in the course of the disease. Eighteen SLE patients (mean age: 40.8 ± 13.6 years) matching these requisites underwent brain SPECT with ^{99m}Tc -HMPAO in the interictal period. EEG and MRI were performed in twelve and ten patients, respectively. SPECT was analyzed through visual and asymmetry combined analysis as well as by voxel-based statistical analysis (Statistical Parametric Mapping, SPM99) versus a control group of matched normal subjects (height threshold: $p=0.01$).

Results Fifteen (83%) patients disclosed focal hypoperfusion, often in keeping with the main side of pain location, whereas both EEG and MRI gave a positive result in 50% of cases. By voxel-based analysis, significant hypoperfusion was found in 8 (44%) patients, either lateralized to one side or localized to the anterior cingulate cortex (ACC), independent of pain location.

Conclusions Brain perfusion SPECT is a sensitive tool to disclose brain impairment in SLE-related migraine, although the mechanisms of brain damage remain to be elucidated. Besides confirming focal hypoperfusion in a part of the patients, statistical analysis highlighted in four patients interictal hypofunction of ACC, a key structure in the midline network for the cortical elaboration of pain. An integrated neuroimaging and neurophysiological approach is required to disclose the pathophysiological correlates of headaches during CTDs.

CARDIOVASCULAR DISEASES AND HEADACHE

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A complex relationship exists between cardiovascular diseases and headache. In particular, stroke has been associated with both migraine and nonmigraine headache [1].

It has long been debated whether migraine might be considered a possible risk factor for cerebral ischemia. To describe this association, a clearly clinically defined stroke syndrome must occur remotely in time from a typical attack of migraine [1]. A history of migraine may contribute to the risk of stroke through the presence of activation of the clotting system and/or cerebral vasospasm. Several case-control studies investigated the relationship between migraine and stroke and showed that migraine was an independent risk factor for stroke with odds ratios ranging from 2.8 to 4.3 [2]. The association between migraine and cerebral ischemia was limited to women below the age of 35 years, and odds ratios were higher in patients with a history of migraine with aura than in patients with a history of migraine without aura. Other risk factors for stroke might interact with the migraine-induced pathogenesis. Concurrent use of oral contraceptives, high blood pressure, or smoking had more than multiplicative effects on odds ratios for ischemic stroke associated with migraine. Moreover, migraineurs, particularly with aura, have a higher cardiovascular risk profile than individuals without migraine [1]. In fact, compared to controls, migraineurs were more likely to smoke, less likely to consume alcohol, and more likely to report a parental history of early myocardial infarction [1].

Another condition that might help explain and contribute to the association of migraine and stroke is patent foramen ovale (PFO) [1].

PFO has been associated with cryptogenic stroke episodes caused by paradoxical embolism. Moreover, PFO is over represented in migraineurs, and conversely, the frequency of migraine in PFO-associated cryptogenic stroke is twice than expected. Therefore, the excess stroke risk of migraine could result from the association with PFO through paradoxical embolism. Closure of the patent foramen has been associated with suppression of migraine attacks, possibly because a venous to arterial passage of activated platelets or chemical substances may trigger headache by overwhelming the filtering capacity of the lung.

Recognition of the interaction between migraine and cardiovascular disorders as well as comorbid vascular risk factors in migraineurs is important since it may impose therapeutic challenges, life-style modifications, and further investigation to reduce the global vascular risk.

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ENDOCRINE DISEASES AND HEADACHE

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Headache is the most common neurological symptom presenting to family physicians, neurologists, and to the Emergency Department. Some endocrinological disturbances can be associated with headache. Recently, in chronic migraine patients with medication-overuse, a reduction of growth hormone (GH) and TSH responses after GHRH and THRH as well as an increase of ACTH and cortisol levels after hCRH have been described. In contrast, headache can be an important symptom of disease of the endocrine system.

Pituitary tumours are often associated with troublesome headache, both chronic and episodic. Although dural stretch and cavernous sinus invasion are widely considered the mechanism responsible for pain, evidence demonstrates that headache is a recognized feature of small, non invasive functional tumours, and pituitary size itself is unrelated to headache, suggesting that tumour activity may be important in some forms of pituitary tumour-associated headache. The commonest tumours are prolactinomas, which are microadenomas in 52% of cases, and GH-secreting pituitary tumours, which are 68% macroadenomas. Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) has been found only in these kinds of pituitary tumours, and primary stabbing headache is also more common in these two groups. In acromegaly, headache may occur in 55%–85% of presentations as well as in about 60%–70% of prolactinomas.

The mechanism of pituitary tumour-associated headache is currently unknown, and also, the involvement of some neuropeptides as in primary headache is not supported.

Headaches due to endocrine diseases in childhood are rare, but any child with chronic headaches should be given serious consideration. The most serious etiology is a tumour of the hypothalamic-pituitary region such as craniopharyngioma, characterized by headache, visual disturbances, GH and gonadotropin failure.

The role of thyroid dysfunction in headache remains uncertain. In 102 hypothyroid patients, approximately 30% had bilateral, continuous, non pulsatile headache, which disappeared with hormone therapy. In contrast, a larger population-based study reported that TSH was lower amongst headache sufferers than in those without headache complaints.

The association between hypertension, including endocrine hypertension, and headache has been a contentious issue. Recently, it has been

found that headache and hypertension classified at moderate to severe stage were not associated. On the other hand, pheochromocytoma is related to a paroxysmal catecholamine release from the tumour, and headache occurs in more than 80% of patients: it may be severe, frontal or occipital and throbbing or steady.

CHRONIC PAIN AND HEADACHE

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Introduction Epidemiological studies show that a number of chronic/recurrent pain conditions, both somatic (fibromyalgia-FMS) and visceral (dysmenorrhea-DYS, Irritable Bowel Syndrome-IBS) are significantly more frequent among headache sufferers than in the general population. Conversely, the percentage of FMS patients, as well as of DYS and IBS patients who also suffer from headache is significantly higher than that of headache patients in the population not affected with these diseases. These data support the notion of some common underlying mechanism for the pain of all these conditions, at least in subsets of patients. Based on these premises, the aim of the present study was to evaluate and compare the state of general sensitivity to painful stimuli in different groups of headache patients concomitantly affected or not with one or more of the chronic/recurrent pain conditions described above.

Methods Four groups of headache patients (H) were considered: 1) without concomitant FMS/DYS/IBS; 2) with FMS; 3) with DYS or IBS; 4) with FMS + DYS and/or IBS. All groups were age- and sex-matched. Patients of the various groups did not differ significantly regarding the number of years they had been suffering from headache (tension-type or migraine) and mean number of monthly attacks. Patients of the FMS groups did not differ significantly regarding the number of years they had been suffering from diffuse chronic musculoskeletal pain. In all groups, pain thresholds to electrical stimulation in skin, subcutis and muscle were measured in multiple body sites (deltoid, trapezius and quadriceps) not coinciding with the areas of spontaneous pain from any disease. Measurement was made in the pain-free interval and with a wash-out of at least 72 hours from any drug potentially interfering with pain sensitivity.

Results The lowest electrical thresholds at all body sites and all tissues were found in group 4 (H+FMS+DYS/IBS), followed by group 2 (H+FMS), group 3 (H+DYS/IBS) and group 1 (H), in that order. The trend for variation among groups was significant ($p < 0.01$).

Conclusions The results indicate a progressively higher state of generalized hypersensitivity towards painful stimuli in headache patients when concomitant chronic/recurrent pain conditions are present. They suggest different levels of central sensitization in subgroups of headache patients, which are expressed clinically with progressively higher manifestations of chronic/recurrent pain conditions, both somatic and visceral, but all typically characterized by the lack of any identifiable organic cause, such as FMS, DYS or IBS.