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ABSTRACTS OF THE 18th NATIONAL CONGRESS OF THE ITALIAN SOCIETY FOR THE STUDY OF HEADACHES

Prevention of headache suffering: from early diagnosis to effective measures

October 7-10, 2004
Taormina, Sicily

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PREFACE

This Supplement contains the abstracts of the invited speakers and oral presentations of the XVIII National Congress of the Italian Society for the Study of Headaches (SISC) "*Prevention of headache suffering: from early diagnosis to effective measures*" – Taormina, Sicily, 7-10 October 2004.

Specific factors have prompted the SISC in preparing this Supplement at this time: SISC is growing well, therefore, English abstracts can encourage diffusion of the Society's best scientific results in the field of headaches in the last year. In addition, since the younger generations of Italian headache researchers have greater international relationships, the Supplement seemed a choice in line with their scientific life.

Finally, to publish the abstracts of the Congress in the SISC's official journal, now in its fifth year, represented a moment of pride and an opportunity that had to be seized.

The main topics of the Congress centre on early headache diagnosis and appropriate treatment as the targets in preventing headache chronicization. The prevention of chronic headaches, in fact, represents the modern, imperative task for both SISC and other multidisciplinary national and international headache societies.

As President of the Congress it is a privilege to present this Supplement and I sincerely hope that it will be received favourably by the headache community. I hope that it will stimulate headache research findings and contribute to a greater visibility of the Society.

This volume is dedicated to the SISCs' Past Presidents, Prof. Virgilio Gallai and Prof. Franco Michele Puca, who had in common one characteristic: the continuous search of new horizons towards which the Society could work.

Lastly, I wish all the participants a pleasant and productive Congress.

Marcello Fanciullacci
President
Italian Society for the Study of Headaches

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LECTURERS

THE SCIENCE OF MIGRAINE THERAPY FIVE YEARS AFTER RECOGNIZING THE ROLE CENTRAL SENSITIZATION AND CUTANEOUS ALLODYNIA PLAY IN THE PATHOPHYSIOLOGY OF THIS MALADY

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In recent years, we discovered that the network of neurons that sense pain signals from the dura, changes rapidly during the course of a single migraine attack and that the treatment of an attack is a moving target. We found that if the pain is not stopped within 10–20 minutes after it starts, the first set of neurons in the network, those located in the trigeminal ganglion, undergo molecular changes that make them hypersensitive to the changing pressure inside the head which explains why migraine headache throbs and is worsen by bending over and sneezing. We found that if the pain is not stopped within 60–120 minutes, the second group of neurons in the network, those located in the spinal trigeminal nucleus, undergoes molecular changes that convert them from being dependent on sensory signals they receive from the dura by the first set of neurons, into an independent state in which they themselves become the pain generator of the headache. When this happens, patients notice that brushing their hair, taking a shower, touching their periorbital skin, shaving, wearing earrings, etc become painful, a condition called cutaneous allodynia. Based on this scenario, we showed recently that the success rate of rendering migraine patients pain-free increased dramatically if given before the establishment of cutaneous allodynia and central sensitization. The molecular shift from activity-dependent to activity-independent central sensitization together with our recent conclusion that triptans ability to disrupt communications between peripheral and central trigeminovascular neurons (rather than inhibiting directly peripheral or central neurons) explain their clinical effects. Both our clinical and pre-clinical findings of the last 5 years point to possible short- and long-term advantages in using early-treatment approach in the treatment of acute migraine attacks.

MIGRAINE: A HISTORICAL AND ARTISTIC PERSPECTIVE

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This widely experienced ailment has possibly inspired artistic creativeness in some instances; much more frequently, it has been the subject of written or pictorial representations by patients, sharing with us in this way their peculiar suffering through a non verbal language.
What are the more interesting, although somewhat debated instances, in which migraine has influenced art in its figurative but also written expressions? Who were the main artists who were known, or presumed to be migraineurs? Is this form of recurring ailment, eminently subjective and so intimately perceived, with its emotional as well as physical involvement, teaching us emblematically about the comprehensive attitude that should be adopted toward the patient in all his human aspects; showing in our daily practice the relevance of caring along with curing?

CLINICAL AND PHARMACOLOGICAL IMPLICATIONS OF THE NEW CLASSIFICATION OF HEADACHE

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With the recent publication of the second edition of the Classification of Headache Disorders (ICHD-II), the International Headache Society (IHS) has accomplished the second act of a tremendous effort in systematizing the clinical approach to headaches that started back in 1988, with the realization of the first edition of the classification. The 1988 IHS classification represented an absolute novelty in the headache field, which, being based on a limited amount of evidence, was expected to undergo a short-term revision. The revision was, in fact, postponed for several years because it took the headache specialists a long time to become familiar with the new system and to field-test it.
When the scientific community finally felt that enough evidence had been collected for a second edition, the ICHD-II Subcommittee worked intensively collecting and debating data, elaborating and discussing proposals. The main body of the newly published ICHD-II is formed by 4 parts: (1) *Primary Headaches* (Migraine; Tension-type Headache; Cluster Headache and Other Trigeminal Autonomic Cephalalgias; Other Primary Headaches); (2) *Secondary Headaches* (Groups V-XII); (3) *Cranial Neuralgias, Central and Primary Facial Pain and Other Headaches* (Groups XIII and XIV); (4) *Appendix*.
The classification of primary headaches is descriptive (symptom-based), while secondary headaches are classified according to the etiological process. Based on the hierarchical model, already adopted in the first edition, ICHD-II is equally intended for research and clinical practice, for the headache specialist, and for the general practitioner. All headache disorders are classified into major groups, and each group is then subdivided one or more times, the desired detail of the diagnosis depending on the purpose and on the "user".
As the first edition, ICHD-II diagnoses attacks, not patients, and it is scarcely focused on the evolution of the disease. This may seem a limitation in the usefulness of this taxonomic system in the clinical field, however, the restriction was necessary because of the lack of evidence on the evolution of the various forms of headache. The impact of genetics upon ICHD-II was limited because available evidence does not allow as yet the identification of monogenic entities within the present clinically-defined heterogeneous phenotypes.
In order to fuel the virtuous circle represented by evidence-based taxonomic criteria that are improved by research findings and, in turn, stimulate research advances, the ICHD-II committee has created the *Appendix*, which describes a number of orphan disorders or proposals of new forms that need validation.

CGRP ANTAGONISTS FOR THE TREATMENT OF MIGRAINE

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During migraine attacks, plasma levels of the potent vasodilator calcitonin gene-related peptide (CGRP) are elevated in migraine patients. Preclinical data with the first non-peptide high affinity CGRP antagonist BIBN4096BS in animal models related to migraine will be reviewed and discussed.
For instance, in the animal model, hemodynamic changes were induced by either CGRP injection or electrical stimulation of the trigeminal ganglion and facial blood flow changes (FBF) were monitored [1]. Here, BIBN4096BS fully reversed the evoked vasodilation with ED_{50}s of 0.003 and 0.05 mg/kg in marmoset monkeys and rats, respectively.
In healthy volunteers, a 2.5 mg dose of BIBN4096BS significantly attenuated human α-CGRP-induced increase in cerebral blood flow. The same dose relieved headache pain 2 hrs after the start of treatment in 65.6% of migraine patients (versus 26.8% of placebo) in a multicenter, double blind, placebo-controlled, randomized clinical trial [2]. Together, the data demonstrate that counteracting CGRP function during a migraine attack is a novel approach to treat migraine headache.

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MIGRAINE IS A RISK FACTOR FOR SUB-CLINICAL BRAIN LESIONS

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Clinical series suggest an increased prevalence of cerebral infarction and white matter lesions (WML) in migraine patients. Not known is whether these lesions are prevalent in the general migraine population. We conducted a population-based MRI study to determine the prevalence of cerebral infarcts and WML in migraine cases from the general population and to identify migraine characteristics associated with these lesions. We randomly selected migraineurs with aura (MA, n=161), migraineurs without aura (MO, n=134), and controls (n=140) who were frequency matched to cases for age, sex, and place of residence, from a large population-based sample of Dutch adults aged 30 to 60 years. Brain MR scans were evaluated for infarcts, by location and vascular supply territory, and for periventricular and deep WML (DWML). The risk (odds ratio (OR)) of these brain lesions was examined by migraine sub-type (with or without aura) and monthly attack frequency (<1 attack, ≥1 attack), controlling for cardiovascular risk factors and use of vasoconstrictor migraine agents. All participants underwent a standard neurological examination; no abnormalities were found.
Compared to controls, migraine cases were at increased risk for infarcts in the cerebellar region of the posterior circulation territory. The adjusted risk varied by migraine sub-type and attack frequency: the highest risk was in MA with ≥1 attack/month. Among women, the risk for high-DWML-load was increased in migraineurs; this risk increased with attack frequency (highest in those with ≥1 attack/month), but was similar in migraine with or without aura.
These population-based findings suggest that migraineurs with and without aura are at increased risk for sub-clinical brain lesions. The more attacks, the greater the risk. Given the high prevalence of migraine, these findings are of potential public-health importance and may have implications for management guidelines for migraine.

ADVANCES IN NEUROIMAGING OF PRIMARY HEADACHES

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Headache is perhaps the most common of medical problems and may be considered as either primary, where headache and the associated symptoms are the key problem, such as migraine and cluster headache, or secondary, where headache is due to some clear pathological process [1]. Both clinical problems share an underlying anatomy and pain processing physiology that is concentrated around the projections to the trigeminal nucleus. Modern neuroimaging is shedding considerable light on the age-old neurological question for primary headache: *where is the lesion?*
Pain from intracranial sources arises from the dura mater and the large blood vessels with the brain substance being insensate for the most part. Pain-producing intracranial structures are innervated by the first, ophthalmic, division of the trigeminal nerve and much of the dural innervation sweeps back gathering together in the middle cranial fossa to form the tentorial nerve which joins the ophthalmic division shortly before it enters the trigeminal ganglion. Intracranial structures below the tentorium cerebelli are innervated by branches of the C_2 root. It has now been shown clearly in experimental animals that both supratentorial and infratentorial pain projections end up synapsing on second order neurons in the trigeminal nucleus caudalis and the superficial dorsal horns of C_1 and C_2, a functional group of neurons collectively called the trigeminocervical complex [2]. This pattern of innervation leads to the well-known referral patterns of the many headache syndromes that do not respect the cutaneous innervation patterns of the head. An important concept in the context of the innervation of the pain-producing intracranial structures is that vascular change is secondary to neural activation so that migraine and cluster headache should properly be referred to as *neurovascular* headaches not as *vascular* headaches [3].
Positron emission tomography (PET) during acute migraine has shown activations, increases in regional cerebral blood flow, in regions known to be involved in pain, such as anterior cingulate cortex and insula cortex. Furthermore, PET studies demonstrate activations in the brainstem in the dorsal midbrain and dorsolateral pons [4, 5] that are not seen in other primary headaches, such as cluster headache [6]. These data suggest that brainstem areas are either fundamental to the attack onset or to its resolution; certainly they are particular to migraine. Brain imaging offers insights into migraine pathophysiology by studying the problem in humans. An understanding of the pathophysiology of migraine must ultimately result in better patient management.

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INVITED SPEAKERS

HEADACHE MANAGEMENT IN PUBLIC HEALTH CARE OF THE CALABRIA REGION PSR 2004/2006

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Introduction Headache is the most common symptom that patients complain of to neurologists. Headache specialists play an important role in patient referral, physician education, improving headache diagnosis and optimizing treatment within primary care. Primary care plays an important role and contributes to improve headache management.
Materials and methods During the period October to December 2002, a survey was conducted on a random sample of 500 general practitioners' (GPs) in Calabria. The questionnaire included questions focusing on GPs demographics and practice characteristics.
Results Of 500 questionnaires distributed, 455 responses were received for a response rate of 91%. Results of logistic regression analysis, performed on the responses given by GPs who knew that the cost-benefits analysis examined the costs and benefits of treatments on patients' health status, indicated who had a fewer number of years in practice (OR=0.96; 95% C.I.=0.93–0.99; p<0.019), who attended courses on epidemiology or evidence-based medicine (OR=1.66; 95% C.I.=1.03–2.69; p=0.038), and who would not modify the patient's treatment when scientific evidence indicated that it was more expensive than the new treatment (OR=0.72; 95% C.I.=0.58–0.89; p=0.003). Two-thirds of those samples (65%) thought that disability in headache patients was of significance to illness diagnosis and regression analysis showed that GPs who disagreed that the clinical approach to migraine required a clinical effectiveness evaluation by performing controlled clinical trials (OR=0.51; 95% C.I.=0.32–0.82; p=0.0005), who were older (OR=1.63; 95% C.I.=1.14–2.31; p=0.007), and who were female (OR=0.52; 95% C.I.=0.28–0.97; p=0.039), were significantly more likely to believe that disability is a prominent diagnostic feature in headache patients.
Discussion Despite a number of important advances in the diagnosis classification, and treatment of headaches over the past decade, there is still widespread under-consultation, under-diagnosis, and under-treatment of headaches in primary care. In our survey, 70% of GPs performed preventive treatments for headache patients in their practice and the results of regression analysis showed that this took place in a primary-practice setting. Patients in a primary-practice setting may therefore be more likely to benefit from behavioural interventions than patients seen in subspeciality headache clinics. This pattern reflects 3 important and persistent barriers to improved headache care: failure to consult, failure to appreciate disease severity, and failure to recognize and assess the impact of headache on the sufferer's quality of life.
Conclusions Improving communication between patients, physicians and headache specialists will help achieve better outcome in terms of recognition of headache severity and treatment needs. Continuing education and raising awareness of the impact of headache will help overcome barriers to migraine care and improve migraine management.

ORGANIZATIONAL EVOLUTION OF THE HEADACHE CENTRES: FROM EARLY DIAGNOSIS TO EFFICACY MEASURES

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The history of public assistance in the multidisciplinary field of headache disorders began in Italy in the 1950s, with the opening of the Headache Centre in Florence, where the first theoretical-practical educational courses took place for many of us. After this staging post, many headache centres were born, and today they are regarded as the "driving force" for the diffusion of the assistance standards: Pavia, Turin, Rome, Milan, Parma, Vicenza, etc.
At the end of the 1970s (SISC headache educational course, Belgirate, 1977), we began discussing the definition of assistance standards for a correct Headache Centre organization.
Afterwards, it came to an often indiscriminate use of inpatient admission and neuroimaging examinations, to effectuate a screening of headache patients, who often bring the "indulgent" doctor to create a diagnostic, frustrating loop, resorting to the umpteenth diagnostic test, which is more or less useful and reliable, and always returning to the therapeutic starting line. *Nunc, quid agendum?*
In this sea of diagnostics according to the criteria suggested by the different IHS classifications, the creation of Headache Centres of excellence, of I, II, III level (SISC 1980s), put an efficacious and useful brake on the expenditure of resources.
The Regional Reference Centres for Headaches – those operative at a national level are here alphabetically listed – L'Aquila, Pavia, Milan, Rome, Vicenza, seem now to be able to offer an organizational model integrated with structures which are merely ambulatory, with day hospital admission only for weaning therapies, rehabilitation procedures, or targeted diagnostics. We have to offer a comprehensive response to the increasing health requirements in the headache disorders area, yet respecting the mandatory and sometimes unwelcome rules of both the DRG and LEA (Essential Levels of Assistance). Both the appropriateness of admission for headache disorders and their payment will become the operative challenges, to allow the extension to every region, of a complete public assistance for chronic headache patients.
Further information
To consult and examine in detail DRG, LEA and Headache Disorders, visit online the official sites of the Ministry of Health, dedicated to the doctors involved in this operative management.
DRG: http://ministerosalute.it/programmazione/sdo/ric_informazioni/sceltadrg.jsp
LEA: http://www.ministero.salute.it/programmazione/lea/lea.jsp or private www.drg.it

INTERUNIVERSITY CENTRES AND SCIENTIFIC RESEARCH: EXPERIENCE OF THE PAVIA CENTRE

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SOCIAL BURDEN OF MIGRAINE: A HEADACHE CENTRE EXPERIENCE

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Migraine is a common and debilitating condition that affects 8% to 12% of the general population. Epidemiologic studies show that migraine affects 28 million Americans, approximately 18% of women and 6% of men, with a higher prevalence in those who are white. Migraine is a major cause of absenteeism from and decreased productivity at work, exerting also a significant burden on the individual in terms of disability and reduced quality of life [1–3].

In addition to the impact on an individual's life, the cost of migraine is also high. The cost of a disease derives from the burden of illness on the patient, their family, and society. The cost of migraine is high for both patients and society. The annual direct cost of migraine, including all medical care and possible economic repercussions for the patient (in the case of private health care) or the state (public health care), is about $1 billion; some studies have estimated the indirect costs as high as $9.6 billion in the United States [3–6].

Even if triptans are more expensive than NSAIDs, Lofland showed that in the 6 months after sumatriptan therapy was initiated, health care resource use and time lost from workplace productivity and nonworkplace activity were reduced, while health-related quality of life and patient satisfaction scores improved for the managed care migraineurs enrolled in this study [3].

Otherwise, triptan administration is not the only solution for knocking down the burden of migraine. It is indispensable to reduce the misdiagnosed and under-treated migraine. Our group, working in the Emergency Department, found that in 90% of patients migraine was misdiagnosed and under-treated; a correct diagnosis reduced the direct costs (-50% neuroimages required) and improved the health-related quality of life of patients.

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THE EXPERIENCE OF A TERRITORIAL HEADACHE CENTRE IN A NEUROSCIENCE DEPARTMENT: THE SYNERGY WITH GENERAL MEDICINE

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Introduction Headaches are disabling and very diffuse pathologies with a remarkable socio-economic burden. On the basis of statistical data from the major industrialized countries, most patients do not consult a physician, but resort to self-medication or tolerate the headache; when they consult a physician, they generally consult a General Practitioner (GP). For this reason, GPs serve a basic role and frequently are the first stage in the route of medical care, especially in Italy, where they control the patient's admittance to the specialized health-care system.

Unfortunately, in agreement with the literature, our experience confirms that GPs do not always, adequately, play their role of "filter", because of their diagnostic-therapeutic mistakes with inappropriate investigations and inefficacious therapies. In contrast, GPs sometimes do not get the consistent support of the specialist and they often judge Guidelines as too difficult to apply. To improve relations between the GP and Specialist, we think it is convenient to make more frequent professional contacts to transform the GP into an active element in the management of the patient, through the activation of different instruments of communication.

Methods We identified the following instruments: (1) A report about our patient's management, to send to the GP with the object of sharing diagnostic-therapeutic decisions, avoiding unnecessary diagnostic assessments, and limiting, as far as possible, pharmacological complications deriving from the interactions with drugs taken for associated pathologies; (2) Meetings for information and professional training on Headaches and Guidelines to assure a very good and lasting support of the GP to the clinical statement suggested by our Centre; (3) The realization of screening by means of a few "key" questions, according to Lipton's experience [1], that GPs will address to their own headache patients to identify the migraineurs.

Discussion The collaboration between a Territorial-Specialist and GP is the basis of a medical net care system that is as valid as it is able to identify patients and to take them through a reliable and efficacious clinical course. The sensitization and the involvement of the GP aims at identifying patients on the basis of IHS criteria and the methods specifically selected for the GP. In this way they will be not only the first examiners but, thanks to their increased efficiency, also the only filter of the patients referred to the territorial headache centre, which is recognized as the main structure of diagnostic investigation.

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THE GENOMEUTWIN-MIGRAINE PROJECT

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European populations and epidemiological cohorts are of special interest in the current era of genomic research aiming to characterize the background of common human diseases. The genome sequence, detailed information of genetic variations between individuals, high-throughput molecular technologies, and novel statistical strategies create new possibilities to define genetic and life-style risk factors behind common health problems. Studies of large population cohorts are needed to transform the genetic information into a detailed understanding of the predisposing factors in diseases affecting most human populations.

European twin cohorts provide a unique competitive advantage for investigations of the role of genetics and environment or life style in the etiology of common diseases. The GenomEUtwin applies and develops new molecular and statistical strategies to analyse unique European twin and other population cohorts to define and characterize the genetic and environmental components underlying diseases like obesity, migraine, coronary heart disease, and stroke, representing major health-care problems worldwide. This project is supported by the European Commission under the programme *Quality of Life and Management of the Living Resources* of the 5th Framework Programme and involves, among other countries, Italy. Since 2001, the National Institute of Health of Italy is the repository of the National Twin Registry, which is the world's largest population twin registry, comprising approximately 650000 probable twin pairs born and resident in Italy until December 31, 1995.

With the availability of this registry and the high prevalence of migraine in the general population, an Italian study on twins affected by migraine will better define the impact of genetic and environmental factors on the etiology and pathophysiology of the disease. The large size of the Italian population and its rich genetic heterogeneity could in fact expand the present knowledge on migraine genetics. Moreover, the diffusion of Headache Centres throughout Italy may allow the identification of wide cohorts of migraine patients. The GenomEUtwin-migraine project will consist of the following steps: (1) identification of all probable twin pairs among migraine patients referred to the National Institute of Health from selected Headache Centres by matching the database of patients with the National Twin Registry; (2) direct

interview of all twin pairs in whom at least 1 subject is affected by migraine (*affected* twin pairs) by means of specific registry and medical questionnaires; (3) neurological and physical examination and blood collection from all *affected* twin pairs; (4) genetic analysis with creation of a biological bank; and (5) statistical analysis.

FOOD AND HEADACHE: REAL FACT OR MYTH?

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A link between headache and food has been supposed since ancient times. In the past, nausea and vomiting during a migraine attack were often considered related to the previous consumption of certain foods. Nowadays, many patients, and a great number of doctors too, think that certain foods may trigger headache attacks, but the effective role of dietary constituents as triggers is still a matter of an intensive debate.
Among primary headaches, migraine is certainly the subject of the greatest number of studies regarding this aspect.
In 1972, Dalessio introduced the term "dietary migraine", to clearly distinguish those forms in which some particular kind of food is recognized as a trigger of the attacks.
Situations in which the headache attacks are triggered exclusively by the consumption of a particular food are clearly distinguished from others, in which, other triggers may be recognized besides food.
According to many studies, about 30% of migraine patients report that there is a temporal relation between their headache attacks and the previous consumption of certain foods, especially cheese, chocolate, citrus fruits, and alcoholic drinks.
Unfortunately, until now, double-blind challenge studies have not confirmed these observations.
The mechanism by which foods might trigger a headache attack is still very far from being clear.
The incriminated foods are disparate and to date, a single common chemical entity has not yet been found.
Hypotheses have been made, over the years (allergic mechanism, metabolic alteration of some phenolic compound, vasoactive amine, altered serotonin release from platelets, chemical entities acting on H1-Histamine receptors, and as 5-HT_2 serotonin receptor agonists). None of these have been found to be true.
Tension-type headache (TTH) attacks have always been considered not to be linked to food consumption, due to TTH's completely different pathogenetic mechanism.
Recent studies, however, showed that about 25% of TTH patients report that certain kinds of foods may trigger their attacks.
Finally, in cluster headache, alcoholic drinks are the only recognized dietary factor which may trigger the attacks during the cluster period.
Further studies are needed to answer these questions. These kind of studies, however, are difficult to perform, due to a series of variable factors.
If the role of food as a trigger of headache attacks could be more clearly defined, the possibility of a more specific therapeutic approach would arise, and this could lead to a better quality of life for patients.

MIGRAINE AND COELIAC DISEASE

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Objectives Coeliac disease (CD) is a genetically-determined chronic inflammatory intestinal disease induced by a gluten environmental precipitant [1]. Subclinical CD has been associated with various neurological disorders (i.e., neuropathy and cerebellar ataxia) [1]. Recent reports suggested a possible association between CD and migraine [2]. The aim of our study was to assess CD prevalence in migraine patients, regional cerebral blood flow in migraine patients with and without CD, and effects of gluten-free diets on migraine patients with CD.
Materials and methods Ninety migraine patients (63 F/27 M, 37±8 yr) were consecutively enrolled; 236 blood donors (147 F/89 M, 35±9 yr) without migraine history were the controls. Serum anti-transglutaminase and anti-endomysial antibodies were measured in all participants. In positive cases, diagnosis was confirmed endoscopically. Patients with CD underwent gluten-free diets and were under observation for 6 months. A brain SPECT study was performed before and after gluten-free diet.
Results Four of 90 (4.4%) migraine patients were positive for coeliac disease compared to 0.4% of controls ($p<0.05$). One patient did not have any migraine attacks during the entire follow-up period; an improvement in migraine frequency/duration/intensity was observed in the remaining 3. SPECT studies showed a regional baseline reduction of brain tracer uptake in all 4 patients; it completely disappeared after a successful gluten-free diet.
Discussion Possible mechanisms behind this association are: (1) autoimmune phenomena: serum antibodies from patients with CD strongly react with human brain blood-vessel structures *in vitro* [3]; (2) a chronic strong release of cytokines and molecules with vasoactive properties from the gut of patients with active CD [4].
Conclusions This study suggests an association between migraine and CD. If larger randomized controlled trials will confirm these preliminary findings, serological screening for CD could be proposed as part of migraine management.
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OSMOPHOBIA IN MIGRAINE AND TENSION-TYPE HEADACHE

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The diagnosis of primary headache is based on the presence of codified clinical features referred by the patient; nowadays, not a single pathognomonic criterion has been identified. Clinical experience shows that intolerance to smell is commonly mentioned by migraine patients. In the II century B.C. Arethaeus the Cappadocian already asserted that the sense of smell was altered during the course of an attack, and in the XIX century Gowers, noticed that "a peculiar odour" could be a headache trigger. Despite this, the relationship between osmophobia and migraine has not been studied in depth. We recruited consecutive patients from our Headache Centre with diagnosis of migraine with aura (MA) and without aura (MO) and tension-type headache (TTH). Patients with two or more forms of primary headaches were excluded. Four hundred and ninety-six patients participated in the study (age 37.5 years ±11,8); of whom, 359 MO, 47 MA, and 90 TTH (69 episodic; 21 chronic). Among migraine patients, 42.9% with MO (154/359) and 40.4% with MA (19/47) reported osmophobia during the attacks; none among the 90 TTH patients suffered this symptom. As an offending

smell, food-related odour was mentioned by 51% of migraine patients with osmophobia, perfumes by 64%, cigarette smoke by 58%, and other types of smells by 6%. The olfactory stimulus triggered the attack in 11%. Cigarette smoke and women's perfumes were the smells more frequently indicated. We conclude that osmophobia appears as a very specific marker to discriminate adequately between migraine (MO and MA), and tension-type headache.

VIDEO DISPLAY TERMINALS EXPOSURE AND HEADACHE

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Introduction In the past two decades remarkable changes have occurred in the workplace, above all as a consequence of the use of video display terminals (VDT). More frequently, headache musculoskeletal complaints, eye discomfort, palpitation and precordial pain, depressed mood, irritability, sleep disorders, lack of appetite, sweating and skin symptoms have been detected among users of VDTs.
Objective The aim of the present study was to evaluate workers' exposure to VDT as a risk factor for developing headache.
Methods The study was carried out on 86 healthy subjects, 43 VDT users (33 females, 10 males; mean age 40.7 years ±9.04) and 43 non-VDT users (34 females, 9 males; mean age 40.1 years ±9.1), employees from "IRCCS Mondino Foundation, Pavia". For each patient we collected: time of use, weekly VDT exposure, and clinical data. Headache patients were evaluated by a headache diary based on IHS classification.
Results In the VDT users group, 51.1% were affected by headache (13 MWOA, 7 ETTH, 1 MWA and CH), 84.4% referred visual disturbances and 60.5% visual disturbances with headache. In the non-VDT users group, 40% referred headache (12 MWOA, 6 ETTH), 46.6% referred visual disturbances and 66.6% referred visual disturbances with headache.
Conclusions In our study no difference in developing a headache was found between VDT users and non-VDT users. However, we found evidence that in the group of VDT users with headache, 69% presented headache "*de novo*" or worsened after 5 years of VDT use. Therefore, we conclude that the prolonged exposure to VDT represents a facilitating or aggravating factor in headache, that when present results in visual and/or ocular disturbances.
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NEW INSIGHTS INTO TRIGEMINOVASCULAR ACTIVATION IN MIGRAINE: A ROLE FOR SECRETONEURIN

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Background Numerous experimental evidence supports the role of the 33 amino acid neuropeptide secretoneurin in neurogenic inflammation [1]. The involvement of this neuropeptide in trigeminovascular activation underlying migraine attacks has never been investigated.
Objective To determine the levels of secretoneurin in the internal jugular blood taken from migraine without aura (MwoA) patients assessed during attacks and to verify the relation between these levels and those of the end-products of nitric oxide, the nitrites, and those of endothelin (ET)-1.
Patients and methods Ten MwoA patients were admitted to the hospital during attacks. Internal jugular venous blood samples were taken immediately after catheter insertion, at 1, 2, and 4 hours after attack onset, and within 2 hours from its cessation. The levels of secretoneurin and ET-1 were measured by sensitive radioimmunoassays, those of nitrites by high-performance liquid chromatography.
Results A significant increase in secretoneurin levels was found in the internal jugular venous blood of MwoA patients compared to the time of catheter insertion (ANOVA: $p<0.0001$) with a peak at the first and second hours ($p<0.02$ and $p<0.01$). A parallel increase in nitrite levels was observed at the same time-points, which were correlated with the levels of secretoneurin (R=0.51, $p<0.01$ and R=0.62, $p<0.03$). Higher levels of ET-1 were found at each time of attack with respect to the time of catheter insertion but no correlation was evident between ET-1 values and those of nitrites and secretoneurin.
Discussion The present study suggests the involvement of secretoneurin in the pathogenic events accompanying trigeminovascular activation in migraine. This neuropeptide seems to play a role in stimulating endothelial cells as suggested by the increased levels of nitrites. This action on cerebral endothelium can also be exerted in concert with calcitonin gene-related peptide [2]. The rise in ET-1 levels in the jugular blood seems to be a response to shear stress, instead of being a specific compensatory response to the effect of secretoneurin on cerebral endothelium.
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NEUROBIOLOGY OF CHRONIC MIGRAINE

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Objective To present a systematic review of the present status of knowledge about the neurobiological mechanisms underlying transformation of episodic migraine into chronic migraine.
Results Chronic migraine (CM), formerly known as transformed migraine, is a headache disorder that affects 2–3% of the general population. It is particularly frequent in tertiary care structures and is an important clinical problem for headache specialists. Analgesic overuse, sleep disturbances, depression, and anxiety are often comorbid with CM. The costs and burden of CM are significant.
The pathophysiology of CM is still poorly understood. Within the last 2 decades there has been an explosion of new information on the mechanisms underlying chronic pain. Neurobiological studies have provided new insights into the pathogenesis of chronic migraine. *Genetic factors* play an important role in CM but the types and the number of genes involved in the disease are, at present, unclear. Certain features of chronic migraine, namely, increased headache frequency, expansion of headache area, and cutaneous allodynia, may imply *sensitization* of nociceptive neurons in the trigeminal pathway. Neurophysiological studies have shown that repetitive activation of the trigeminal nerve can lead to a biological and functional change in trigeminal nucleus caudalis neurons, characterized by a

decrease in nociceptive threshold and receptive field expansion. Results from a number of experimental studies have indicated that *chronic analgesic exposure* leads to changes in serotonin content and density of 5-HT2A receptors in the central nervous system. This plasticity of the serotonin-dependent pain control system may accelerate the process of sensitization, a biologic outcome that is expressed clinically by the development of chronic migraine associated with analgesic overuse. Hypothalamic involvement may be a key feature of chronic migraine. *Neuroendocrine studies* have shown an abnormal pattern of hormonal secretion in the disease and suggested a possible hyperdopaminergic state in patients with CM. Finally, MRI studies have provided evidence that CM is associated with a progressive impairment in iron homeostasis within the periacqueductal gray, a centre of the descending antinociceptive neuronal network.

Conclusions Despite no clear explanation of the mechanism underlying migraine transformation, experimental data suggest that the process is related to a progressive sensitization of the cerebral antinociceptive systems. Abnormal modulation of these systems may explain the shift of the migraine phenotype from episodic to chronic headache. The neuronal plastic changes in chronic migraine make the antinociceptive systems an important target for several types of interventions.

SALIVARY CORTISOL, DHEA-S AND TESTOSTERONE IN CHRONIC MIGRAINE

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Chronic migraine (CM) is the most disabling form of headache among those in the ICDH-II. The failure in treating CM is often due to a superimposed medication-overuse headache (MOH). As described by the new classification of the International Headache Society, it is caused by frequent use of antiheadache compounds for more than 15 days/month in most patients, however, using the medication daily. In this study we evaluated 20 CM sufferers, women only, 14 of them affected by MOH, and six treated with botulinum toxin type-A (BoNT-A) one month after withdrawal from MOH. The control group consisted of 15 subjects, age- and BMI-matched with other groups. None of the subjects had been under therapy with corticosteroids for at least 6 months before the study. The HPA axis activity was specifically monitored by measuring salivary hormone levels, which were found to be highly correlated with free plasma levels, thus allowing the stressful event of venipuncture to be avoided. Samples of saliva were collected by the Salivette (Sarsted, Italy), a sampling device which allows quick and hygienic saliva collection through a polyester swab. In order to evaluate the circadian rhythm of cortisol, DHEA-S, and testosterone, the participants were instructed how to collect saliva samples at home, which was performed twice a day (08:00 h and 20:00 h). In order to evaluate the response to a mild physical stressor, the participants attended our laboratory for exercise activity (which consisted of 2.5 minutes of step-climbing exercise) from 10:00 AM to 12:00 AM. Immediately before the start, at the end of the test and 10 minutes after completion of the test, saliva samples for hormone assays were taken and blood pressure and heart rate were measured. MOH in CM is found to be associated with an impairment of cortisol and DHEA-S circadian variation. CM treated with BoNT-A, both in morning and evening measurements, showed intermediate cortisol levels between controls and abuser group. Furthermore, the ratio between testosterone and cortisol levels, which is an indicator of anabolic-catabolic balance, appeared to be lower in CM patients, both MOH affected and BoNT-A treated.

HABITUATION IN SHORT-LATENCY EVOKED POTENTIALS

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Evoked potentials were extensively studied in migraine during the last decade. Almost every modality of stimulation has been used, but particularly visual and auditory stimuli. Compared to all other electrophysiological measures performed in migraineurs, *habituation* of evoked, i.e., amplitude reduction during sustained stimulation, was most consistently found abnormal interictally. There is no habituation, or even potentiation, of pattern-reversal visual evoked potentials (PR-VEP) in the N1-P1 and P1-N2 components during sustained pattern-reversal stimulation in migraineurs between attacks, compared to healthy volunteers [1]. This lack of habituation normalizes during the attack [2] and is present also when using other sensory modalities, such as auditory [3] and somatosensory stimuli [4]. Besides habituation, another interesting electrophysiological pattern interictally abnormal in migraine is the *intensity dependence of auditory evoked potentials* (IDAP). IDAP is indeed high in migraineurs resulting in a steep amplitude-stimulus intensity function slope, but it is supposed to be as well a mere consequence of lack of habituation of the auditory evoked cortical potential [3].

Although habituation is a complex neurobiological phenomenon, it might depend, for cortical evoked potentials, on the cortical pre-activation excitability level. According to the "ceiling theory", a low pre-activation level of sensory cortices allows a wider range of suprathreshold activation before reaching the "ceiling" and initiating a "reducing" response, i.e., habituation. This theory, applied to evoked potential findings in migraineurs, could explain both the low first block amplitude for most evoked potentials and the lack of habituation on trial repetition. The pre-activation level of cortical excitability depends on the so-called "state-setting, chemically addressed connections" that originate in the brainstem and involve serotonin and noradrenaline as transmitters. Low interictal activity of these systems, especially of the raphe-cortical serotonergic pathway, could be responsible for the observed lack of habituation of cortical responses in migraineurs.

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HABITUATION OF EVENT-RELATED POTENTIALS AND NOCICEPTIVES

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Introduction The majority of evoked and event-related potentials studies in migraine have shown two abnormalities: increased amplitudes of averages of large numbers of trials and lack of habituation in successive trial blocks during the pain-free phase, with the ictal normalization of evoked potential amplitudes and habituation. During the interictal phase, a reduced habituation pattern of early and late LEPs' component in response to repetitive noxious stimuli was found in respect to control subjects. Furthermore, during migraine attack, patients showed a

pattern of increased amplitude of LEPs and a decreased subjective pain threshold.
Objective The aim of the present study was to assess the habituation of both LEPs and pain sensation during the ictal and interictal condition in migraine patients, in comparison with the habituation pattern of healthy controls.
Materials and methods Eight migraine patients were selected and compared with 10 healthy controls. Two consecutive series of 20 averaged LEPs were recorded on FZ, CZ, and PZ derivations in patients and controls, stimulating the right and left hands and supraorbital zones at an intensity level set at a level 2.5 below the detection threshold; the subjective sensation was requested for each stimulus using a 0–10 point VAS. Patients were evaluated during the attack and in attack-free conditions.
Results In normal subjects the N2a-P2 waves amplitude showed a tendency toward habituation across the two repetitions, which correlated with the habituation of the subjective rating of the stimulus. During the interictal phase, patients showed a significant increment of the N2a-P2 amplitude in the second repetition when the face was stimulated, with an increase of the pain rating, which was clear also for the stimulation of the hands; in migraine patients there was a lack of correlation between the LEPs amplitude and the subjective sensation. During the attack, both the LEPs amplitude and the pain rating did not show any significant change in respect to the interictal condition. The percent LEPs amplitude variation across the two repetitions correlated with the main indices of migraine severity, mainly when the supraorbital zone was stimulated.
Discussion and conclusions The abnormal cortical excitability in migraine, causing the altered habituation pattern of multi-modal evoked responses, could condition an anomalous behaviour of the nociceptive cortex during the interictal phase of migraine: it persists during the acute phase, and correlates with the frequency and duration of migraine, as a factor which may subtend the onset and chronicization of headache.

ELECTROPHYSIOLOGICAL EVIDENCE FOR SENSITISATION PHENOMENA IN MIGRAINE

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Clinical studies showed that acute migraine attacks are accompanied by increased cephalic/cranial skin sensitivity to touch, heat, and cold. As established in animal models and pre-clinical studies, this hypersensitivity probably reflects sensitisation of the primary nociceptors and central trigeminovascular neurons.
In humans, electrophysiological studies of trigeminal pathways are useful to investigate peripheral and central mechanisms underlying this disorder. Some authors found prolonged latency of the R2 component of the blink reflex, which was interpreted as a marker of brainstem dysfunction; other studies did not confirm this finding. Recently, using a novel "nociception specific" blink reflex permitting a more specific stimulation of Aδ and C fibres, an increased R2 area was found in migraineurs on the side of the headache, especially during the attack.
Another useful tool for exploring the trigeminal system in humans is the electrically elicited corneal reflex. A lower threshold for the corneal reflex is found interictally in migraineurs compared with controls. This reduction is bilateral even in migraineurs presenting strictly unilateral headache. These findings provide additional evidence pointing to a dysfunction of this system in migrainous patients.
In order to clarify the pathophysiological mechanisms of migraine it could be useful to explore the pain processing on the outside referred-pain area (extracephalic). The nociceptive flexion reflex (NFR) is a reliable and objective tool for exploring pain control systems in humans. In a recent report we studied the function of the pain modulating systems subserving diffuse noxious inhibitory controls (DNICs) in primary headache, evaluating the RIII parameters during CPT. The data obtained showed a significant facilitation during the cold-pressor test in respect to the inhibition observed in controls. This study demonstrated a dysfunction in systems subserving DNICs in both migraine and CTTH. Impairment of endogenous supraspinal pain modulation systems may contribute to the development and/or maintenance of central sensitisation in primary headaches. Other preliminary data from the population of chronic migraine patients showed a significant reduction of the RIII reflex and temporal summation threshold with increased reflex area. These data suggest that in migraine sufferers, the sensitisation of central nociceptors occurs not only in the trigeminal district, but also widely involves the spinal cord.
Taken together, electrophysiological investigations of the trigeminal networks in migraine are in favour of segmental hypersensitivity and/or decreased control of descending inhibitory pathways, confirming that sensitisation of central trigeminal nociceptors occurs not only during, but may even persist interictally, and the frequent bilateral location of the abnormalities suggests a centrally located dysfunction.

TRANSCRANIAL MAGNETIC STIMULATION TO INVESTIGATE DYSFUNCTION OF CORTICAL ACTIVITY IN MIGRAINE

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Transcranial magnetic stimulation (TMS) can assess and modulate cortical excitability. This last goal can be achieved by repetitive TMS (rTMS). Excitability of the visual cortex has been studied in migraine through phosphene threshold (PT), (i.e., the minimum intensity of magnetic stimulation needed to evoke phosphenes).
Contradictory results have emerged, with some authors finding PT levels reduced and others increased in migraineurs.
A few rTMS studies have been conducted in migraine. Bohotin et al. [1] found that 10 Hz rTMS (a facilitatory frequency) favours recovery of habituation of visual evoked potential (that is reduced in migraineurs), while 1 Hz rTMS (an inhibitory frequency) was able to disrupt habituation in normal subjects. The authors speculated that migraineurs have a reduced cortical activation that can be reverted by facilitatory rTMS; moreover, 1 Hz rTMS reducing cortical activity can establish dysfunctions similar to migraine in healthy subjects.
However, the effects of different rTMS frequencies can dramatically change depending on the pre-existing cortical excitability. Zieman et al. [2], showed that low-frequency rTMS determines paradoxical facilitation in motor cortex when delivered in a condition of cortical deafferentation that is known to reduce cortical inhibition.
We showed that low-frequency rTMS has paradoxical facilitatory effects on the striate and extrastriate cortex in migraine [3, 4]. We interpreted it as a result of reduced efficiency of cortical inhibitory circuits unable to be up-regulated by rTMS. In support of this hypothesis, we recently also found a dysfunction of cortical activity in the motor cortex of migraineurs. Through the technique of paired pulse stimulation we showed that migraineurs present reduced intracortical inhibition at baseline. After 1 Hz stimulation, a paradoxical potentiation of intracortical facilitation (ICF) occurs, opposite to the suppression of ICF induced by the same trains in healthy controls.
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LASER EVOKED POTENTIALS FOR ASSESSING FACIAL PAIN

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Trigeminal nociceptive pathways play a crucial role in chronic facial pain. Currently, laser evoked potentials (LEPs) are the most widely agreed-upon method for studying trigeminal nociceptive pathways. Laser-generated radiant heat pulses selectively excite free nerve endings in the superficial skin layers and can activate Aδ and C nociceptors or warm receptors. Low-intensity pulses directed to the skin of the face evoke pinprick sensations and brain potentials (Aδ-LEPs), both induced by the activation of type II AMH mechanothermal nociceptors. The afferent volley is conducted along small-myelinated (Aδ) primary sensory neurones, and relayed to the spinal trigeminal nucleus and brain. Aδ-LEPs consist of a widespread negative-positive complex (N2-P2) with a maximum amplitude at the vertex. This signal is generated by deep midline structures, probably the anterior cingulate gyrus, and bilateral opercular-insular regions. The main current aim of clinical Aδ-LEP studies in facial pain syndromes is to provide information on Aδ-fibre function and pathophysiology of neuropathic pain.
Patients with symptomatic trigeminal neuralgia (TN) and about 50% of those with idiopathic TN have abnormal Aδ-LEPs. Hence, Aδ-LEPs may indicate trigeminal dysfunction also in patients with normal trigeminal reflexes and no evidence of structural lesion of the trigeminal system. Possibly Aδ-LEPs, because they are mediated by a small number of afferents, are diagnostically more sensitive than trigeminal reflex testing. Naturally, the finding of normal Aδ-LEPs by no means excludes the diagnosis of idiopathic TN. This diagnosis only relies on the clinical description of paroxysmal pain.
In patients with supraorbital postherpetic neuralgia (PHN) Aδ-LEPs are constantly abnormal. However, Aδ-LEPs abnormalities do not correlate with severity and characteristics of the pain, thus suggesting that the pain in PHN does not chiefly arise from a dysfunction of Aδ fibres. In our experience patients with burning-mouth syndrome and atypical facial pain have always normal Aδ-LEPs. In patients with temporomandibular disorders (TMD), Aδ-LEPs have a normal latency, but the mean amplitude is slightly reduced with respect to control values. Although this data demonstrates that TMD patients have a trigeminal nociceptive pathways dysfunction, this dysfunction may be a consequence of chronic pain rather than having a pathophysiological role in TMD.
In conclusion, Aδ-LEPs provide a sensitive and reliable tool for evaluating the trigeminal nociceptive Aδ pathways in facial pain syndromes. Currently, the main limitation to their use is the relatively scarce availability of laser stimulators.

HEMODYNAMIC EVALUATION OF CEREBRAL VASOMOTOR REACTIVITY IN JUVENILE MIGRAINE PATIENTS: A TRANSCRANIAL DOPPLER STUDY

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Transcranial Doppler Sonography (TCD) is a non-invasive technique that can measure local blood flow velocity in large intracranial arteries. TCD can provide an index of relative flow changes in response to physiological stimuli (e.g., hypocapnia and hypercapnia), which tests vasomotor reactivity (VMR) of the distal cerebral arteriolar bed. TCD vasomotor reactivity testing can detect impairment of cerebral hemodynamics in patients with different cerebrovascular disorders including migraine. In this study we aimed to investigate cerebrovascular reactivity in the anterior and posterior parts of the circle of Willis in children with migraine by means of TCD. Thirty-five young patients, (22 males, 13 females; aged 8 to 17 yrs) affected by migraine: 19 with aura (MwA) and 16 without aura (MwoA), were included as outpatients. Diagnosis of migraine was made according to the International Headache Society criteria (1988). All patients were studied in an attack-free period and had discontinued prophylactic therapy at least two months before the study. Duration of the disorder was at least 6 months. Exclusion criteria included cardiac or systemic disease. Patients were free of symptoms 48 hrs before the study. Twenty headache-free, age and sex-matched subjects were selected as a control group. Duplex sonography excluded stenotic lesions of the extracranial vessels. Basal blood flow velocities and the Pulsatility Index (PI) of the middle cerebral arteries (MCAs) were bilaterally recorded through the transtemporal window at a depth of 52 mm while the blood flow velocity and the PI of the basilar artery (BA) were recorded through the transforaminal window at a depth of 76 mm. VMR was studied by recording both the increase and decrease of the blood flow velocities in the MCAs and in the BA after hypercapnia, reached by maximal apnea test, and after hypocapnia, reached by hyperventilation. Basal mean values of the blood flow velocities and the PI of the MCAs and of the BA did not differ significantly in both groups of patients (MwA and MwoA). No significant differences in VMR in the anterior and posterior sections of the circle of Willis were detected in patients with MwA or MwoA (as a whole or as single entities, respectively) compared with controls. Functional assessment of the cerebral microcirculation by a non-invasive technique seems to be a useful tool in identifying patients with migraine at higher risk of major cerebrovascular events.

DIAGNOSING MIGRAINE ACCORDING TO THE ICHD-II GUIDELINES

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The revised diagnostic criteria provide a fairly new tool for making the diagnosis of migraine (Chapter 1), given the new entities that have been included in the present classification, such as chronic migraine or sporadic hemiplegic migraine. There are also subtypes that have been excluded, such as opthalmoplegic migraine, now included in Chapter 13. The probability of diagnosing a migrainous attack is proposed in code 1.6, suggesting that the longitudinal observation of attacks for a given period of time may provide a definite diagnosis for which the criteria are not satisfactory upon first observation. This possibility has a procedural implication, i.e., the need for patient follow-up, although guidelines strictly serve to diagnose the attacks. The same applies to those migraine subtypes which have been, at least in part, associated with genetic defects, such as familial or sporadic hemiplegic migraines. The motor disturbance only fits these diagnoses and the very fine differential diagnosis with basilar-type migraine is founded on this specific symptom. Again, longitudinal observation of the latter subtype may lead to changing the diagnosis if the motor disturbance appears during an attack of expected basilar-type migraine [1]. Genetics are also extending the similarities between these two subtypes [2]. The relevance of premonitory symptoms during an attack has been sorted out, and though there is not enough evidence for making them mandatory as diagnostic criteria [3], they provide useful information in clinical practice, whereas some accompanying symptoms, namely osmophobia, are supported as possibly useful in the appendix section of the guidelines.

The criteria *per se* do not represent the main change in the ICHD-II guidelines, given that they are proposed on the basis of valid and reliable evidence. The main body of the guidelines is better represented by the notes, the comments, and the appendix, because those parts are open to discussion. The hope is that in the next revision there will be more "pathogenesis"-based" criteria to better delineate the boundaries or to break down the apparent discontinuity between different migraine subtypes.

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CHAPTER 4 OF ICHD-II: OLD CONCEPTS AND NEW VIEWS

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In the recently published *International Classification of Headache Disorders 2nd edition* (ICHD-II) – chapter IV, previously entitled "*Primary Miscellaneous Headaches*" (IHS 1988), emerges as one of the chapters that underwent the most profound revisions, as indicated by its title, which has now been changed to *Other Primary Headaches*. It has become increasingly clear, over recent years, that many of the forms included in this chapter raise major problems with regard to their differential diagnosis from other conditions, since some of them may mimic, especially at their onset, serious forms of symptomatic headache due to organic disease of underlying structures. Therefore, the ICHD-II Subcommittee has made a considerable effort to group under this chapter all the possible forms of primary headache that do not fit within the first three chapters of ICHD-II and to provide detailed diagnostic criteria for each one of them. Therefore, chapter IV of ICHD-II has been enriched by the addition of newly identified entities, whose clinical features have been adequately documented in the literature. These new entities are: *primary thunderclap headache, hypnic headache*, *hemicrania continua* and *new daily-persistent headache*, and they have been added to the previous: *primary stabbing headache*, *primary cough headache*, *primary exertional headache* and *primary headache associated with sexual activity*.

Conversely, other forms originally included in the "*Primary Miscellaneous Headaches*" chapter of the first IHS classification, such as the "external compression headache" or the "cold-stimulus headache", have been moved, in view of their specific pathogenetic mechanism, to chapter XIII of the ICHD-II (*Cranial neuralgias and central causes of facial pain*).

Headaches listed in chapter IV of ICHD-II are probably more common than previously thought. Most of these forms are first observed in Emergency Departments because of the suddenness of their onset and their pharmacological treatment is almost exclusively based on anecdotal reports. A positive response to indomethacin has been reported in some of them and has been elevated to the role of diagnostic criterion in the case of *hemicrania continua*.

In the years to come, a strong effort will be required by the scientific headache community in order to field-test the proposed criteria for the various forms of "*Other primary headaches*", to conduct *ad hoc* studies for the clarification of their pathogenetic mechanisms – about which little is currently known – and to perform controlled studies for evaluating the effectiveness of options suggested in isolated reports.

MEDICATION-OVERUSE HEADACHE: CLINICAL AND THERAPEUTIC PROBLEMS

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The interactions between chronic headache and medication overuse are complex and not yet fully clarified. In particular, the mechanisms by which medication overuse takes part in the chronicization process are still object of hypotheses. Certainly, medication overuse complicates the therapeutic approaches to chronic headache. Medication overuse hampers the effect of prophylactic therapies, and only the interruption of the overuse, over a variable period of time, leads to the disappearance, or at least the reduction in the frequency of headache. Only at that point it is possible to start the prophylactic treatment with a well-founded probability of success. Unfortunately, interrupting medication overuse is not an easy task, due to both the severity of the pain symptomatology and to rebound headache which can compel the patient to resume medication.

Objectives The aim of our research was to analyze patients with medication-overuse headache, with respect to the characteristics of drug medication behaviour and its consequences for headache treatment.

Patients and methods We studied a consecutive series of 50 patients, newly admitted to the in-patient service of the Headache Centre of the University of Modena and Reggio Emilia. Data were collected by means of a questionnaire, specifically prepared for this study, recorded into a specific database and analysed by SPSS 6.1.2 program, version for Windows 98.

Results The combination of indomethacin plus caffeine plus prochlorperazine, and triptans were the medications most frequently overused by our patients; only a few patients overused ergot preparations. The majority of patients used the same type of drug daily. All patients referred they increased the frequency of self-medication because the headaches were getting worse. For most patients medication overuse made the headache more endurable, thus allowing them to work or function more or less normally in daily life. Only a minority experienced withdrawal symptoms after discontinuation of the medication overuse**.** After detoxification, antidepressants were the class of drugs most used for prophylaxis.

Discussion During chronic use of a medication indicated for acute treatment of headache, the therapeutic results do not derive solely from the drug but also from the organism's adaptation to the repeated use. This time-process of compensatory adjustments might partly explain both the chronicization of headache and the withdrawal symptoms when medication overuse is interrupted.

Conclusion Medication-overuse headache should be prevented because its management is very difficult. It is necessary to address, at the same time, both the chronic pain condition and the medication overuse.

APPLICABILITY OF ICHD-II CRITERIA FOR PRIMARY HEADACHES: VERIFICATION WITH THE AID OF A COMPUTERIZED DEVICE

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Background Diagnostic requirements for primary headaches in the new classification system ICHD-II appear to be improved and certainly represent an evolution of the previous criteria included in the first IHS classification edition [1, 2]. Some modifications were made to the old criteria concerning all primary headaches and a new entity, chronic migraine, was introduced among the complications of migraine.

Objective With the aim to verify the applicability of classification criteria for primary headaches of the new classification system, we developed a computerized, structured medical record based exclusively on the proposed new classification system for primary headaches. This computerized system examines all the diagnoses of primary headaches on the basis of the variables needed to fulfil their mandatory criteria.
Methods The program, developed with the help of an expert, is called "IHS Diagnostic Criteria for Primary Headaches" version 2.0 ITA, and is strictly based on the ICHD-II operational diagnostic criteria for primary headaches.
The clinical sheets relative to 200 consecutive patients attending our headache Centre in 2004 were examined and included all items needed to make a diagnosis of one of the primary headache disorders according to the new ICHD classification.
Results The software was able to furnish a single diagnosis in 82% of the cases, while in 15% of these, the output diagnoses were multiple (up to 4), and in many cases were of "probable forms". In the remaining 3% of the cases, the diagnosis was 14.1 *Headache not elsewhere classified*, because they did not fit into any of the existing chapters of primary headaches and the headache was not attributable to another disorder.
Discussion The introduction of "probable subtypes" for the episodic and chronic forms necessitates a careful re-examination of these definitions and will lead to suggestions for overcoming possible drawbacks in the diagnosis that, however, is ultimately entrusted to the clinician.
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PSYCOBIOLOGICAL ASPECTS IN CHRONIC TENSION-TYPE HEADACHE

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Knowledge of the possible pathophysiological mechanisms of tension-type headache (TTH) is mandatory to postulate the "sites" of action of psychological factors.
Both peripheral and central phenomena of sensitization seem to be involved in the chronic form of TTH (CTTH). The former one consists of a decrease in the pain threshold of pericranial myofascial nocisensors as a result of repeated stimulation by neurotransmitter release following microtraumatisms of muscle fibres and/or tender insertions due to a spontaneous activity in myofascial trigger points. The latter represents the most important mechanism in CTTH and mainly consists of a segmental sensitization of second order neurons in the spinal dorsal horn/trigeminal nucleus secondary to prolonged nociceptive input from pericranial myofascial tissues. Moreover, the findings of decreased mechanical, thermal, and electrical pain thresholds, both in cephalic and extracephalic structures in patients with CTTH, also suggest changes in supraspinal pain modulation.
Psychological factors might play an important role in both peripheral and central mechanisms of sensitization. The Italian Collaborative Group for the Study of Psychopathological Factors in Primary Headaches assessed that about 85% of patients with TTH had at least one, and almost 50% of patients had two psychiatric disorders or psychosocial stressors; affective disorders were more frequent in the chronic than in the episodic form. A subsequent study, when comparing, by correspondence, the same TTH patients versus migraine patients from headache centres in Italy, showed that CTTH with pericranial muscle disorder correlated with anxiety and depression, whereas CTTH without pericranial muscle disorder correlated with somatoform disorder. The influence between psychological problems and CTTH may be bidirectional with each other increasing the risk for the other. For example, depression might be a consequence of chronic headache but it might also make the progression of an episodic into a chronic headache easier. Repeated or sustained conditions of mental stress may induce an activation of myofascial trigger points resulting in peripheral sensitization. Moreover, it is well known that the raphe magnus nucleus and the locus coeruleus exert a descending inhibitory modulation of pain at the level of spinal dorsal horn/trigeminal neurons by means of serotonergic and noradrenergic pathways, respectively; therefore, an impairment of these neurotransmitters may contribute to central sensitization. In contrast, several psychological disorders are associated with changes of some neurotransmitters such as noradrenaline and serotonin. Altogether these data suggest a common neurobiological dysfunction for psychiatric disorders and CTTH, consisting of an involvement of serotonergic and noradrenergic systems.

QUALITY OF LIFE MARKERS IN MIGRAINE

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It is well known that migraine induces disability and an impaired quality of life, work, social activities, and family life, even between attacks. The impact of migraine on quality of life has been traditionally evaluated by the health-related quality of life (HRQoL) instruments that can detect changes over time in response to at least major changes in migraine therapy. The SF-36, a general HRQoL measure, and several migraine-specific HRQoL instruments, have proved useful endpoints for migraine clinical trials. Their role in clinical practice is, however, yet to be established (Becker, 2002); besides, it is not clear which clinical features have the greatest impact on a migraineur's quality of life and if specific concomitant aspects, such as possible compromised quality of sleep, excessive daytime sleepiness, or chronic fatigue, might contribute to quality of life impairment in migraine.
The aim of this study was the assessment of sleep quality and daytime functioning parameters, such as sleepiness and fatigue, and the verification of their possible relationship with traditionally assessed quality of life dimensions. One hundred consecutive patients (84 F, 16 M; mean age±S.D. 39.9±11.4 years), fulfilling the diagnostic criteria for migraine without aura (IHS 1988, 2004) were enrolled and 24 normal subjects (20F, 4M; mean age±S.D. 36.6±14.1 years) represented the control group. The Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, and Fatigue Severity Scale were employed. The impairment in subjectively estimated quality of sleep and complaint of chronic fatigue was significantly more represented in migraine without aura patients than in controls. According to our data, both altered sleep quality and fatigue occurred in episodic migraine in the absence of any psychiatric disorders; thus, it might be hypothesized that they depend on the pathogenetic mechanisms of migraine themselves. Finally, both poor sleep and fatigue were related to quality of life as assessed by the means of SF-36, so it might be suggested that these parameters contribute to the estimated quality of life in episodic migraine patients.

MUSCLE TENDERNESS IN DIFFERENT HEADACHE TYPES AND ITS RELATION TO ANXIETY AND DEPRESSION

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To assess the extent to which muscle tenderness may relate to anxiety, and depression in patients with migraine and tension-type headache,

both episodic and chronic. Four hundred and fifty-nine patients with episodic migraine (EM, 125), chronic migraine (CM, 97), episodic tension-type headache (ETTH, 82), chronic tension-type headache (CTTH, 83), and EM + ETTH (72) were enrolled. For each patient a psychological assessment on the Axis 1 of the DSM-IV and muscle palpation of pericranial and cervical muscles were carried out. A Pericranial Muscle Tenderness Score (PTS) and a Cervical Muscle Tenderness Score (CTS) were calculated (range 0–3). Logistic and linear regression analyses were employed to assess relations between muscle tenderness, demographic variables, and psychiatric disorders in the different patient groups. Odds ratio for "male gender" was higher in groups with tension-type headache. Only EM patients showed a positive association with increasing age. Anxiety and depression were significantly associated with CM. A significant negative correlation of PTS and CTS was observed in EM patients. In relation to male gender, the PTS was significantly lower in EM, ETTH, and CTTH; CTS was significantly lower in EM, CM, and CTTH. Anxiety and, even more so, anxiety and depression combined were positively associated with higher PTS and CTS in EM patients. Anxiety and depression were also positively associated to higher CTS in patients with EM+ETTH. In CTTH patients, only PTS was positively associated with anxiety and depression.
We conclude that in patients with EM the presence of anxiety or anxiety and depression combined considerably increases the level of muscle tenderness in the head and, even more, in the neck, and might facilitate the evolution into CM.

HEADACHE, INSOMNIA AND PSYCHIATRIC DISORDERS: FROM PAIN TO MENTAL SUFFERING

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The study of pain, as an experience elicited by nociceptive afferences, has been well investigated by recent psychological research, while the relationship between pain and mental suffering has been quite forgotten by psychopathological speculation. Correlations between somatic pain and mental suffering, now included in the psychiatric concept of comorbidity, on the other hand, received strong interest until the middle of the past century. This issue has been raised again with the growth of neurosciences, as demonstrated by studies on the relationship between headache, insomnia, and psychiatric vulnerability. Studies about facilitating effects of insomnia on headache were preceded by those on protective effects in sleep. Clinical observations were later confirmed by evidence on the relationship between sleep deprivation and headache, and by the hypothesis of a self-enhancing loop between insomnia and headache. Therefore, relationships between headache and anxiety as well as between headache and depression are no longer questionable. The pervasive association between depression or anxiety, chronic insomnia and primary headache could be viewed within the context of the psychopathology of somatization and conversion, both milestones of the psychoanalytical concept. In this context, certain painful manifestations are results of neurotic defences, which unconsciously refuse mental suffering leading to a headache or insomnia. Similarly, in hypochondria the transformation of anguish into somatic diseases occurs at the expense of losing reality judgment which weakens to a delusional state. Modern psychiatry simplifies this issue. It relegates insomnia associated with mental disorders to comorbidities and disregards headaches *sine materia* by considering them part of the clinical phenomenon of anxiety and mood disorders, or the core symptom of Somatoform Pain Disorder. Primary headache, chronic insomnia and psychiatric disorders can be viewed also as mutual facilitating processes. The failure of one single aspect, i.e. somatic pain expressed as headache, autonomic phenomena as insomnia, or mental suffering as a psychiatric disorder, gradually leads to an overall imbalance. The development of functional brain imaging methodologies is now defining neurobiological bases of the differences and similarities between pain and mental suffering. Available data that neuronal networks underlying nociception and mental suffering are widely overlapping, suggests different aspects of the same dimension, where life events, mental experiences and neurometabolic processes are partial aspects of the same psycho-neuro-biochemical loop as body and mind of the psychophysical unity of each person.

TIME COURSE OF HEALTH-RELATED QUALITY OF LIFE, BODILY PAIN, ANXIETY, AND DEPRESSION IN PRIMARY HEADACHES

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In this preliminary study, the time course of quality of life (QoL), bodily pain, anxiety, and depression were documented in outpatients at the basal visit, and at 3 and 6 months follow-up in sixteen headache outpatients (3 men and 13 women with a mean age of 29.31 years, range 21–62). During the study, patients received only symptomatic treatment (simple or combination analgesics and triptans). No psychological therapies were introduced. QoL was assessed using the medical outcomes study *Short Form Health Survey* (SF-36), a generic, self-administered instrument, which has been widely used in several chronic disorders [1]. The *McGill-Melzack Pain Assessment Questionnaire* was used to assess the quality and intensity of the bodily pain [2]. The *Beck Depression Inventory* (BDI) was applied for assessment of depression [3]. Finally, the *State-Trait Anxiety Inventory –form Y* [4] was used to assess anxiety traits.
In 7 of the 16 patients (43.75%), QoL was globally restored to the basal visit level three months after recruitment. Nearly identical prevalences were observed in the 3-month follow-up and the 6-month follow-up. The patients' perception of the bodily pain showed only marginal changes or remained stable at the two follow-up time points. Depression was a common finding at the basal visit (75% had a BDI score indicating a mild to moderate depression or a moderate to severe depression). At the six month follow-up in 6 of the 16 patients (37.5%) a degree of reduction of the depressive disorder was observed. The percentage of patients with anxiety traits (81.2%) also showed a declining trend in 12 of the 16 patients (75%).
The results of this preliminary report highlight the importance of health status evaluation as an essential step in the longitudinal assessment of patients with headache attending a headache centre.

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COMORBIDITY OF MIGRAINE AND EPILEPSY

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In clinical practice, the finding of headache and epilepsy in the same patient and, moreover, in the presence of ictal and interictal epileptiform EEG patterns in patients with headache, is well known. These associations have stimulated research in the clinical and pathogenic relationships between headache and epilepsy.

Studies of the incidence of this association in epileptics and headache sufferers and an analysis of the link between the two different types of attacks have led several authors to support a non-casual clinical association between epilepsy and headache. So far, the pathophysiology of this condition remains unknown [1].
In adult patients, several studies demonstrated, according to IHS criteria, that the most common types of headache associated with epilepsy were migraine and tension-type. However, the rate of unclassified headaches has been remarkably high [2].
Probably, the most common relationship between seizures and migraine is when migraine-like headaches occur after seizures. Postictal headaches are often indistinguishable from migraine and are equally common in patients with or without a family history of migraine.
Epileptiform abnormalities have been revealed in 9–13% of patients with migraine; this rate is significantly higher than expected from the normal population. Simple and complex partial seizures, primary and secondary generalized seizures, and tonic-clonic seizures have been reported associated with headache.
It can be difficult to differentiate seizure disorders from migraine phenomena (and vice versa) in some patients. It is particularly a problem in children with atypical clinical presentations with or without abnormal EEGs [3].
In the absence of EEG recorded seizures, it is not uncommon to introduce an anticonvulsant if the history suggests a severe problem compatible with a diagnosis of epilepsy. Remission of the suspected events under anticonvulsant medication may indicate that the initial diagnosis of epilepsy was correct. However, there is evidence that in some patients, migraine phenomena also respond to these drugs. Valproate, gabapentin, topiramate, and tiagabine have been demonstrated to be efficacious. Furthermore, epileptic patients with a history suggesting migraine require a combination of both antiepileptic and antimigraine drugs in order to achieve full control of epilepsy.

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THE COMORBIDITY OF MIGRAINE AND VASCULAR DISORDERS

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The relationship between migraine and vascular disorders has been repeatedly investigated without convincing evidence concerning the mechanisms that could be implicated in their comorbidity. In a previous study, with the aim of identifying vascular disorders in the relatives of children and adolescents with migraine (143 subjects) and of controls (164 subjects), we found evidence of a common pathogenetic mechanism underlying migraine and vascular disorders. Indeed, the results revealed an increased risk of vascular diseases in the families of migraine patients, which may reflect an age-related phenotype of common genetic origin.
Objective In order to verify the results of our previous research, we extended our study to include a broader population.
Materials and methods We investigated the family history of new cases: 20 migraine with aura patients (MA), 69 migraine without aura patients (MO), and 162 controls. We also studied additional risk factors (atrial fibrillation), other confounding variables (smoking, oral contraceptives) and the presence of headache in the families of the new cases recruited. We also enrolled another control group, consisting of 81 tension-type headache sufferers (TTH), in order to verify whether the association with vascular disorders is specific to migraine, or if it is also present in other headache varieties.
Results The results of our previous study were confirmed in the wider sample of 639 subjects (54 MA, 177 MO, 81 TTH, and 327 controls): we found a significantly higher prevalence of at least one vascular disease in the parents and grandparents of migraine patients (MO+MA) compared with controls and TTH patients (p=0.043). However, the analysis of the data collected from the new samples enrolled (332 subjects: 20 MA, 69 MO, 81 TTH, and 162 controls), allowing us to account for other confounding variables (i.e., smoking and oral contraceptives), did not show a significant difference in the prevalence of vascular disease between cases and controls.
Conclusions The vascular risk in the families of migraine patients is not higher than that expected in the general population, thus excluding a common pathogenetic mechanism underlying migraine and vascular disorders.

COMORBIDITY BETWEEN HEADACHES AND PSYCHIATRIC DISORDERS

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RELATION BETWEEN THE CENTRAL NERVOUS SYSTEM, ENTERIC NERVOUS SYSTEM AND VISCERAL PAIN

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In general, pain is an alarm symptom responsible for individual responses aimed at avoiding potentially harmful events essential to promoting longevity. However, aberrant pain, including that of visceral origin, can lead to severe, debilitating conditions that pervade all aspects of life. The experience of pain most commonly begins with a noxious stimulus that is transmitted along nociceptive pathways to the brain. Specifically, signals arising from viscera, e.g., the gastrointestinal tract, are conveyed along sensory pathways (by Aδ and C-fibres) to the sensory ganglia (either spinal or nodose), transmitted to the dorsal horn of the spinal cord (laminae I and II) and finally, after this complex processing are sent to the central nervous system where they are integrated with cognitive and emotional information to produce an appropriate response. Chronic pain represents a key symptom in a variety of functional gastrointestinal disorders (FGIDs), particularly irritable bowel syndrome (IBS). Although the pathogenetic mechanisms leading to chronic pain in FGIDs are still far from being fully elucidated, clinical and experimental evidence clarified the major aspects involved in pain neuropathophysiology. An increased perception of visceral stimuli, generally referred to as hypersensitivity, which can often be observed in patients with FGIDs, may occur at three primary levels (i.e., the enteric nervous system, the spinal cord, and the brain). Specifically, visceral hypersensitivity may arise as a result of: (1) Mucosal inflammation triggers hypersensitivity through the close interaction between enteric nerves and an increased number of inflammatory cells (e.g., mast cells, T lymphocytes, macrophages), which have been detected in the intestinal mucosa of patients with IBS. These inflammatory cells release a variety of mediators, including cytokines, nitric oxide, histamine, and proteas-

es influencing sensory nerve function. Neuro-immune interactions evoke increased visceral sensory perception and this may contribute to abdominal discomfort and pain; (2) Persistent up-regulation of noxious sensory input results in neuroplastic changes occurring in the dorsal horn of the spinal cord. These changes include either an abnormal increase of nerve terminals containing sensory neurotransmitters (e.g., substance P and/or calcitonin gene-related peptide) or transmitter-receptor up-regulation; (3) Psychosocial stressors, including abuse, may trigger functional bowel disorders. In particular, acute stress can affect digestive motor function and visceral perception contributing to symptom generation. Recent studies show that stress induces the release of corticotropin-releasing factor (CRF) that may be responsible for mast cell activation and mediator release.

MIGRAINE AND TENSION-TYPE HEADACHE IN CHILDREN UNDER SIX YEARS OF AGE: ANALYSIS OF COMORBIDITY FACTORS

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Objective To assess the evolution of idiopathic headache with early onset and to investigate the influence of early somatic complaints, life-events and psychological factors at onset and during the course of headache. We also investigated the validity of the ICHD-II criteria for idiopathic headache in pre-school children.
Methods Prospective evaluation of 25 consecutive headache patients referred before the age of six to our Departments of Child and Adolescent Neuropsychiatry. Headache diagnosis was based on both ICHD-II criteria and "intuitive" clinical criteria. All patients were assessed by a structured interview to detect early developmental disorders, interictal somatic complaints, and life-events (DSM-IV). All patients underwent clinical observations and assessment of psychological factors by means of interviews and CBCL (ICD-10). All these evaluations were performed at recruitment (TO) and follow-up (T1). Chi-square test was performed.
Results Twenty-five children (12 M; 13 F) were monitored through a clinical follow-up (mean duration, 4.2 years; range: 2.2–6.6 years). Headache evolution at T1: 16/25 (64%) remission (HR); 9/25 (36%) persistence (HP). An ICHD-II diagnosis of migraine without aura (MO) or tension-type headache (TTH) was possible in only 9/25 cases (36%) at onset (T0): 5/9 MO and 4/9 TTH. At follow-up (T1), an ICHD-II diagnosis was possible in 100% of the children with HP: 1/9 MO and 8/9 TTH.
Early developmental disorders were present in 11/25 children with a significantly higher prevalence in HP compared to HR patients (78% vs 25%). No significant differences were found between HP and HR patients with reference to interictal somatic disorders at T1.
We detected a life event associated with the headache onset in 40% of our patients, and associated with headache evolution in 24% of them.
Psychological disorders were detected in 16/25 (64%) cases at T0 but no significant differences were found in their prevalence between HP and HR patients at T1.
Conclusions Our results suggest that ICHD-II criteria are too restrictive for the classification of MO and TTH in pre-school children. Nevertheless, a diagnosis based on the same criteria was possible after a few years follow-up.
We found a significant association between early somatic disorders and headache persistence: early somatic disorders could have not only a predictive role on the headache onset, but also a negative prognostic value. The high rate of psychiatric disorders detected at recruitment was not related to headache persistence at follow-up. On the contrary, life-events play an important role both at onset and during the course of the symptom.

CLINICAL AND PROGNOSTIC VALUE IN MEASURING HEADACHE DISABILITY

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In 1980 disability was defined by the WHO as "any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being". In 2001 "*The International Classification of Functioning, Disability and Health*" was published by the WHO and the disability language was changed into "residual function" rather than "handicap". This makes it easier to understand that also headaches can cause disability not only during the acute pain but also in the interictal phase.
It can be clinically relevant to measure headache disability, not only for legal purposes, but also at patient follow-up and to improve communication with the treating physician. Headache disability can be measured by disability scales such as HDI, MIDAS, HIT or by quality of life scales (SF-36, MSQ, MqoLQ, MSQOL, etc). Nevertheless, none of these are ideal and there is no expert consensus on the gold standard to be used. MIDAS is the best studied and validated scale in Italy, but can only be used in evaluating the impact of prophylactic headache treatment, it does not consider interictal disability and is not sensitive in differentiating moderate to severe disability in chronic headache. At present, there is no scale to be used as a diagnostic tool, but both MIDAS and HIT can be used at follow-up to evaluate the efficacy of a preventive treatment. A QoL scale can be added to evaluate interictal disability and balance treatment efficacy vs tolerability.
In conclusion, there is a definite need of more complete, flexible, and reliable methods to evaluate headache disability.

CHRONIC DAILY HEADACHE IN ADOLESCENCE: A FOLLOW-UP STUDY

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PATENT FORAMEN OVALE AND MIGRAINE: COMORBIDITY OR RISK FACTOR?

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The first description of paradoxical embolism appeared in the literature in 1877, hypothesizing a clot passing through the patent foramen ovale (PFO).
The prevalence of PFO in the healthy population is approximately 20–25%. During the past 20 years an association of PFO with stroke, migraine headache and decompression sickness has been suggested.
A case control study was performed to assess the association between PFO and patients with migraine. It concluded that the prevalence of right-to-left shunt (RLS) in patients with migraine with aura was significantly higher (48%) than in healthy controls and was similar to the prevalence of RLS in young patients with stroke. Later, a consecutive unselected cohort of migraine patients was studied. It was found that PFO was associated with migraine with aura but not with migraine without aura.
We could speculate that an aspect of migraine, such as aura, is explained by paradoxical embolism, which shunts brain platelet aggregates or neuromediators, normally inactivated by pulmonary filter, thus initiating the attack. In contract, migraine with aura has long been suspected as a risk factor for stroke in young adults on evidence of focal alterations in cerebral blood flow sharing aura; stroke may occur during migraine attack and headache is present in about 25% of strokes.

Focusing on these results it seems clear that the risk of stroke in patients having both conditions is higher. But these observations might also be subject to bias: firstly, because cardiac imaging is performed most frequently in young persons and this may justify the high incidence of PFO in this group; secondly because migraine has a prevalence in persons between 25 and 55 years of age as well.
At this time, following the conclusions of Wilmshurst, we should perform a PFO closure in selected patients with migraine, so as to achieve a dual effect: reduce the risk of stroke and abolish the symptoms of migraine. But other evidence describes the transformation of migraine with aura in a daily pattern after disclosure of RLS. Questions persist and much of the current evidence is circumstantial or anecdoctal.

VASCULAR RISK FACTORS IN MIGRAINE: RIGHT-TO-LEFT SHUNT – PATENT FORAMEN OVALE

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Patent foramen ovale (PFO), with or without coexistent atrial septal aneurysm, is generally considered to be associated with brain disorders, including first-ever ischemic stroke in young patients, cryptogenic stroke, migraine, and cerebral decompression sickness in scuba divers. Some authors do not confirm the association between isolated PFO and increased risk of ischemic stroke or recurrent stroke. The size of PFO and the degree of right-to-left cardiac shunt (RLS) in these disorders are debated. The presence of large PFO and high-degree RLS was demonstrated to increase the risk of cryptogenic stroke, recurrent stroke, the number of silent ischemic brain lesions in divers, migraine with aura, and cerebral decompression sickness. Other studies showed that either percutaneous or surgical closure of PFO decreases the number of recurrent ischemic strokes, improves migraine symptoms, decreases the number of decompression cerebral ischemic events, and supports the positive relation between high degree RLS and the aforementioned pathologies. Contrast transcranial Doppler ultrasonography (c-TCD) is a complementary method to contrast-enhanced transesophageal echocardiography (c-TEE) for RLS diagnosis. Its sensitivity approaches 90% and specificity approaches 92% compared with c-TEE. c-TCD does not require sedation of the patient, thus ensuring better collaboration during the Valsalva maneuver (VM). It does not provide any information concerning either the morphology of the interatrial septum or the size of PFO. The degree of RLS with c-TCD is expressed in numbers of microbubbles passing through the middle cerebral arteries. The application of VM was standardized for c-TCD RLS diagnosis at an international consensus meeting and more recently by Droste et al.

HEADACHE IN THE ELDERLY

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Objective Although the prevalence of headache in the elderly is relevant, until now few studies have been conducted in patients over the age of 65 years. We report the prevalence of headache in a population of subjects aged 65 years and over seen at our Headache Centre.
Materials and methods We retrospectively analysed the clinical charts of 5036 consecutive patients >18 years of age referred to our Centre from 1995 to 2003, with specific attention to the subgroup of patients over 65 years of age.
Results We could identify 319 patients aged 65 years and over (6.3% of the total population). Primary headaches were diagnosed in 80.9% of the patients, secondary headaches were found in 10.6% of the subjects, while cranial neuralgias, central and primary facial pain and other headaches accounted for 8.5% of the cases. Among the primary headaches, the prevalence was almost identical for migraine without aura (26.3%), chronic tension-type headache (26.3%), and chronic migraine (25.2%). Patients suffering from both migraine without aura and tension-type headache accounted for 12.0% of the cases. Less frequent were migraine with aura (4.7%), episodic cluster headache (2.7%), hypnic headache (1.6%), episodic tension-type headache (0.8%), and chronic cluster headache (0.4%). There was a great preponderance of females, who represented 79.1% of the cases. The most frequent secondary headache was cervicogenic headache (73.6% of cases); we diagnosed giant cell arteritis in 11.8% and chronic post-traumatic headache in 5.9% of the patients with secondary headaches, respectively. In the group of cranial neuralgias and other headaches we diagnosed patients with trigeminal neuralgia (48.1%), post-herpetic neuralgia (7.4%), and headache not elsewhere classified (44.5%).
Discussion The onset of headache occurred before the age of 45 years in most cases of primary headaches, in particular in chronic migraine (90.8%), migraine without aura (66.2%), and chronic tension-type headache (64.7%), while hypnic headache typically started after the age of 65 years (75.0% of subjects). In 2 patients the onset of migraine with aura occurred over the age of 65 years and in 3 patients episodic cluster headache appeared for the first time after the age of 65 years. In geriatric patients with cluster headache we did not find any male preponderance (50.0% of the cases).
Conclusions Overall, the prevalence of headache in the elderly seems to be remarkable and noteworthy. Further clinical studies should be carried out, also with the aim of defining possible therapeutic guidelines for geriatric patients.

ASSESSMENT OF THE EFFICACY AND TOLERABILITY OF TRIPTANS IN CLINICAL PRACTICE

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In most cases a triptan is prescribed to a patient suffering from migraine who has been taking OTCAs for years, alone or combined with caffeine, antiemetics, barbiturates, etc.
A proper use of triptans is therefore indispensable to correctly assess whether they are efficacious and/or toxic in a completely different setting from the one in which controlled clinical trials are conducted. Patient's judgments on the treatment are therefore fundamental to assess if it is ineffective and/or causes toxic effects.
The physician knows that the efficacy and toxicity among triptans are similar in clinical practice and that the response is individual and closely connected to the patient's compliance and expectations. Most side effects of triptans appear the first time they are taken and their efficacy is rarely the same each time they are taken. It is therefore advisable to agree with the patient upon the use of the triptans: triptans are indispensable drugs to treat migraine, but they are not miraculous. To prevent the patient from stopping treatment or from trying different triptans and then returning to self-medication, the patient must agree to fill out a form on the efficacy and toxicity of the drug being taken. Naturally, before preparing this form, the physician has to decide whether to use the same parameters of efficacy and tolerability in clinical practice and controlled clinical trials.
Whatever instruments are used to assess the drug, there are some key elements to consider: time when the migraine attack started; time when the drug was taken; presence of autonomic symptoms or aura; intensity of the pain when it started and at the moment when the drug was taken; duration of attack; should there be any relapse, at what time it appeared; should there be any side effects, their intensity and duration. The information gathered must then be discussed with the patient to decide whether to continue or modify the treatment. Data on the efficacy and tolerability of triptans, also if combined with other drugs, could help to identify sub-groups of patients suffering from migraine who are non-responders to triptans and/or prone to toxic effects.

A NEW QUESTIONNAIRE FOR ASSESSMENT OF ADVERSE EVENTS ASSOCIATED WITH TRIPTANS – METHODS OF ASSESSMENT INFLUENCE THE RESULTS

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Triptans are the treatment of choice for migraine sufferers with disabling attacks. The proportion of patients reporting side effects after any acute treatment may vary in regard to the method of assessment. We prospectively surveyed adult headache sufferers, who had been using the same triptan for at least 3 months (from March 2001 to December 2003). Participants were asked about their headache and treatment history. Subjects then completed a standardized questionnaire, assessing adverse events in two different ways. First, subjects were asked if they had any adverse events when using the triptan. If they answered yes, they were asked to list them and grade their severity as mild, moderate, or severe. After returning the first part of the questionnaire, subjects received a second form, where 49 possible adverse events were listed. We contrasted and correlated both sets of answers. We surveyed 148 subjects (87.8% female, mean of 39.5 years). Most patients (65.6%) reported no side effects in the unprompted questionnaire. However, most of them (56.8%) reported at least one side effect in the prompted questionnaire. Most patients who reported side effects in the unprompted questionnaire said they had just one adverse event (X%), while most reported 2 or more side effects in the prompted questionnaire (Y%). Both in the unprompted (X%) and in the prompted (Y%) questionnaires, most side effects were rated as mild or moderate. Seven (4.7%) subjects graded their adverse events as severe in the prompted questionnaire, but had not self-reported them. We conclude that when assessing triptan adverse events, the method of data collection may dramatically influence the results.

THE PROBLEM OF NON-RESPONDERS TO TRIPTANS

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ASSESSMENT OF EFFICACY AND TOLERABILITY OF PROPHYLACTIC DRUGS

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TOLERABILITY OF ANTIMIGRAINE DRUGS IN CHILDREN AND ADOLESCENTS

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Migraine is a common complaint during childhood and adolescence. Although epidemiologic studies performed in paediatric age groups show that 3–5% of school-aged children experience periodic attacks of migraine and that this proportion increases to 20% through adolescence, there are few controlled clinical trials regarding symptomatic and prophylactic drug treatment.
Analgesics and NSAIDs are the most frequently used drugs in childhood and adolescence for the symptomatic treatment of migraine attacks of slight or moderate intensity. The first-choice drug under age 12 is acetaminophen. This drug is well tolerated and side effects are infrequent and of slight intensity. Ibuprofen is also well tolerated and few mild side effects have been recorded in the two control studies carried out for the assessment of its effectiveness for the treatment of acute juvenile migraine. Acetylsalicylic acid is not recommended under age 14 because of the potential occurrence, although rare, of Reye's syndrome. Ergot derivatives in the past played an important role in the treatment of spontaneous migraine attacks, particularly in adults, but their role was strongly confined to a small number of patients by the triptan revolution. The principal adverse events of ergot derivatives are like those found in adults: nausea and vomiting, abdominal pain, diarrhea, and muscular cramps. They have not been reported in the limited experience with ergot derivatives in children and adolescents complaining of migraine.
Although they are considered first-choice drugs for moderate and severe migraine attacks in adults, triptans are still under study in migraine patients under age 18. The Italian Health Ministry rules do not approve their use in patients under age 18. They can only be legally given if the therapeutic plan for their use has been previously approved by the Ethics Committee and after informed consent of the patient/parents. Promising results have been obtained, particularly for sumatriptan in nasal spray formulation, and zolmitriptan and rizatriptan, with a high tolerability and safety profile. Unlike the adult studies, the oral triptans tested in children have not been effective when compared to placebo.
Triptans used in juvenile migraineurs demonstrated to be well tolerated. The percentage of side effects such as somnolence, asthenia, and dizziness are lower than those recorded in adults. Chest tightness, constriction, or pain have never been reported. For sumatriptan nasal spray, taste disturbance was the most commonly reported adverse event. No drug-related severe adverse events or clinically relevant changes in laboratory parameters, electrocardiogram, or vital signs were reported in all studies concerning triptan use in children.

TRIPTANS AND MORE

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The introduction and the development of the 5-$HT_{1\ B\text{-}D}$ agonists, the *triptans*, have generated an impressive rush of studies on migraine and headaches, giving the researcher a tool for exploring the pathophysiology of migraine attack.
Pharmacological studies have developed various new molecules with different chemical structures from sumatriptan, the first triptan structurally derived from serotonin, but with the same pharmacological activity.
The most important differences among the triptans are in pharmacokinetics, mainly bioavailability, which, for example, after oral administration varies from 13% for sumatriptan to 70% for naratriptan. A greater lipophilicity that increases passage through the blood-brain barrier is not essential for the activity of triptans: in fact sumatriptan seems to be able to bind pontine structures at therapeutic concentrations to the same extent of zolmitriptan (Dobson, 2004).
Serotonin-1F receptor (5-HT_{1F}) agonists may relieve acute migraine without causing vasoconstriction. Selective 5-HT_{1F} receptor agonists (LY334370; LY344864) are effective in preclinical migraine models and are non-vasoconstrictors. LY334370 is effective in acute migraine, and does not cause any symptoms/signs of coronary vasoconstriction. Preclinical experiments and clinical observations infer a role for selective 5-HT_{1F} agonists in migraine (Ramadan, 2003).
Calcitonin gene-related peptide (CGRP) may have a causative role in migraine. In an international, multicentre, double-blind randomized clinical trial, 126 patients with migraine received intravenously, BIBN 4096 BS, a highly specific and potent non-peptide CGRP-receptor antagonist, at doses of 0.25, 0.5, 1, 2.5, 5, or 10 mg vs placebo over a period of 10 minutes. The 2.5 mg dose was selected for its response

rate of 66% as compared with 27% for placebo (p=0.001). The overall rate of adverse events was 25% after i.v. administration of BIBN 4096 BS at the dose of 2.5 mg and 20% for the BIBN 4096 BS group as a whole, as compared with 12% for placebo. The most frequent side effect was paresthesia. There were no serious adverse events so that the authors concluded that BIBN 4096 BS was effective and safe in treating acute attacks of migraine (Olesen, 2004).

ANGIOTENSIN INHIBITION: A NEW STRATEGY FOR MIGRAINE PREVENTION?

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Most of the recommended drugs for migraine prophylaxis cause adverse events that preclude long-term treatment and have limited efficacy. Thus, there is a need for new preventive drugs that have greater efficacy and are better tolerated.
A promising new approach is the use of molecules able to reduce the level of angiotensin II, either by inhibiting the angiotensin converting enzyme (ACE) or by blocking the angiotensin II type 1 (AT_1) receptor. After some exploratory small-scale studies, two recent randomised, double-blind, placebo controlled studies have proven the efficacy of the ACE inhibitor lisinopril and the AT_1 blocker candesartan, respectively. The efficacy of lisinopril in migraine prophylaxis was discovered by serendipity, observing an impressive improvement of migraine in a patient treated with this drug for hypertension. In a subsequent randomised, controlled crossover study, 60 patients affected by migraine with or without aura were treated for 3 months with lisinopril 20 mg once daily and for another 3 months with placebo. In the 47 participants with complete data, days with migraine were significantly reduced by 21% (CI 9–34%). Responders (subjects in whom days with migraine were reduced by at least 50%) were 14 (29.8%) for active treatment vs placebo and 17 (36.2%) for active treatment vs run-in.
In another randomised, controlled crossover trial, 60 patients received for 3 months candesartan cilexetil 16 mg daily and for another 3 months placebo. In a period of 12 weeks, the mean number of days with headache (primary endpoint) was 18.5 with placebo vs 13.6 with candesartan (p=0.001) in the intention-to-treat analysis. The number of responders was 23 (40.4%) out of 57 for days with migraine.
Other indirect clues pointing to the efficacy of reducing angiotensin levels to prevent migraine come from a meta-analysis involving 12000 patients who were treated with AT_1 blockers for other conditions, but in whom headache was reduced by one third compared to those taking placebo, and from a recent Italian study showing that among 1537 hypertensive patients treated with nitrates, the use of ACE inhibitors reduced headache caused by nitrates by 50%.
The mechanism of action of ACE inhibitors and AT_1 blockers in migraine prevention is unknown. Whatever the mechanism of action, however, the efficacy and the excellent profile of tolerability of ACE inhibitors and, even more, of AT_1 blockers potentially indicate these substances as first-line drugs for migraine prophylaxis.

ANTIEPILEPTIC DRUGS IN CHRONIC HEADACHE

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Objective About 40% of headache sufferers referring to tertiary headache centres complain of chronic headache [1]. The management of chronic headache is often difficult not only because of the high frequency of attacks but also because of its possible association with psychopathological symptoms, psychiatric disorders, and analgesic overuse [2]. No therapeutical guidelines are available for chronic headache. In the past years antiepileptic drugs (AEDs) have begun to be used both in headache and mood disorders treatment. The aim of this study was to compare the efficacy and tolerability of valproate, lamotrigine, gabapentin, and topiramate on both headache and psychopathological comorbidity of chronic headache patients.
Materials and methods A sample of adult patients, who were consecutively referred to the Headache Disorder Centre, Department of Neurological and Psychiatric Sciences, University of Bari, and affected by chronic headache, was enrolled. All patients underwent a detailed clinical interview to gather information about headache subtype. The Symptom Check List 90R was administered to all of them to identify the possible association with psychopathological disorders. Patients were randomly assigned to valproate, lamotrigine, gabapentin, or topiramate treatment. A headache diary was delivered to collect data concerning headache course during therapy. Drug efficacy was evaluated after a three-month therapy period. Drug tolerability was assessed by investigator observation, patient self-reporting and clinical laboratory data, when necessary.
Results Results show a high percentage of headache response in all chronic headache subtypes and in all treatment groups. All drugs were well tolerated. An improvement was found in patients with anxiety and depressive symptoms.
Discussion These results suggest that AEDs can be an effective and well-tolerated therapeutic option in chronic headache management. These drugs might act on the nociceptive system and prevent both peripheral and central sensitization which are considered the basic mechanisms of chronic pain [3]. AEDs acting through potentiation of GABAergic pathways might furthermore have "sedating" effects, whereas AEDs acting through the reduction of glutamate release may have "activating" effects on mood [4].
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A STUDY ON PHARMACOEPIDEMIOLOGIC DATA IN HEADACHE TREATMENT IN THE POPULATION OF CATANZARO

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Introduction Headaches and migraines occur in a large proportion of the population. The prevalence of headache increases with age and is as high as 5% in the adult population.
Our aim was to study and compare pharmacoepidemiology of headache treatment in two different settings: inside and outside a specialized Centre.
Method We asked 32 physicians of Catanzaro to directly administer a detailed questionnaire to their headache patients. The questionnaire sought information concerning demographic characteristics, occurrence, and frequency of headache, possible risk factors for onset of headache and the usage patterns of specific headache medications.
Results We analysed the differences in headache treatment between 612 subjects at the first visit ('naive') (F/M: 2.41; mean age =

37.31±14.09 years) and 620 subjects at follow-up (F/M: 3.18; mean age=44.30±15.37 years) at the Headache Centre of Catanzaro. Most patients suffered from migraine. At the first visit, 49.4% of them were taking drugs prescribed by a doctor; 41.5% were taking over-the-counter analgesics (OTCAs); 9.1% were not taking any drug. At follow-up, 81.3% of patients were taking prescription drugs; 15.8% OTCAs; 2.9% were not taking drugs (overall chi-square=139.229, $p<0.001$). Non-selective analgesics were the most-used drugs. Triptans were used by 9.1% of 'naive' patients and by 31.8% of patients at follow-up (Fisher's Z=7.655, $p<0.001$). Nimesulide was the most-used drug. A prophylactic treatment was given to 16.8% of 'naive' patients, and to 58.2% of patients at follow-up (Fisher's Z=12.135, $p<0.001$). Antidepressants were the class of drugs most used for prophylaxis. Amitriptyline was the drug for prophylaxis most frequently used by patients at the control visit, while flunarizine was the most frequently used by 'naive' patients. Before being examined in a specialized centre, few patients took prescription drugs, triptans, or prophylactic drugs; specialized care increased the proportion of patients taking prophylactic drugs, and changed the type of acute treatment used to specific medication for headache.
Conclusions The present results suggest that antiinflammatory drugs were the most-used drugs in the management of headache symptoms. These drugs could explain the high frequency of chronic headache episodes and drug-drug and drug-food interactions.

ECONOMIC EVALUATION OF CHRONIC TENSION HEADACHES

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Objective To measure the cost of botulinum toxin type A (BTX-A) treatment of chronic tension-type headache.
Design A retrospective chart analysis and prospective pharmaceutical economics analysis was completed.
Setting Day Hospital of the Regional Referral Headache Centre at Sant'Andrea Hospital in Rome.
Patients In phase I clinical charts were randomly selected for 100 patients treated from February 2002 to January 2003. In phase II chronic tension-type headache patients were treated from February 2002 to January 2003.
Intervention Patients were treated with 100 U of BTX- A every three months for one year.
Measurements and results Treatment outcomes ranged from complete resolution of headache symptoms to a worsening of symptoms resulting in discontinuation. Headache medication use before and after treatment was analyzed. After BTX-A treatment, 85% of patients experienced at least some degree of pain relief and reduced their use of analgesics.
The cost of treatment was based on drug acquisition costs, supplies, and professional time needed to administer treatment. The average cost of conventional headache medications before BTX-A treatment was € 853.43, and after treatment was € 450.47. The cost of BTX-A treatment was € 642.00. Adding the cost of adjunctive conventional medications brought the total cost of BTX-A treatment to € 1,092.47.
Conclusions The reduced percentage of patients using a variety of headache medications after BTX-A treatment likely results from a reduction in their headache symptoms.
BTX-A treatment reduced use of conventional headache medications and expenditures although the net cost of treatment increased with BTX-A use.

LITERATURE REVIEW OF TRIGEMINAL AUTONOMIC CEPHALALGIAS AND HEMICRANIA CONTINUA IN ASSOCIATION WITH ORGANIC PATHOLOGIES: ONE-YEAR AFTER THE NEW ICHD-II CLASSIFICATION

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Objective The aim of the study was to identify all relevant papers in the literature reporting cases of chronic paroxysmal hemicrania (CPH), SUNCT syndrome and hemicrania continua (HC) in association with organic pathologies.
Materials and methods On the basis of our previous review, we extended a systematic search of case reports from 1975 to 2003 and critically reviewed the diagnoses and possible pathogenetic link between the lesion and the headache according to new IHS criteria (ICHD-II, 2004).
Results We detected 22 cases which presented as CPH-like (17 females (77.3%) and 5 males (22.7%); mean age at onset of symptoms: 41.04±17.88 years). Twelve cases were presented as SUNCT-like syndrome (6 males (50%) and 6 females (50%); mean age at onset: 38.75±15.93 years). We also found eleven "symptomatic" cases of HC (8 females (72.7%) and 3 males (27.3%); mean age at onset: 36.00±12.96 years).
Discussion The mean age in "secondary" cases approximately reproduces the ratio seen in idiopathic cases, except for SUNCT-like syndrome, where the age in idiopathic cases is generally higher. CPH-like and HC-like are more common in females, as in primary cases; in "secondary" SUNCT syndrome, the gender ratio is 1:1, while in primary cases a male preponderance was generally observed.
In CPH-like cases, the most commonly associated pathology is the neoplastic one, followed by inflammatory/infectious diseases. In HC-like cases, post-traumatic cases are predominant. SUNCT-like cases are frequently associated with vascular and bone malformations in the posterior fossa. Most recent observations showed cases of SUNCT syndrome also associated with neoplastic lesions within the cavernous sinus and pituitary adenomas. These results are somewhat different from those seen in cluster-like cases, where the most frequently observed pathology in association with the headache was vascular in nature.
Conclusions We present new data about some trigeminal autonomic cephalalgias and HC associated with organic pathologies. We stress the importance of a complete neuroradiological investigation in these headache syndromes, especially in the presence of atypical symptoms.

HEADACHE ATTRIBUTED TO HEAD AND/OR NECK TRAUMA: A COMMENT ON ICHD-II CHAPTER 5 BASED ON CLINICAL DATA

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General comment The main changes to Chapter 5 in the new classification include separate sections for head injury and whiplash, more accurate and objective criteria for qualifying and grading the type and severity of traumatic events, and new diagnostic subgroups (5.5, 5.6, 5.7). However, the evidence of causation remains based on a very strict time-interval (7 days) for both the acute and the chronic forms, with the consequence of having many patients not-classified.
Clinical data The lack of case-control prospective studies and the different criteria and methods adopted even in recent years by different authors have largely contributed to the generation of controversial data on many issues regarding post-traumatic headaches.
From the analysis of the literature and the revision of our case series, some aspects seem to be in contrast with certain statements and opinions

that are at the basis of the new classification of Chapter 5. Namely, the most severe traumas are less frequently associated with headache symptoms, whose development is significantly delayed from the event (over 1–3 months) and frequently related to a nearly full recovery of cognitive function. Furthermore, the post-acute phases seem to be generally characterized by a well defined complex of symptoms (indicating brain/cervical dysfunction), but by a rather variable and poorly defined headache picture (particularly, after mild head trauma). Only later (weeks after injury), sometimes with a free-interval, chronic forms of headache develop with clinical characteristics reproducing primary headache forms or other headache pains attributable to definite disorders. Thus, the transition from an acute to a chronic condition is not simply a matter of time, but probably involves different mechanisms also inducing substantial differences in the clinical expression of symptoms. *De novo* migraine headaches following mild head injury, in particular, seem to be largely independent from the expression of an acute post-traumatic headache, postulating a role of injury in the modulation of migraine threshold in predisposed individuals. However, the role of trauma-related cervical abnormalities should also be considered as a pathogenetic factor in the production of late-onset syndromes resembling cervicogenic headache in the chronic and long-lasting post-whiplash headaches.
Conclusions Post-traumatic headaches offer a *in vivo* model for pathogenetic considerations regarding different types of primary and secondary headaches, with relevant therapeutic implications.

HEADACHE ATTRIBUTED TO CRANIAL AND CERVICAL VASCULAR DISORDER

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Headache attributed to cranial or cervical vascular disorder is reported in Chapter 6 of the *International Headache Society Classification, second edition*. The chapter includes headache attributed to ischemic stroke or transient ischemic attack, to non-traumatic intracranial haemorrhage (intracerebral haemorrhage and subarachnoid haemorrhage), to unruptured vascular malformation (saccular aneurysm, arteriovenous malformation, dural arteriovenous fistula, cavernous angioma, and encephalotrigeminal or leptomeningeal angiomatosis), to arteritis (giant cell arteritis, central nervous system angiitis, and secondary central nervous system angiitis), to carotid or vertebral artery pain (arterial dissection, post-endarterectomy headache, carotid angioplasty headache, intracranial endovascular procedures, and angiography), to cerebral venous thrombosis, and to other intracranial vascular disorder (CADASIL, MELAS, benign angiopathy of the central nervous system, pituitary apoplexy). In many of these conditions headache is overshadowed by focal signs and/or disorders of consciousness. In others, such as subarachnoid haemorrhage, headache is usually the prominent symptom. In a number of other conditions that can induce both headache and stroke, such as dissections, cerebral venous thrombosis, giant cell arteritis and central nervous system angiitis, headache is often an initial warning symptom. The classification of secondary headaches is based on the same criteria: *Criterion A* specifies the headache characteristics; *Criterion B* requires the presence of the causative vascular disorder; *Criterion C* defines the causal association (commonly simply a close temporal association); and *Criterion D* stipulates that the headache greatly improves or disappears after the cure or remission of the causative disorder. A limit in the possible application of these criteria is that for most of the headaches attributed to cranial and vascular disorders the characteristics as specified in *Criterion A* are not well defined. Moreover, *Criterion D* is not always applicable because some forms *do not* resolve nor greatly improve within the specified time. When this is not the case, or before the specified time has elapsed, a diagnosis of *Headache probably attributed to vascular disorder* is usually applied. The alternative, when headache does not resolve or greatly improve after 3 months, is a diagnosis of A6.8 *Chronic post-vascular-disorder headache*. The new edition of the *International Headache Society Classification* better defines *Headache attributed to cranial or cervical vascular disorder*, reporting also emerging diseases. Furthermore, its framework allows a better characterization of each headache and will hopefully stimulate more nosological research into headache attributed to cranial or cervical vascular disorder.

HEADACHE ATTRIBUTED TO DISORDER OF HOMOEOSTASIS

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"*Headache attributed to disorder of homoeostasis*", Chapter 10 of the new IHS classification, is difficult to interpret because of the complexity of the clinical description. The new classification, in fact, has made numerous modifications to this group of headaches no longer classifying them as "*Headache associated with metabolic or systemic disease*" but as "*Headache attributed to disorder of homoeostasis*", focusing, therefore, the attention on the etiology of these disorders.
Those headaches that appear to be in close temporal relation with the metabolic alterations, that involve a marked worsening of a pre-existing headache, that introduce clear evidence that the disorder of homoeostasis could aggravate the primary headache and, finally, that show improvement or resolution of the headache after relief from the disorder of homoeostasis, are classified under this category.
The new classification has also introduced "*Headache probably attributed to disorder of homoeostasis*" when the disorder cannot be effectively treated, or when there is no spontaneous resolution of the disorder, and "Chronic post-homoeostasis disorder headache" when the disorder of homoeostasis remits, but the headache does not resolve or improve after three months.
The new criteria have revised headache attributed to dialysis, headache attributed to fasting, and headache attributed to hypoxia and/or hypercapnia, and have conferred a nosografic value to "*Diving headache*" in this latter subgroup. Also in this subgroup, headache in subjects with sleep apnoea headache has been better characterized and several studies have given importance, regarding the genesis of the disorder, to the mechanism of hypercapnia.
"*Headache attributed to arterial hypertension*", which includes several forms, and "*Cardiac cephalalgia*", which appears during acute myocardical ischaemia, have been moved into Group 10; while "*Headache attributed to hypothyroidism*", which in the previous classification was considered together with other metabolic pathologies, as syndromes not sufficiently validated, was added.
In conclusion, the classification of these headache forms, under Chapter 10 of the new IHS classification, will be confirmed or modified based on future studies.

HEADACHE AND AIDS

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The recent Classification of the "International Headache Society" considers headaches secondary to HIV and AIDS as specific entities, that are coded at point 9 "*Headache attributed to infection*". With regard to this, it should be said that, presently, there are few data in the literature that can support the identification of the subgroup 9.3 "*Headache attributed to HIV/AIDS*", as coded by the present classification.
In the acute phase of HIV infection, some authors have reported that headache frequently occurs as part of the infectious disease syndrome,

that also includes fever, chills, malaise, myalgia, arthralgia, and asthenia. This headache has no specific features.
Headache may also be a symptom of aseptic meningitis that is a frequent complication of HIV infection. In this case headache has to be coded at point 9.1 "*Headache attributed to intracranial infection*". In this same group a variety of headaches that may occur in patients with AIDS have to be included. Headache, in fact, may be associated with other diseases, such as meningitis and/or encephalitis due to cerebral cryptococcal infection or toxoplasmosis. When headache is due to Kaposi's sarcoma, endocranial hypertension is involved.
Tuberculous meningitis may also occur in immunosuppressed patients. In this condition, obstructive hydrocephalus is a frequent complication. Headache, in this case, may have some specific features due to intracranial hypertension.
Some authors have investigated the changes of idiopathic headaches (migraine and tension-type headache) in patients with AIDS. It has been found that migraine tended to decrease during the course of this disease, whereas tension-type headache tended to increase.
In HIV/AIDS, headache may also be caused by some treatments.
The study of headache in patients with HIV/AIDS is not easy because of the wide variability of individual conditions and the interference of different factors and complications.
Prospective studies on headache associated with HIV/AIDS infections are warranted in order to lend support to the existence of this entity that the International Headache Society Classification has just coded at point 9.3.

GUIDELINES FOR MIGRAINE: UPDATE ON SYMPTOMATIC DRUGS

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The subcommittee for the Symptomatic Treatment of Migraine collected and evaluated the available literature, from the end of 2001 to the present, concerning drugs for acute migraine treatment. All articles reported on Medline and Pubmed were examined, whereas abstracts were excluded.
The levels of evidence, the scientific strength of evidence and the clinical judgment were redefined for each symptomatic drug, integrating information available in the first edition of the guidelines (2001) with that found in the past 2 years. The levels of recommendation (I-IV) were reformulated for approval by the subcommittee.
As in the previous version, recommendation class I includes all triptans and among NSAIDs: acetylsalicylic acid, lysine salicylates, ibuprofen, and naproxen sodium, as well as dihydroergotamine in all formulations. Among triptans, frovatriptan has recently been approved for the Italian market, while sumatriptan nasal spray for the treatment of migraine attacks in adolescents is under examination by the Ministry of Health.
Under recommendation class II, ergotamine s.c. and i.m., diclofenac oral route, ketoprofen, ketorolac, naproxen, paracetamol with and without codeine, and some antiemetics to be administered i.v. (prochlorperazine, chlorpromazine and, metoclopramide) have been placed under recommendation class II.
New drugs are under observation for inclusion in this class, i.e., calcitonin gene-related peptide receptor antagonist BIBN 4096 BS i.v. and the novel AMPA/GluR5 antagonist, LY293558 i.v., which have recently been demonstrated to be efficacious and well tolerated in acute migraine.
Other drugs to be discussed for inclusion in recommendation class II are dipyrone i.v. and droperidol i.m., as well as sodium valproate i.v. for acute migraine treatment in the Emergency Department, on the basis of the results of recent randomized, double-blind, placebo controlled studies.
Based on recent evidence in the literature, indomethacin, prochlorperazine, and caffeine could shift from recommendation class III to recommendation class II. Rofecoxib 25 and 50 mg oral route, on the basis of evidence of effectiveness and good tolerability for the acute treatment of migraine, can also be considered for inclusion in this class.
Recommendation class III includes association drugs with butalbital, for which the risk of abuse is emphasized, oral ergotamine with and without caffeine, and rapid dissolution piroxicam. Drugs with scarce or limited evidence are reported in recommendation class IV, such as nimesulide, desamethasone and i.v. hydrocortisone, granisetron and oral metoclopramide, the latter two to be considered as adjuvants for nausea and vomiting.

PROPHYLACTIC TREATMENT OF MIGRAINE

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Recent studies on migraine pathogenesis suggested some newer targets for preventive drug therapy, such as cortical GABA-dependent hyperecitability and excitatory amino acids.
The mechanism of action of antiepileptic drugs is not completely understood, but they all share a common role in enhancing gamma-aminobutyric acid-mediated inhibition.
Sodium valproate is the most used anticonvulsant in migraine preventive treatment. Also, lamotrigine has been used in antimigraine treatment, mainly to prevent high frequency migraine with aura.
Topiramate is effective for migraine prevention and its cognitive side effects are of less concern with the lower doses needed for migraine. Topiramate seems to be a good therapeutic option for about half of the patients with refractory migraine. In these patients, response is usually excellent. Intolerance due to adverse events appears only in one-fifth of the cases and at low doses (Pascual, 2003).
Botulinum toxin type A shows promise as a safe, tolerable, and effective drug for migraine prevention, with the unique advantages of almost no systemic adverse events and a long interval between treatments, while the high cost could reduce wide use. The angiotensin converting enzyme receptor blocker candesartan, and the ACE inhibitor, lisinopril, appear to be effective and well tolerated in the prevention of migraine in patients without hypertension. Tizanidine, an α_2 central agonist, seems to be effective in controlled clinical trials, as hydroxocobalamin, but it is necessary to compare these results with those of other preventive treatments. The phytoestrogens have been tested as preventive in menstrual migraine with promising results. Tiagabine, levetiracetam, zonisamide and montelukast require more controlled trials.
Resource utilization is an important aspect in evaluating the economic impact of migraine prophylaxis. Adding a preventive medication to migraine management reduces the use of other migraine medications, as well as visits to physician offices and Emergency Departments. In addition, both acute and preventive drugs are associated with lower utilization of computed tomography and magnetic resonance imaging scans. Therefore, migraine preventive drug treatment is effective in reducing resource consumption when added to therapy consisting only of an acute medication (Silberstein, 2003).

THERAPEUTIC GUIDELINES FOR CLUSTER HEADACHE: AN UPDATE

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The search was conducted on PubMed from the date of publication of the SISC guidelines to April 2004.
Pharmacological acute treatment In an open label trial, 5 mg olanzapine alleviated pain quickly and had a consistent response across

multiple treated attacks in both episodic and chronic forms. In a double-blind placebo-controlled randomized trial, patients with episodic or chronic cluster headache, whose attacks lasted at least 45 minutes were effectively treated with 20 mg sumatriptan nasal spray.

Pharmacological prophylactic treatment In an open trial, gabapentin, at the daily dosage of 300 mg t.i.d., was administered for 60 days in episodic cluster headache and for 6 months in the chronic form. The drug induced remarkable effects on both forms. In a pilot study, baclofen, which was given 15 to 30 mg daily for the cluster period and 2 weeks afterward, was effective and retained its efficacy on repeated clusters. The preventive use of naratriptan, 2.5 mg once or twice daily, mostly as an add-on to high-dose verapamil treatment (480–960 mg/day) in patients with cluster headache improved the headaches. Intravenous boluses of 250 mg methylprednisolone on 3 consecutive days, followed by prednisone (90 mg/day) as a prophylactic treatment for episodic cluster headache, made the attacks significantly less frequent in the active phases.

Non-pharmacological treatment Fourteen cluster headache patients were treated with greater occipital nerve block as transitional therapy (treatment initiated at the same time as preventive therapy). Headache intensity, frequency and duration were significantly decreased comparing the week before with the week after the nerve block. Seventeen patients underwent trigeminal nerve root section for intractable chronic cluster headache. A follow-up period ranged from 3 months to 19 years and showed that trigeminal nerve section was an effective treatment with acceptable morbidity. A case of a patient suffering from episodic cluster headache who responded to radiofrequency ablation of the cervical zygapophyseal joints was reported. After the ablative procedure there were no noticeable side effects. Five patients with intractable chronic cluster headache were treated with long-term, high-frequency, electrical stimulation of the posterior hypothalamus. Since the treatment, all patients continued to be pain-free after 2 to 22 months of follow-up monitoring and no adverse events were observed.

SYMPTOMATIC AND PROPHYLACTIC THERAPY OF TENSION-TYPE HEADACHE

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Tension-type headache is the most common type of primary headache. Its lifetime prevalence in the general population ranges from 30–78% [1]. The division into episodic and chronic forms has shown to be very useful both in clinical practice and in research. Either the episodic or chronic forms can be further subdivided into a subtype associated with pericranial tenderness and a subtype without pericranial muscle tenderness. Therapy should be chosen according to headache frequency, attack duration, and intensity. Possible comorbidity with other disorders is also to be considered in the management of tension-type headache patients. Simple analgesics and NonSteroidal Anti-Inflammatory Drugs (NSAIDs) are first-choice drugs in the treatment of episodic tension-type headache. Among them, acetylsalicylic acid, ketoprofen, ibuprofen, naproxen, and acetaminophen are the best supported by scientific literature. Combination preparations of NSAIDs with caffeine or codeine are more effective than simple molecules, but they should not be taken frequently in order to avoid symptomatic abuse and headache chronicity. Amitriptyline is the best documented and most widely used prophylactic drug for tension-type headache. Its effect might be due not only to 5-HT reuptake inhibition but also to other mechanisms, such as norepinephrine reuptake inhibition, NMDA receptor antagonism, and blockade of muscarinic receptors [2]. Several open-label studies and a double-blind, placebo-controlled study have suggested that tizanidine, which is an alpha-2 adrenergic agonist that inhibits the release of norepinephrine in both the spinal cord and brain, can be effective in tension-type headache therapy [3]. Recent clinical results have suggested that botulinum toxin type A may be a promising treatment option for patients with chronic tension-type headache [4].

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NON-PHARMACOLOGICAL THERAPIES

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Non-pharmacological therapy (NPT) of primary headaches considers two main aspects: advice to patients and therapy (symptomatic and/or prophylactic).

Bearing in mind that many differences exist among the various forms of headache, patients are first invited to adopt and to keep what are generally called "healthy daily life habits": stop smoking; cut alcoholic drinks consumption; maintain the sleep-waking cycle; eat at given hours and practice some sport. Of course, when some particular trigger of the headache attacks is identified, it should be avoided, if and when it is possible.

Patients' characteristic behaviours, related to the pain onset, represent the so-called non-pharmacological symptomatic therapy (sleep or rest in a silent or quiet place; hot or cold local applications on the pain site, etc.). There are no scientific data that these methods are of some effective value.

NPTs have been used over the years as a prophylaxis: acupuncture; behavioural therapy; hyperbaric oxygen therapy; hypnotherapy; orthodontics or gnathologic techniques; physical therapy; and various surgical therapies.

Relaxation, biofeedback and cognitive-behaviouristic therapy are the main forms of the so-called behavioural therapy. This kind of therapy, and sometimes psychotherapy, may be useful in treatments for anxiety and depression, frequent co-morbid manifestations of various headache forms.

Finally, many different treatments are included under the name "physical treatment": hot and cold applications on the aching site; massages; ultrasounds; TENS; stretching exercises to improve one's posture; physical exercises; and traction exercises.

At present, the effectiveness of the various NPTs in the treatment of primary headaches has been proved for some techniques (biofeedback), but it is still controversial for others.

NPTs represent, in any case, a possible treatment for headache in all those situations when it is better to completely avoid the use of drugs (pregnancy, breast feeding, serious concomitant illnesses, etc.) and they may be useful in association with pharmacological therapy, when this is not too problematic for the patient. This therapy may also be useful in some special situations, such as: ineffective or inadequate response to drug therapies; absence of patient's compliance; patient's refusal to use drugs; psychiatric comorbidity; environmental trigger factors, which show a temporal relation with the onset of the crises; and less than four days per month of headache.

TREATMENT OF CHRONIC MIGRAINE AND MEDICATION-OVERUSE

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According to the 2nd edition of "*International Classification of Headache Disorders*", migraine is classified as "chronic" when occurring on 15 or more days per month for more than 3 months". Most cases of chronic migraine start as migraine without aura, and chronicity may be regarded as a complication of episodic migraine. Usually, if migraine attacks occur on 15 or more days per month, medication overuse is present. But a sample of patients presents both migraine attacks and tension-type headache, so it is difficult for patients to estimate how many attacks fulfil one or another set of criteria. In all cases, the first step of treatment is to stop the intake of drugs used for many years and to start an intravenous therapy and a preventive treatment program. Another preliminary step is the identification of comorbid psychiatric conditions and exacerbating factors. If large amounts of butalbital-containing analgesic combinations are used, phenobarbital should be administered in order to prevent withdrawal symptoms. Similarly, benzodiazepines and opiates must be gradually reduced. In some cases in-patient treatment is required.

PET THERAPY: A NEW THERAPEUTIC STRATEGY FOR CHILDHOOD HEADACHE

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Pet therapy is behavioural therapy that has been implemented for the past few years for the treatment of psychic discomfort and other psychosocial disturbances [1, 2].
We implemented a preliminary experimental stage for 6 months where 15 children and adolescents suffering from headache and psychosocial disturbances (anxiety, family, or school discomfort, etc.) attended 1 weekly session for 8 to10 weeks.
In the evaluation of headache, a >50% improvement was obtained, also for the associated symptoms, and in the parent-child compliance.
We then proposed Pet therapy to headache suffering subjects, for whom the pathology was mainly linked to an environmental uneasiness.
A treatment cycle of 12 sessions per week of 1–2 hours each was established with psychotherapists and pets. An evaluation test and headache assessment with a chart were carried out before and after therapy (projective and psychometric tests: drawing of the family, the tree; the CDI and FAB-C tests).
Pet therapy in our group is conducted by 3 psychotherapists who attended Delta Society courses.
The pets permanently available for Pet therapy are 3 dogs, 2 Persian cats, and about 50 canaries in an aviary. The dogs, the cats, and the ferrets are brought by their owners, whereas the aviary belongs to our hospital.
Pet therapy is conducted in a garden of about 800 m^2, with some trees, a playground, and a small wooden house for winter activities, on the hospital premises devoted exclusively to these activities.
Our study included 34 patients (pt): 15 females; 19 males, aged 4 to 16 years (MwoA 16 pt, MwA 2 pt, ETTH 8 pt, CTTH 8 pt,), ranging from 4 to 16 years divided into 2 groups, pre/post-puberty.
Evaluating the headache graph at the beginning and end (after 6 months) of treatment, a significant reduction in the frequency (6.1±1.7; 3.6±1.3 $p<0.002$) and duration (7.3±1.9h; 4.9±1.4h; $p<0.05$) of the crisis was observed.
The psychological characteristics evaluated through the various tests indicated, especially for CDI (15.5–8.5) and FAB-C (13.5–10.3), a considerable improvement also in this aspect.
These are preliminary data and the patients are few, but if further studies confirm them, Pet therapy could be an important therapeutic approach also for headache in childhood.

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CEREBROVASCULAR DISEASE AND MIGRAINE: PATHOGENETIC IMPLICATIONS AND THERAPEUTIC OPPORTUNITIES

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The association between migraine and cerebrovascular disease has been described in several studies. An increased risk of stroke in migraneurs has been reported: data from the literature showed that this association becomes significant in women less than 45 years old who are smokers, hypertensive, taking oral contraceptives, and confirmed that migraine, especially with aura, represents a risk factor for ischaemic stroke in women of childbearing age. Recent investigations documented that the prevalence of right-to-left shunt (RLS) in patients with migraine with aura (MA) is significantly higher than in healthy controls and similar to the prevalence of RLS in young patients with cryptogenic stroke. These findings suggested the possible role of RLS in both the increased risk of stroke in migraineurs and the pathophysiology of aura. Despite several studies that documented an increased occurrence of patent foramen ovale (PFO) in MA and emphasized its role in the pathophysiology of aura, no data have been available until now concerning the possible correlation between the entity of RLS and the clinical picture in MA patients. We studied a sample of 42 consecutive patients affected by migraine with aura according to IHS diagnostic criteria (1988) with RLS documented by means of Transcranial Doppler ultrasound. According to these data RLS does not affect either clinical presentation or entity of RLS, at least as estimated by Transcranial Doppler testing, and fails to correlate with several parameters that are clinical markers of severity in migraine with aura (i.e., mean duration of aura, frequency of attacks, days/month with migraine, MIDAS score). Percutaneous closure of PFO in cryptogenic stroke for selected patient is advisable and this treatment has been documented to modify the course of migraine with aura in patients with such comorbidity. Nevertheless, conflicting data on the possible benefit of PFO closure in MA have been documented. The therapeutic implications of cerebrovascular disorders and RLS comorbidity in migraine patients are still being discussed.

THE ROLE OF PHARMACOTHERAPY IN THE PREVENTION OF CHRONIC MIGRAINE

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Episodic migraine should be considered a chronic progressive disorder with marked deterioration of quality of life. Up to 2.4% of the general population experiences chronic migraine (CM); the principal factors that predict its onset and persistence are female gender and high headache frequency. In addition, migraine patients are at risk for subclinical cerebellar infarcts, that rises with increasing attack frequency. It is reasonable to assume that attack frequency and severity are directly correlated with the development of structural damage and disability and

to use them as surrogate markers of disease progression. Therefore, the group of migraine patients with high frequency of marked disabling and prolonged attacks deserve clinical vigilance to prevent the progression of the disease – we should begin thinking of abortive and prophylactic pharmacotherapy as a disease-modifying agent. Central sensitization plays an important role in the pathophysiology of CM: two thirds of migraine patients develop central sensitization, arguably a form of progression of the attack. The development and maintenance of cutaneous allodynia later in the attack is propelled by sensitization of the central trigeminovascular neuron that receives converging sensory input from the meninges as well as from scalp and facial skin. Probably the cumulative effects of repeated migraine attack generating central sensitivity over the years will provoke an age-related progression of the disease and the clinical onset of chronic headache. Taking triptan as soon as possible prevents allodynia and therefore might be an important strategy to prevent permanent instauration of central sensitization and onset of CM. In contrast, the overuse of abortive medication might accelerate disease progression. Migraine patients, in fact, are particularly predisposed to develop chronic headache in association with medication overuse (30–50%). Overuse prevention is a paramount goal of CM prevention. Prophylactic drugs might contribute to arrest the process of migraine chronicization, but their long-term effects on the natural history of migraine have not yet been well studied. However, it is reasonable to recommend lengthy prophylaxis for patients with factors indicating migraine progression, to greatly decrease attack frequency. In contract, there is evidence that patients with high headache frequency but not daily headache show greater improvement with prophylaxis than patients with daily headache. The first migraine attacks in patients with high risk of chronicization may soon be viewed as a signal to begin aggressive protective pharmacotherapy, most likely, with new procedures and drugs, with the aim of preventing CM.

PHARMACODYNAMIC AND PHARMACOKINETIC INSIGHTS IN HEADACHE PATIENTS WITH DRUG OVERUSE

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A substantial proportion of headache patients overuse acute medications. Overuse has been considered to be responsible, in many cases, for the development or maintenance of chronic daily headache (CDH). Our aim is to evaluate recent experimental and clinical data on the pathophysiology of this syndrome. The biochemical basis of CDH is not known, but the 5-HT system seems to be involved. Indeed, chronic overuse of acetaminophen induces alterations of this system both at the level of CNS and platelets, in some animal models. Similarly, some abnormalities in 5-HT levels and in 5-HT receptors have been found in patients with CDH.
Since triptans are the most effective anti-migraine drugs used and show agonist action mainly at 5-HT(1B/1D/1F) receptors; their effect after chronic use and/or after overuse deserves particular attention. In a recent study [1], the effects of protracted triptan treatment have been evaluated in rats on 5-HT1 receptor mRNA expression and function in tissues related to migraine pathophysiology. Despite a reduction in 5-HT(1B/1D/1F) receptor mRNA, no significant effect was detected in two functional assays. Therefore, the significance of 5-HT receptor expression in migraine pathophysiology as well as pharmacokinetic implications need further analysis. In another recent study [2], the outcomes of analgesic overuse have been evaluated by comparing a group of patients who discontinued medication overuse to a group who continued the overuse. After one-year of follow-up there was a decrease in the frequency of headache in 73.7% of group 1 (successfully detoxified) and in only 17.2% of group 2. Similarly, the duration of head pain was reduced by 61.2% in group 1 and 14.8% in group 2. Rigorous prescribing guidelines as well as successful detoxification are therefore needed when treating patients with drug overuse.

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REHABILITATION PROCEDURES FOR MEDICATION-OVERUSE HEADACHE (MOH)

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Chronic headaches represent a disorder with high social impact producing direct and indirect costs. Daily intake of analgesic drugs is the clinical evolution of this disorder. MOH is a new form of secondary headache with various clinical manifestations appearing after the sudden suspension of analgesics, ergot-derivatives, barbiturates, and triptans, taken alone or in association, according to the quantitative profiles defined by IHS (ICDH-II, 2004).
The MOH detoxification procedure has to be intended as part of a wider therapeutic project, which comprehends the detoxification and the rebound phase, the treatment of the complications, and, in particular, the phase of relapse prevention.
A multidisciplinary approach to MOH can be held in Day Hospital (weaning phase) and subsequently in the outpatients department (therapeutic re-programming).
The principal endpoints supporting the rehabilitative treatment of MOH are:
- Removal of the psychophysical pain with daily i.v. therapy;
- Efficacy of the doctor-patient relationship to assure treatment continuity also after drug abuse;
- Specific therapies for each patient;
- Involvement of the patient in his therapeutic project.

The therapy is divided in *light* and *heavy* analgesic intake: an outpatient treatment will be sufficient in the first case, and a day hospital treatment in the second.
The rebound syndrome following MOH is based on the alteration of one or more of the following neuronal systems: noradrenergic hyperactivity, modification of the NMDA receptors, alteration of the GABA-Benzodiazepine receptor, and hyperactivity of the HPA axis.
The psychological aspect that combines the pain with analgesics use is important in the comprehension of this headache type and the concomitant abuse. Many patients feel forced to take analgesics to calm the pain. Therefore, our task will be to suggest adequate drugs preventing the return of headache chronicity and/or natural crises coming back after hangover MOH removal.

CHRONIC HEADACHE AND MEDICATION-OVERUSE: LONG-TERM FOLLOW-UP AFTER DETOXIFICATION

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The recent revision (2004) of the International Headache Society (IHS) "*The International Classification of Headache Disorders*" defined the clinical characteristics, the type and dosage of drugs, and the duration of the medication-overuse headache.

All experts agree on the necessity in interrupting the overused medication to stop the chronic headache and to obtain positive results with the subsequent prophylactic therapy.
Head-to-head controlled trials on different therapeutic approaches are lacking and consequently guidelines for the treatment of medication-overuse headache are currently not available.
Long-term follow-up studies after detoxification are few and report a relapse in 39–66% of patients.
Fifty (46 F, 4 M) daily abusers of analgesics with chronic headache were re-evaluated four years after detoxification. All patients were admitted to the Trieste Headache Unit and treated with abrupt stoppage of overused medication, intravenous hydrating therapy and intravenous therapy with benzodiazepines (i.e., delorazepam) and S-adenosylmethionine. Symptomatic and antiemetic drugs were used only in case of severe rebound headaches.
A questionnaire on demographic characteristics, working and recreational activities, incidental comorbidities, features of the headache and use of medications was administered to patients. They underwent neurologic and general examination.
Thirty-two percent of patients had one or more relapses of medication-overuse headache, whereas the remaining 68% had less than 15 headache attacks per month and no longer experienced analgesics abuse.
Predictive factors for relapse were urban domicile, small family, cigarette smoking, lack of hobbies, comorbidity with depression and arterial hypertension, and inadequate prophylactic therapy. An extension of the analyses to other variables is under way.
The positive results confirm that these patients should be treated early with detoxification and subsequent prophylactic therapy.
Comparison studies evaluating different therapeutic strategies are warranted.

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ORAL PRESENTATIONS

EPISODIC AND CHRONIC MIGRAINE: PATHOGENETIC ASPECTS

FACILITATORY EFFECTS OF 1 HZ RTMS IN MOTOR CORTEX OF PATIENTS AFFECTED BY MIGRAINE WITH AURA

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Objective We previously showed paradoxical facilitatory effects of low-frequency rTMS on the striate and extrastriate cortex of patients suffering from migraine with aura [1, 2].
In this study we evaluated the effects of 1 Hz rTMS on excitability of inhibitory and facilitatory circuits of the motor cortex to explore if the abnormal pattern of excitability extends beyond the sensory cortex also involving motor areas in migraine with aura.
Materials and methods Nine patients affected by migraine with aura and 8 healthy controls were included in the study. The hot-spot for activation of the right abductor pollicis brevis (ABP) muscle was checked by means of a figure-of-eight coil and the motor threshold (MT) was recorded on this point. A train of 600 magnetic pulses at 1 Hz frequency and 90% MT intensity were delivered to the hot-spot. Before and after rTMS, the excitability of intracortical inhibitory and facilitatory circuits were assessed by means of a paired pulse paradigm (conditioning stimulus: 80% MT, and test stimulus: 120% MT) with two different interstimulus intervals: 2 msec (inhibitory) and 10 msec (facilitatory). Amplitude of the responses was expressed as the percentage of motor evoked potential (MEP) to the test stimulus alone.
Results At baseline conditions, migraineurs showed significantly reduced levels of intracortical inhibition (ICI), as compared to controls. Intracortical facilitation (ICF) in controls was significantly decreased by 1 Hz rTMS, whereas it was increased in migrainers. ICI levels were not significantly affected by low frequency stimulation.
Discussion Our results showed that the motor as well as sensory cortex of migraine patients present an abnormal modulation of cortical excitability, where a relevant role is likely played by the inefficiency of inhibitory circuits.
Conclusions This study further contributes to the hypothesis of reduced cortical inhibition in migraine with aura.
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EVALUATION OF CORTICAL BLOW FLOOD USING fMRI IN A SUBJECT AFFECTED BY MIGRAINE WITH AURA DURING AND AFTER THE ATTACK

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Objective Recent studies have emphasized an altered BOLD signal (Blood Oxygenation Level-Dependent) in subjects affected by migraine with aura. Several authors have therefore studied these types of subjects using functional magnetic resonance imaging (fMRI) during migraine attack or during the period between two attacks, thus highlighting an abnormal response of regional cortical blood flow (rCBF) in the occipital areas by administering a visual stimulation task. However, it is very difficult to plan a study on subjects during the migraine attack, because one can not predict when a spontaneous attack may occur. In fact, many studies succeeded in observing the BOLD signal during an attack, because the visual stimulation task, at times, triggers it. Thus, we assessed a subject with fMRI in two different moments: during the migraine attack, and after a fortnight in order to observe the differences in rCBF.
Materials and methods In order to enroll a patient during migraine attack, we told all our outpatients affected by migraine with visual aura to contact us as soon as the attack began. Thus, it was possible for us to carry out a fMRI on a 27-year-old male using a visual stimulation task. After a fortnight, the task was repeated and we also carried out an EEG, TMS, VEP, and a blood test.
Results The fMRI data showed a markedly reduced activation in the occipital areas during the migraine attack, while the data obtained from the subsequent fMRI also showed a reduced activation, almost like the first. The EEG was altered for the presence of epileptiform activity.
Discussion Our results showed a different pattern of activation of the occipital areas correlated with migraine symptoms. Furthermore, the electrophysiological data obtained demonstrated altered activity due to the patient's disorder in agreement with the literature. We thus support the concept of cortical spreading depression which is, according to recent literature, a fundamental pathophysiologic mechanism that triggers migraine with aura attacks.
Conclusions Our results, however, need to be verified on a larger sample, even if we realize that it is difficult to coordinate this series of examinations during a migraine attack.

NEPRILYSIN LEVELS IN MIGRAINE ATTACKS

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Background Neprilysin (neutral endopeptidase, EC 3:4:24:11, CD10) (NEP) is a Zn metallopeptidase which has been demonstrated to intervene in limiting neurogenic inflammation through the degradation of sensory neuropeptides [1]. The involvement of this endopeptidase in antagonizing neurogenic inflammation consequent to trigeminovascular activation during migraine attacks is not known.
Objective The aim of this study was to investigate the circulating and cellular expression of NEP in the internal jugular blood of migraine without aura patients (MwoA) assessed during an attack.
Patients and methods Ten MwoA patients were admitted to the hospital during the attacks. Internal jugular venous blood samples were taken immediately after catheter insertion, at 1, 2, and 4 hours after attack onset, and within 2 hours from its cessation. NEP levels in plasma from the internal jugular blood were assessed using a fluorimetric technique. Neprilysin, expressed as the antigen CD10, was determined in jugular blood cells as mean fluorescence intensity (MFI) and as percentage of positive cells by two-colour immunofluorescence.
Results Plasma levels of NEP tended to be significantly increased from the second hour after catheter insertion ($p<0.01$) and remained elevated for the entire attack. They then returned to values lower than those measured at the onset of attacks.
A similar trend was observed for the percentage of CD10-positive cells in jugular venous blood and MFI, which peaked at 2 and 4 hours after attack onset.
Discussion Trigeminovascular activation during migraine attacks causes the release of sensory neuropeptides, such as CGRP and neurokinin A. Based on the results of the present study, it can be hypothesized that NEP intervenes in limiting neurogenic inflammation by cleaving and inactivating a proportion of these peptides released during migraine attacks [2].

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HIGH PLASMA LEVELS OF PROLACTIN IN CHRONIC MIGRAINE

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It is not always clear why a migraine transforms from an episodic into a chronic form.
Considering the close correlation in women between hormones and migraine, we tested for thyroid hormones and plasma prolactin levels in all new patients who came to our Centre because their migraine worsened in the last year. All of the patients underwent a general physical and neurological examination, MRI, and angio MRI, Rx of the cervical spine, and extensive blood screening, also including sexual hormones, TSH, FT3, fT4, prolactin levels, ACTH, cortisol, and subsequently also an endocrinologic evaluation. In some case, they also underwent other examinations because of the presence of other pathologies (e.g., hypertension). We screened 15 patients with chronic headache who had a normal neurological exam and a negative neuro-radiological evaluation, having migraine and/or tension-type headache during the last year. They were 14 females and 1 male. Ten of them had a pure chronic form of migraine, 2 a chronic tension-type headache, and 3 patients had both types. Among the pure chronic migraine type, 6 patients had high plasma levels of prolactin, ranging from 1200 to 3200 pm/l. They were all female, aged from 22 to 57 years, none except one had menstrual alterations, nor any other symptom of hormonal disorders; the most peculiar aspect was that the characteristics of their headache did not change, and they responded completely to the international criterion for defining migraine. In the other 4 patients with chronic migraine, the male patient had an important chronic sinusitis of the maxillary and ethmoidal sinuses, another patient had an important intolerance to some type of flours, and after having eliminated that ingredient from her diet, she was almost completely headache free, another had an important cervical spine disorder, and the fourth had a history of antiinflammatory drug abuse. All patients with high levels of prolactin promptly responded to the reduction in prolactin alone, obtaining an important decrease in the intensity and number of attacks. We can conclude that thorough screening of the hormonal profile, in our case prolactin, is often useful, and it is possible to identify a symptomatic cause of migraine chronicity, also in the absence of any signs or symptoms of hormonal disorders.

NOCICEPTIN IN THE CEREBROSPINAL FLUID OF CHRONIC MIGRAINE AND FIBROMYALGIA PATIENTS

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Backgroud Nociceptin is the endogenous ligand of the G-coupled, naloxon insensitive ORL-1 receptor. An increased expression of both nociceptin and the ORL-1 receptor has been demonstrated in the dorsal horn of the rat spinal cord in experimental pain models, thus indicating the involvement of the nociceptin/ORL-1 system in the mechanisms of pathological pain. No studies have been carried out until now on the levels of nociceptin in chronic migraine and fibromyalgia.

Objective The aim of the present study was to verify the CSF levels of nociceptin in 20 chronic migraine (CM) patients, 20 patients with an antecedent history of migraine without aura diagnosed as having probable chronic migraine (PCM) and probable analgesic-abuse headache (PAAH), as well as in 20 patients affected by primary fibromyalgia syndrome (PFMS). The CSF levels of prostaglandin PGE_2 were also determined in all patient groups. Control values for nociceptin and PGE_2 were obtained from the CSF of 20 control subjects, for whom the CSF examination and other instrumental investigations excluded diseases of the central and peripheral nervous system.
Methods CSF levels of nociceptin and PGE_2 were determined by sensitive immunoassays.
Results Levels of nociceptin and PGE_2 were significantly higher in the CSF of both patients with CM and PCM+PAAH compared with control subjects (nociceptin=$p<0.01$ and $p<0.02$, PGE_2=$p<0.03$ and $p<0.02$), without significant differences between the two groups. Patients with PFMS also had significantly higher levels of both nociceptin and PGE_2 ($p<0.02$ and $p< 0.01$, respectively), which did not differ from those in CM and PCM+PAAH patients. In PFMS patients no significant differences emerged between nociceptin and PGE_2 levels in patients with and without analgesic abuse.
CSF values of nociceptin were positively correlated with PGE_2 values in both patients with CM (R=0.62, $p<0.01$) and PCM+PAAH (R=0.60, $p<0.02$). A statistically significant correlation was also found between nociceptin and PGE_2 levels in the CSF of PFMS patients (R=0.48, $p<0.01$).
Discussion Experimental findings suggest an anti-analgesic action of nociceptin originating in the brain, which is coupled to a descending neuronal pathway mediated by spinal PGE_2 [1]. This pro-nociceptive action of nociceptin can be hypothesized in both chronic migraine and fibromyalgia, where it seems to be related to PGE2 secretion and does not appear to be influenced by analgesic abuse.
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PRIMARY HEADACHES: CLINICAL ASPECTS

ATTACHMENT STYLE AS A PREDICTOR OF DISABILITY IN A CLINICAL POPULATION OF PATIENTS WITH EPISODIC MIGRAINE

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Objective To assess the relative role of socio-demographic variables, migraine characteristics, and psychological factors in influencing migraine-related disability.
Methods The sample included 197 outpatients with episodic migraine. Measures included: disability (MIDAS), adult attachment style (ASQ), depressive symptoms (BDI), trait anxiety and anger (STAI – T and STAS – T). Statistical analysis was based on a stepwise regression model using total MIDAS score as dependent variable and age, gender, number of migraine days per month, duration of attack, pain severity, BDI, STAI – T, STAS – T and ASQ scales as predictors.
Results The model was highly significant (F=14.11, $p<0.001$) and accounted for 25.1% of the total variance in disability. Number of migraine days per month (beta=0.32, $p<0.001$), duration of attack (beta=0.17, $p=0.008$), pain severity (beta=0.16, $p=0.012$), gender (beta=0.16, $p=0.015$) and an insecure style of adult attachment (Confidence scale of the ASQ; beta=-1.71, $p=0.007$) emerged as significant predictors of migraine-related disability.

Conclusions These findings show that attachment style is a significant predictor of disability in patients with episodic migraine even after controlling for the confounding effect of severity.

COGNITIVE DYSFUNCTIONS IN MIGRAINE: NEUROPSYCHOLOGICAL INVESTIGATION TOOLS AND VARIABILITY OF RESULTS

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Cognitive dysfunctions in migraine patients have been reported by several authors. These findings, however, are controversial. While some studies claimed the presence of deficits, others did not confirm these results. This variability may depend on clinical variables (type of migraine, duration of disorder, side of pain, attack frequency, therapy) but may also be influenced by the neuropsychological tests chosen to study the patients. In previous studies, we found significant differences in attention and memory performances related to the type of migraine and the side of pain. The aim of the present study was to investigate the possible effect of neuropsychological tests on the detection of cognitive dysfunctions. In this preliminary paper our investigation was limited to attention, verbal, and visual memory. Fourteen patients suffering from migraine were studied. Informed consent was obtained. According to the International Headache Society criteria, 8 patients were diagnosed with migraine with aura, and 6 were diagnosed with migraine without aura. The mean age and education were, respectively, 35.14±9.6 years and 13.07±3.2 years. Exclusion criteria included other types of headache, a history of central or peripheral nervous system diseases, trauma, systemic diseases, and major psychiatric disorders. We used the following tests: Symbol Digit Modalities test, Rey's 15-words Immediate and Delayed Recall and Visual Reproduction test. Comparing our results with normative data, we found the presence of attention defects in 35% of subjects and short and long-term verbal memory and visual memory defects in 14% of the subjects.

Our data suggest that using the neuropsychological tests chosen in the present study and comparing the results with normative data we were able to detect cognitive dysfunctions only in a small number of migraineurs. In conclusion, together with other reported clinical variables, the choice of different neuropsychological tests may also influence the detection of cognitive defects in migraine.

SUBCLINICAL TEMPOROMANDIBULAR AND CERVICAL SPINE DYSFUNCTIONS IN MIGRAINE PATIENTS: PRELIMINARY RESULTS

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Background Epidemiological and clinical studies have disclosed an association between temporomandibular dysfunction and headache, even if the relationship between migraine and disorder of the masticatory system is not completely understood. Nevertheless, aetiological connections between diseases of the temporomandibular system and of the cervical spine as well as between the cervical spine and headache have often been discussed in the past. It has recently been suggested that the trigeminocervical complex plays a crucial role in the pathophysiology of the neck discomfort which accompanies the migraine attack.

Objective Aim of the study was: (1) to investigate the function of the temporomandibular system and of the cervical spine in a population of migraine patients; (2) to verify the presence of a correlation between the clinical features of pain and the subclinical temporomandibular joint and cervical spine dysfunctions.

Materials and methods Twenty migraine patients were consecutively recruited according to IHS criteria (2004). All study subjects were subjected to the following clinical and instrumental procedures: (1) a clinical investigation of the temporomandibular system according to the "Craniomandibular Index" of Friction and Schiffman (1986); (2) electrognathography and electromyography of the temporomandibular joint; (3) physical examination of the cervical spine included items that belong to the diagnostic criteria for cervicogenic headache.

Results We enrolled 20 migraine patients (mean age 35±10 years) and 10 healthy controls (mean age 32±12 years). Migraineurs showed a significantly higher score in the clinical evaluation of both the temporomandibular joint and cervical spine than healthy controls ($p<0.05$). Electrognathography and electromyography data of the temporomandibular joint showed significant differences between patients and healthy controls ($p<0.05$).

In particular, when we considered separately the two groups of migraineurs, we found that patients with "back pain" showed higher levels of clinical and electrophysiological dysfunctions than both patients with "anterior pain" and controls. Duration of illness and frequency of attack were positively correlated with these clinical and electrophysiological data ($p<0.05$).

Conclusion Our data suggest the presence of subclinical temporomandibular and cervical spine disorders in all migraineurs and in particular in those with "back pain". These dysfunctions are correlated with the severity of migraine and may depend on a dysregulation of the trigeminocervical complex. It may be important to identify these clinical features in migraine patients not only for the therapeutic implications but also for understanding the pathophysiological link between the mandibular system, cervical spine, and migraine attack.

A SELF-ADMINISTERED QUESTIONNAIRE FOR SCREENING OF MIGRAINE IN PRIMARY CARE: A PROTOCOL FOR VALIDATION OF THE ITALIAN VERSION OF THE ID MIGRAINE™

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Objective Epidemiological studies show that despite the disability and burden of migraine less than one-half of migraineurs received a diagnosis of migraine and only one-third of them are treated with prescription drugs [1]. Recently, Lipton et al. [2], while evaluating screening tools for the diagnosis of migraine in primary care, validated a three-question based self-administered questionnaire (ID Migraine™), which was able to identify migraineurs in primary care setting with high sensitivity (0.81), specificity (0.75) and positive predictive value (0.93).

The objective of this study was to validate an Italian version of ID Migraine™ in primary care setting; evaluating also the potential application of this tool for epidemiological studies of migraine.

Materials and methods The study will be conducted at 5 headache outpatient services in Sicily. Seventy healthy subjects and 160 consecutive patients affected by migraine and other headaches will be divided into groups (equally balanced) according to age (6–14, 15–54, ≤55 years) and diagnostic criteria (migraine, other primary headaches, symptomatic headaches, and healthy controls); men and women will be selected in about the same percentage. The headache subtypes will be classified by headache specialists according to the criteria of the last IHS classification.
Patients and controls will then receive an Italian version of the ID Migraine™, a self-administered questionnaire composed of three questions. The results obtained with the questionnaire will be compared with the diagnosis made by the headache specialist to assess sensitivity, specificity and predictive positive and negative values of the questionnaire.

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SHIFT WORK: RISK FACTOR FOR HEADACHE

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Introduction Shift work is intended as any kind of work planning which is different from the ordinary daily schedule [1]. In Europe, shift work involves 33% of the employed population, and several studies have indicated that it may represent a stressful condition significantly affecting physical health and favouring the development of heart and gastroenteric diseases, sleep disorders, and changes in biological rhythms and reproductive function [2]. In this study, we have evaluated whether shift work may be associated with headache in a population of hospital workers.
Material and methods According to the medical surveillance protocol of D.Lgs 626/94, a group of 228 subjects working at our Institute were enrolled. We administered a dedicated headache questionnaire based on IHS criteria only to subjects reporting headache.
Results Of the 228 subjects, 157 underwent a clinical examination. Forty-two of them (26.7%) complained of headache, which was diagnosed as follows: migraine without aura (n. 21), tension-type headache (n. 18), episodic cluster headache (n. 2), and migraine with typical aura (n. 1). In 50% of the cases, shift work (14.00h through 22.00h, 7.00h through 14.00h, and 22.00h through 7.00h) was found to be the major risk factor for the development of headache. Prolonged PC use, excess responsibility or rather reduced visibility in one's own acts among the work group, and social and familial problems were the risk factors in the remaining cases. Within the shift workers complaining of headache (n. 21, 18 females and 3 males), 12 subjects had an episodic tension-type headache (57.1%), 8 a migraine without aura (38.1%), and 1 an episodic cluster headache (4.8%).
Conclusions Thus, shift workers often suffer from headache, mainly of the tension type. In this case, in the face of particularly intense and/or prolonged precipitating factors (such as lack of adequate night sleep, altered biological rhythms, and psycho-physical stress), the increased nociceptive afferents may negatively affect the pain control processes and result in headache. In the case of migraine, hormone fluctuations, changes in sleep-wake cycle, stress, anxiety and depression may act on a state of latent dysexcitability triggering the process of cortical spreading depression, the activation of the trigeminovascular system, and thus attack onset [3].

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COMORBIDITIES AND SECONDARY HEADACHES

CENTROTEMPORAL SPIKES IN CHILDREN WITH MIGRAINE, POSSIBLE COMMON PATHOGENETIC BACKGROUND: PRELIMINARY DATA AND METHODOLOGICAL ISSUES

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Objective The aim of the study was to investigate the relation between rolandic centrotemporal spikes (CTS) and headache in children.
Material and methods We conducted a study on patients consecutively referred because of headache to the Department of Child Neuropsychiatry "G.F. Ingrassia" Hospital, A.U.S.L. n. 6, Palermo (Italy) in 2003. The sample consisted of the first 100 consecutively referred children and adolescents with headache. The mean age was 10.8 years; 114 (48%) were males. A control group was formed with the first 100 children admitted to this department without diagnosis of headache, epilepsy and encephalopathies.
The headache was categorized according to the classification of the International Headache Society (IHS).
Results The sample was subdivided into 57 migraine, 17 episodic tension-type headache, 13 chronic daily headache, 3 idiopathic stabbing headache, 8 post traumatic headache, and 2 other secondary headches. Only 4 children, who suffered from migraine (about 7%), presented CTS on the electroencephalogram (EEG). The EEG showed characteristic high-voltage sharp waves in the centrotemporal regions, which are activated with drowsiness and sleep. CTS may represent a neurobiological marker for the increased risk of developing benign childhood epilepsy with centrotemporal spikes (BECTS).
On the contrary, this association was never observed in other groups of headache and in the control group.
Conclusions This study confirms that CTS are not pathognomonic of centrotemporal epilepsy and that CTS and headache in children are statistically related. These findings might reflect a common pathogenetic background.
Focal spikes and sharp waves with predominantly centrotemporal localization are the electroencephalographic hallmark of Rolandic epilepsy (or BECTS). This EEG trait, but not BECTS itself, has been reported to follow an autosomal dominant mode of inheritance with incomplete penetrance and age dependency. Several linkage studies exploring candidate loci have given negative results. The first positive evidence for linkage in families with centrotemporal spikes was found on chromosome 15q14. These markers are localized in direct vicinity to the alpha 7 subunit gene of the AChR (neuronal nicotinic acetylcholine receptor).

HEADACHE AND EPILEPSY: TWO CHRONIC DISORDERS WITH CLINICAL COMORBIDITY

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Introduction Headache and epilepsy are both frequent disorders in childhood. Although comorbidity has been recognized for some time,

headache in epileptic patients is frequently underestimated by the physician because epilepsy is considered a more serious problem of childhood than the former. Both disorders are characterized by recurrent attacks, they share the same age at onset, and often some symptoms, too. In addition, several migraine attacks can be mistaken for epileptic seizures, mainly, when their temporal relationship is close and they are sensitive to antiepileptic drugs.

Objective The aim of this investigation was to study the relationship between epilepsy and migraine among a select sample of patients referred to our Department for both disorders.

Patients On the basis of clinical symptoms, electroencephalography and neuroimaging findings, we recruited 8 epilepsy-referred patients (3 males and 5 females) with headache who fulfilled ILAE and IHS diagnostic criteria for epilepsy and migraine, respectively. We included only idiopathic or cryptogenic epilepsy. Of the 8 comorbid cases, 4 patients had temporal lobe epilepsy (TLE), 3 patients had occipital lobe epilepsy (OLE) and 1 had generalized epilepsy. The mean age of onset of epilepsy and migraine was 7.9 years (range 4–13) and 6.7 years (range 4–12), respectively. Moreover, we found that the migraine attack preceded the epileptic seizures in 3 patients and followed them in 3 patients, too, whereas two children had an interictal attack. Our patients showed an incidence of family history of migraine (4/8) higher than the incidence of family history of epilepsy (2/8). In most patients the antiepileptic drugs, valproate and carbamazepine, were effective in the treatment of epilepsy and migraine.

Discussion It has been reported that the risk of headache is increased in both idiopathic/cryptogenic and symptomatic epileptic patients. Most of the children in our study had partial-onset epilepsy (7/8); nevertheless, previous studies revealed that the headache may be present in both generalized and partial-onset seizures but the latter showed a mild associated increased risk for headache. These findings suggest that the specific location of the epileptic focus may play a significant role in the pathogenic mechanisms of migraine because the occipital lobe is considered the brain structure mainly involved. Several investigations pointed out an increased incidence of epilepsy among migrainous patients as well as a higher ratio of headache among epileptic patients.

It is likely that the association between these disorders is related to a state of brain hyperexcitability due to a threshold decrease resulting from environmental and genetic factors.

A PROSPECTIVE STUDY OF HEADACHE IN MULTIPLE SCLEROSIS PATIENTS

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Background It has not been clearly established and is still controversial whether multiple sclerosis (MS) can cause headaches. Headache, however, has been described in MS patients and classified as either migraine or tension-type, but no distinctive "MS headache" has been defined until now [1]. Some MS patients referred headaches at the onset of their first symptoms and in some cases headaches recurred with subsequent relapses.

Results With the aim to clarify the association between MS and headaches, and in particular migraine, a prospective study was conducted on 110 relapsing-remitting MS patients. Fifty MS patients (45%) reported headaches, compared with 8 of 60 (13%) patients initially suspected to have MS but subsequently proven to have other disorders, and 19 of 100 (19%) age-matched patients with other neurological disorders.

Among patients with MS complaining of headaches, 28 (56%) suffered from migraine (26 without aura), the remaining from tension-type headache, mainly in the frequent form. Eighteen MS patients with migraine and 20 MS patients with tension-type headache suffered from their respective headaches before MS onset.

Ten MS patients with migraine reported that their initial attack or subsequent exacerbations were heralded by a migraine-like headache. Four of these patients had urgently referred to hospital due to the onset of acute headache. Three patients with migraine occurring for the first time during exacerbation of symptoms showed demyelinating lesions on MRI.

Discussion The present study suggests that headache is a frequent complaint of MS patients (54%), which is represented in 25% of cases by migraine. Migraine has been recently identified as a risk factor for susceptibility to MS [2]. Migraine could also be an expression of the pathogenic mechanisms underlying relapses via activation of the trigeminovascular system by autoreactive cells and mononuclear cells through their proinflammatory products. In some rare cases, migraine in MS patients could result from the strategic location of demyelinating lesions in CNS areas believed to be involved in triggering or maintaining migraine attacks, such as putative "migraine generators".

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SPONTANEOUS CSF LEAK SYNDROME

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Objective To investigate clinical, MRI, radioisotope findings, and therapeutic outcome of spontaneous cerebrospinal fluid leak (SCSFL).

Background Spontaneous CSF leakage from dural tear or spinal meningeal diverticula has been suggested as the pathogenic mechanism of SCSFL.

Methods We describe 18 patients (pts) (12 females, 6 males, mean age 35 years) with SCSFL, of whom 1 was affected by Marfan's syndrome (MS) and 1 by type 1 Arnold-Chiari malformation (ACM), seen from 1992 to 2003. The pts underwent brain CT and MRI, spinal MRI and MRI myelography (7 pts), measurement of CSF pressure (14 pts), radioisotope cisternography (RCS) (7 pts), and meningeal biopsy (1 pt).

Results Seventeen pts (94%) had orthostatic headache and 1 non-postural headache. Additional symptoms included nausea, vomiting, dizziness, vertigo, diplopia, rachialgia, and poor anterograde memory. CSF pressure was low in 12 pts and normal in 2 pts, in 4 pts it was not possible to measure because of the presence of bilateral chronic subdural hematomas (BCSH), with mass effect (3 pts) and anticoagulant therapy (1 pt), 8 pts had increased CSF albumin, and 5 pts had pleocytosis. Diffuse pachymeningeal gadolinium enhancement (DPGE) on brain MRI was found in 16 pts (88%) and it was absent in 2 pts (11%). BCSH was found in 4 pts (22%), hygroma in 3 pts (16%), and brain descent in 5 pts (27%), of whom 1 pt showed ACM. Spinal MRI and MRI myelography (performed in 7 pts) showed cervical pachymeningeal enhancement in 5 pts, dorsal syringomyelia in 1 pt with ACM and sacral radicular cysts in 1 pt and sacral bilateral diverticula in the patient with MS. RCS showed CSF leakage sites in 2 pts (28%), limited ascent of the tracer to the cerebral convexity in 2 pts (28%), and early appearance of radioisotope in the bladder in 3 pts (42%). Meningeal biopsy was normal. Lumbar epidural blood patch (EBP) was performed in 2 pts (11%), with headache recovery, the patient with ACM underwent occipital decompression. BCSH with mass effect was drained in 3 pts (16%). SCSFL was misdiagnosed at the time of BCSH draining in 2 pts. In 14 pts (77%) treatment consisted of bed rest with recovery after a period of 3–4 weeks. No relapses were reported during the follow-up, which ranged from 9 months to 6 years.

Conclusions Patients with SCSFL syndrome have distinct MRI and RCS abnormalities and generally respond favourably to bed rest and hydration. Sometimes EBP or surgical treatment is necessary.

SPONTANEOUS INTRACRANIAL HYPOTENSION: AN UNKNOWN CAUSE OF NON TRAUMATIC BILATERAL CHRONIC SUBDURAL HEMATOMA

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Objective To demonstrate that spontaneous intracranial hypotension (SIH) could be an unknown cause of non traumatic bilateral chronic subdural hematoma (BCSH).
Materials and methods From April 2001 to March 2004, 28 non traumatic cases of BCSH were surgically treated in Niguarda Hospital. Twenty-six cases were etiologically diagnosed (cardiac diseases in anticoagulant therapy, hypertension, coagulation deficits, hepatic diseases, etc). Only 2 cases were of unknown causes. We describe these cases.
Results The first case concerns a 58-year-old man with orthostatic frontal headache, vomiting and dizziness. Because the headache worsened, after 23 days, the patient was admitted to our hospital. CT scan revealed a BCSH. He was operated on but the headache did not resolve and CT scan after ten days showed reaccumulation of a right subdural mass. The patient was again treated and the headache improved 2 days after the second operation. MRI with gadolinium 6 months after the onset of symptoms showed a diffuse pachymeningeal enhancement, a sign of SIH. The patient is asymptomatic at 2-year follow-up. The second case involves a 58-year-old man, affected by diabetes mellitus, with acute orthostatic headache and subsequent hearing loss. After 45 days he presented diplopia and mental confusion. Brain CT and MRI without contrast revealed BCSH. The patient underwent craniectomy for BCSH evacuation on the 66th day after headache onset. Despite transient improvement of the headache, CT scans showed recurrence of a subdural mass and the patient was operated on after 12 days on the left side and after 17 days on the right side with headache recovery. A MRI after 3 months showed caudal dislocation of the brain and displacement of the pons against the clivus, signs of SIH. The diplopia disappeared after 4 months.
Discussion SIH due to CSF leakage is an important cause of headache but is not a well recognized entity. The misdiagnosis of SIH can have serious consequences: BCSH, caused by the loss of buoyancy and downward displacement of the brain, can result in the tearing of bridging veins.
Conclusions Misdiagnosed symptomatic subdural masses may require surgical evacuation, but it is quite likely the recurrence rates are increased in these cases. Cerebral and spinal MRI with gadolinium are necessary before surgical treatment in the presence of BCSH of unknown etiology.

JUVENILE HEADACHE I

IMPACT OF HEADACHE AMONG ADOLESCENTS AT A JUNIOR HIGH SCHOOL

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Objective The prevalence of headache may be underestimated among children. We evaluated the prevalence of different headache types in adolescents aged 14 to 15 years at a junior high school and its impact on school performance and quality of life.
Methods The population study was selected by a multistage questionnaire between May and June 2004, in 4 primary schools of L'Aquila. Data were collected by screening questionnaires, consisting of 31 items, administered to all students; a clinical interview, based on 33 questions; and the Migraine Disability Assessment Scale (MIDAS), administered to all headache sufferers. The MIDAS questionnaire is a 7-item questionnaire (with 5 scored items). The MIDAS score was categorized into four grades of increasing disability severity (minimal or absent, mild, moderate, and severe). Headache was diagnosed according to the diagnostic criteria of the International Headache Society, 2nd edition.
Results Among a total of 151 students examined, 48 (31.8%; 95% CI 24.4–39.2) reported recurrent headache episodes (4 men and 44 women, mean age 15±0.6 years). Migraine without aura was diagnosed in 25 subjects, migraine with aura in 3, chronic migraine in 1, probable migraine with aura in 4, tension-type headache in 13, and unspecified headache in 2 subjects. Disability on the MIDAS score was absent or minimal in 17 (35.4%), mild in 12 (25.0%), moderate in 7 (14.6%), and severe in 12 (25.0%) students. In particular, the missed school days in the last 3 months were 2.54±3.25 and the days at school with performance reduced by half or more in the last 3 months were 4.19±5.01. Headache was mostly worsened by stress (21%), study (29%), and sinusitis (33%). A positive familial history of headache was found in 71% of the headache sufferers. Self-medication with analgesics was reported by 31 subjects (65%) with headache. No subject was taking antimigraine drugs or preventive medications.
Conclusions Headache is a common disorder among adolescents in L'Aquila, having a relevant impact on school activity, and requires more appropriate medical treatment.

ASSESSMENT OF TEMPERAMENT IN CHILDREN AFFECTED BY DIFFERENT TYPES OF HEADACHE

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Introduction Temperament is generally defined as a set of inherited personality traits that appear early in life, are relatively stable, cross-situationally consistent, and evident throughout the age span and diverse cultures. Temperamental extremes and specific temperament dimensions constitute risk factors of psychopathological vulnerability and early precursors of impaired adjustment. The aim of our study was to assess temperament in children affected by different types of headache.
Patients and methods Two-hundred children (M/F: 1.1), aged 6 to 15 years (mean age 10.66±3.79), were divided into 4 groups: (A) n=50, affected by tension-type headache; (B) n=52, affected by migraine without aura; (C) n=45, affected by migraine with aura; (D) n=53, control group. Diagnosis of headache was made according to International Headache Society (IHS) criteria. The EAS Temperament Survey was applied; in children it measures the dimensions activity, emotionality, sociability, and shyness. Statistical analysis was performed by Anova and Bonferroni test. A P value of <0.05 was used as the cutoff point of significance.
Results Groups A and B shared statistically significant higher levels of emotionality compared to group D, with no statistical difference between the two groups. Group A also showed higher levels of shyness and lower levels of sociability and activity compared to groups B, C, and D.
Conclusions Tension-type headache could be an expression of psychopathological vulnerability, as demonstrated by the presence of many temperamental extremes in these children, compared to children affected by different types of headache as well as the control subjects.

JUVENILE HEADACHE: WHAT IS THE PHYSICIAN'S OPINION ABOUT THE CHILD'S AND MOTHER'S EXPECTATIONS?

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Objectives The aim of this study focused on the paediatrician's opinions about the child's and mother's expectations with regard to the

diagnostic and therapeutic approaches made by the paediatrician and neuropsychiatrist.
Methods A questionnaire was given to paediatricians during scientific conferences. The questionnaire was composed of questions about their opinion as to the child's and mother's fears, the reasons for medical visits, and their expectations. We also asked their opinions about the use of symptomatic and prophylactic therapy.
Results We interviewed 50 paediatricians. The duration of the first visit was about 20–30 minutes for 66% of the paediatricians and was estimated sufficient by 78% of them. Fifty-eight percent of doctors believed that the principal reasons for the visit were because pain was more frequent, the attacks were severe and there was fear that they could be caused by a brain tumor (respectively 58%, 26% and 24%). According to the opinion of the doctors, the mothers' more important expectations were the reassurance of their fears and the prescription of medical diagnostic tests (respectively 60% and 50%), while 68% of doctors thought that the mothers were rather satisfied with their action. Whereas, they believed that the child wanted to be mainly reassured, to be cured and to have explanations about the reasons of his/her headache (respectively 62%, 48% and 44%). About 90% of paediatricians believed that the use of symptomatic drugs was necessary when the child's pain was severe, while the use of preventive pharmacological therapies was estimated useful and necessary by 74% of the doctors if the headaches were severe and frequent.
Discussion These data suggest that our population of paediatricians evaluated their action as sufficient with regard to treating headache in children, with a good percentage of mothers showing satisfaction. The paediatricians found prescribing medical diagnostic tests useful in reassuring the mother about her fears. The doctors also considered useful the use of drugs in symptomatic and preventive therapy, but in clinical practice most children admitted for the first time to a paediatric headache center had never undergone a preventive therapy, even when suggested by the guidelines.

HEADACHE IN CHILDREN AND QUALITY OF LIFE: RESULTS OF 2 ITALIAN MULTICENTRE STUDIES (2001 – 2003)

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Studies carried out on the quality of life (QoL) in young headache patients are currently the object of increasing interest (Nodari, 2002). In our first multicentre study (2001) (7 Centres), we analyzed 356 primary headache sufferers (171 M, 185 F, aged 10 to 18 years), 207 migraineurs (M) and 149 with tension-type headache (TTH), according to IHS 1988. The Langeveld's instrument (1996) was adapted, validated in the young Italian population (Nodari, 2002) and simplified (46 items). The 4 areas explored were: 1) Functional status, 2) Psychological functioning, 3) Physical functioning, and 4) Social functioning. Moreover, there were two VAS, related to satisfaction with life in general (VAS_1) and satisfaction with health (VAS_2).
The analysis of variance showed significant differences between patients and controls unaffected by headache (n=356) in all the subscales of the questionnaire as well as in the 2 VAS.
In a more recent (2002–2003) multicentre study (13 Centres), we analyzed 3 subgroups: (A) 351 pts (157 M and 194 F, 10 to 18 yrs), 233 with M (208 without aura (MwoA), 25 with aura (MwA)), 118 with TTH (84 ETTH, 34 CTTH); (B) 351 controls, selected using less rigid criteria with respect to those used in the previous study: we included healthy subjects, and subjects with occasional headaches, who had never gone to a headache specialist; (C) 50 headache sufferers selected from public school (23 MwoA; 27 TTH).
The comparison between groups A and B revealed significantly worse scores in 3 subscales ("impact of headache", "somatic symptoms", and "sleep") for group A. No differences were found in QoL subscales in the 2 samples of headache sufferers (A vs C).
In group A worse scores resulted in some subscales with respect to: (1) type of headache, i.e., M vs TTH, and respectively, CTTH vs ETTH; (2) pattern of headache, i.e., worse scores in patients suffering from high frequency and medium-strong intensity of attacks; (3) previous hospitalisations for headache, more school absences, and poorer academic performance.
Conclusion This study confirms the strong impact of headache on the QoL of young patients, with worse scores in children with migraine. Moreover, it shows an inverse correlation between the QoL and the seriousness of the headache pattern, in agreement with other authors (Langeveld, 1997; Hunfeld, 2001). Finally, in the chronic headaches a worse QoL is evident, in agreement with recent findings in this field of study (Hershey, 2001; D'Amico, 2003; Powers, 2003).

QUALITY OF LIFE IN PAEDIATRIC PRIMARY HEADACHE: ASSESSMENT USING THE PEDSQL 4.0

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Health-related quality of life (HRQoL) is an emerging field of clinical research in the paediatric setting. Only in recent years have some questionnaires to measure HRQoL been developed in the paediatric setting, showing a significant impairment of QoL in juvenile headache patients. In particular, the Pediatric Quality of Life Inventory, version 4.0 (PedsQL 4.0) is a modular instrument for measuring HRQoL in children and adolescents ages 2 to 18. The PedsQL 4.0 Generic Core Scales are multidimensional child self-report and parent proxy-report scales that encompass 23 items subdivided in four areas of functioning: (1) physical functioning, (2) emotional functioning, (3) social functioning, and (4) school functioning. It represents a valid, developmentally appropriate measure of QoL for children from age 2 to 18 years. The aim of this study was to compare the Italian version of the PedsQL 4.0 in a clinical sample of primary headache outpatients and in healthy controls.
The PedsQL 4.0 instrument was administered to 2 groups (age 5–18 years): (A) fifty-six headache patients (27 M, 29 F) (age 5–7, n=7; age 8–12, n=37; age 13–18, n=12) and their parents were evaluated. The children were diagnosed according to the current criteria of the International Headache Society (MwA=28, MwoA=3, ETTH=18, CTTH=1); mixed headache were 6; (B) one hundred forty-two healthy controls age and parent-matched (n=142; 72 M, 70 F) without headache were evaluated in school.
Internal consistency reliability for the total scale score was determined by calculating Cronbach's coefficient α, demonstrating a good reliability (≥ 0.70). Self-report and proxy-report demonstrated significant correlation across all scales, with a good interrater-reliability between children and parents ($p< 0.05$). The analyses yielded meaningful differences between groups A and B:

a. age 5–7 years: the parents of children with headache obtained lower scores than the parents of controls on the Physical Scale and Total Scale;
b. age 8–12 years: the parents of children with headache obtained lower scores than the parents of controls on the Emotional Scale;
c. age 13–18 years: adolescents with headache obtained lower scores than controls across all scales.

Moreover, MwA, MwoA, and CTTH patients had lower scores than ETTH patients. QoL scores were lower in patients with higher headache frequency, intensity, and with a longer chronicity.

Internal consistency and interrater-reliability scales were good, demonstrating satisfactory psychometric properties. Some differences emerged between patients and controls in different scales, underlining the weight of particular dimensions in different age groups. Finally, diagnosis, frequency, intensity, and chronicity negatively influenced the QoL of headache patients.

WHEN THE SUFFERING IS NO LONGER TOLERABLE: HEADACHE OR MADNESS?

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Introduction This study was based on the comorbidity data of mental and psychiatric disorders present in young patients referred to our headache centre and that found in the literature.
Methods We conducted a retrospective study, from 2000 to 2002, on patients ranging in age from 6 to 17 years and suffering from primary headache, classifying the data, as gathered by clinical interview, according to IHS classification and DSM-IV diagnostic criteria.
Results We found: 58% of the patients with migraine, 25% with episodic tension-type headache, 13% with chronic daily headache, and 4% with idiopathic cluster headache.
In the entire sample population we found the following mental disorders: 43% with anxiety and depression, 7% with immature personality, 3% with identity disorders, 0.8% with schizophrenic disorders, 4.8% with learning problems, and 4.6% with low intellectual function.
Conclusions These findings suggest that anxiety, depression and headache are often present at the same time, whereas there are few correlations regarding comorbidity between headache and schizophrenic disorders. This poor correlation is to be viewed in the context of an integrated clinical model that considers not only genetic predisposition, different neuronal transmission systems, and neuronal plasticity, but also different patterns of relationships, which are found in the young patients' environment. Headache and psychosis result when the psychological suffering is no longer tolerable.

JUVENILE HEADACHE II

A TOOL TO DISCRIMINATE YOUNG HEADACHE SUFFERERS FROM OTHERS: THE FAB-C

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The psychological characteristics of young headache sufferers (YHS) have a decisive weight in the evolution of a headache. Psychometric instruments must be researched to distinguish YHS from others.
The FAB-C (Feelings, Attitudes, and Behaviours Scale for Children), a test that measures the various emotional and behavioural problems in children and adolescents aged 6–14 years, administered together with CDI (Children's Depression Inventory), in one of our previous studies, enabled us to discriminate YHS from others, thus identifying their specific characteristics (more introverted headache sufferers, those with major behavioural problems, etc.).
In this study, we intended to assess the structure of the tools applied (FAB-C and CDI), through the statistical technique of the Stepwise Discriminant Analysis, that can identify the "model" which better predicts to which group (normal vs. YHS) each individual group belongs. How accurate are the two tools in distinguishing normal subjects from pathological ones?
The FAB-C and the CDI were administered to a sample of 320 subjects (47% M, 53% F, aged 8 to 14 years), of whom 160 were "normal" and 160 suffering from MwoA (80), ETTH (51), and CTTH (29).
Results showed that 73% of those apparently well were classified in the headache sufferer group and 68.7% in the control group. In all, the entire sample (n=320), appearing to be well, were classified in 70.9% of the cases.
Based on these results we suggest that both tests provide a good discrimination between YHS and others. We believe, therefore, that as these tests are easy to administer, they may be useful tools for the identification of the YHS psychological characteristics.

ASSOCIATION BETWEEN DIFFERENT TYPES OF HEADACHE AND NOCTURNAL ENURESIS

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Objective Headache is a common disorder during the paediatric age. Previous studies suggest that nocturnal enuresis (NE) can be associated with headache in childhood. Aim of our study is to evaluate association between different types of headache and NE.
Materials and methods Two-hundred children (M/F: 1.1), aged 6 to 15 years (mean 10.66±3.79), were divided into 4 groups: (A) n=50, affected by tension-type headache (TTH); (B) n=52 affected by migraine without aura (MWA); (C) n=45 affected by migraine with aura (MA); and (D) n=53, the control group (CC). The diagnosis of headache was made according to International Headache Society (IHS) criteria. Statistical analysis was performed by Anova and Bonferroni test. A P value of <0.05 was used as the cutoff point of significance.
Results Twelve children (24%) from Group A, 11 (21.1%) from Group B, 2 (4.4%) from Group C, and 5 (9.43%) from Group D had a history of or were affected by NE.
Statistical analysis showed a significant association between NE and TTH and between NE and MwA. No significant association between NE and MA was present; no statistical differences were present between TTH and MwA and between MA e CC.
Conclusions Our data indicate that TTH and MwA are more frequently associated with NE. In contrast, the prevalence of NE in children affected by MA is comparable to that in control subjects.

RECURRENT AND CHRONIC HEADACHES IN CHILDREN YOUNGER THAN 6 YEARS OF AGE

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Objectives To determine the frequency of headache subtypes, according to IHS criteria, in a population of children under 6 years of age who were visited in a Center for the diagnosis and treatment of headache in youth.
Methods The medical records of the children younger than 6 years at their first visit, admitted for headache between 1997 and 2003, were studied. Headache was classified according to IHS criteria. Children with less than three headache attacks or less than 15 days of daily headache per month were excluded, with the exception of migraine with aura (MwA) when one attack is sufficient to classify it.
Results We examined 1598 medical records of children visited at our Headache Centre during the study period. One hundred and five (6.5%) were children younger than 6 years of age. The mean age at first medical control was 4.8 years±1.3 (range 17–71 months). Males were 59 (56.1%), females were 46 (43.9%). The mean age at onset of headaches was 4.3 years (range 14–69 months). According to IHS criteria we found 37 cases (35.2%) with migraine, 19 cases (18%) with

episodic tension-type headache, 9 cases (8.5%) with chronic daily headache, 17 cases (16.1%) with idiopathic stabbing headache, 18 cases (17.1%) with post-traumatic headache, 7 cases (6.6%) with other non dangerous secondary headaches (O.R.L. disease, post-infectious headache), 3 cases with (2.85 %) dangerous headaches (Arnold-Chiari type 1 malformation, brain tumor) and 1 case (0.95 %) with unclassifiable headache. Six children (5.7%) reported more than one headache subtype. The prevalence of dangerous headaches was higher in our patients than in school-aged children (χ^2 4.70, p<0.05).
Discussion Our study showed some differences with regard to headache distribution in this population versus school-aged children. In fact, in this age group, migraine was the more common headache. In our study population the clinical picture of migraine attacks at an early age differs from that in the older age group by the very infrequent aura, the rare unilaterality, not infrequent gravative pain quality, and the difficulty to describe the quality of pain, while the frequent brief duration of attacks (<2h) was also witnessed at this age. However, we also found an increase of secondary causes among the chronic/recurrent and daily headaches, especially post-traumatic disorders, and potentially dangerous headaches. Finally, our study showed the most prevalence of the idiopathic stabbing headache in preschool children in comparison with other age groups.

CHRONIC DAILY HEADACHES IN THE JUVENILE POPULATION: A MULTICENTRE STUDY. PRELIMINARY DATA AND METHODOLOGICAL ISSUES

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Introduction Chronic daily headaches (CDH) are becoming a common problem in the juvenile population. However, there is no well-defined classification for these patients and most information comes from studies conducted in adult populations.
Objective Our aim was to study a group of CDH patients and to observe the possible presence of psychological, neurophysiological and biological markers.
Methods We included in the study the first 100 consecutive CDH patients (25 patients from each of the four centres involved in the study), the first 50 migraine patients, the first 50 patients with episodic tension-type headache, and 50 control subjects admitted to our centres from 1 April 2004. The inclusion age was from 6 to 14 years. The headache was categorized according to the classification of the International Headache Society (IHS). Every child underwent neurological and general objective examination, EEG, auditory and visual evoked potentials, blood tests and a battery of psychological tests including: TAD test, TMA short form, PSQI, McGill Pain Questionnaire and Visual Retention test.
Results Our present population consisted of 7 CDH patients (3 females and 4 males), mean age 9.7 years. Four patients were classified chronic migraine, and 3 chronic tension-type headache. Almost 43% (3 children) presented pathological scores in one of the psychological tests. No abnormalities were observed in the neurophysiological examinations.
Discussion Our data are preliminary and it is not possible at the moment to reach a definite conclusion. However, the presence of psychological abnormalities in the CDH group was also evident in a small group.

A QUESTIONNAIRE-BASED STUDY ON PREVALENCE AND TREATMENTS OF HEADACHE IN SECONDARY SCHOOL STUDENTS OF CATANZARO

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Introduction Headaches and migraines occur in a large proportion of young students. The prevalence of headache increases with age, recurrent headache occurs in 3% to 5.9% of 3- to 4-year-old children, whereas the prevalence of 1-year headache in 13-year-old children was 82%.
Aim In this study, we evaluated the incidence of headache in young students of secondary schools, examining associated factors and the drug therapy used.
Methods A detailed questionnaire was directly administered to 1,800 students between the ages of 14 and 18 belonging to secondary schools of Catanzaro. The questionnaire sought information concerning demographic characteristics, school years, occurrence and frequency of headache, and risk factors for onset of headache.
Results We recorded that headache symptoms started between 10 and 12 years of age without any significant difference in the sex ratio. In contrast, we found a significant difference in family history of headache or environmental-related factors among students with headache respect to healthy students (p<0.01). The incidence density of recurrent headache was higher in students living in cities (82%) than in those who lived in the countryside (28%), in smokers or drinkers compared to non-smokers and non-drinkers (p<0.01). Self-medication was reported by 51.8% of the students with headache. The most commonly used drugs were anti-inflammatory drugs (nimesulide and acetylsalicylic acid; 50% and 42%, respectively). In 75% of the students this treatment resolved the acute manifestations but in 5–10% it induced the development of chronic headache.
Discussion Starting secondary school appears to increase significantly the incidence density of overall headache. The increase is almost exclusively attributable to occasional headache. Subsequently, it is important to develop preventive intervention methods and to prepare people to cope with the life changes that are caused by starting secondary school. Moreover, the risk for chronic headache associated with medication overuse was more than six times higher than the risk for chronic headache without medication overuse. These results are in agreement with previous studies, that report that analgesic overuse predicted the persistence of chronic daily headache.
Conclusions Results of our study suggest that a better management of headache symptoms and therapy could reduce the frequency of headache episodes, with a reduction of drug-drug and drug-food interactions. This study could confirm the findings of other population groups that morbidity from headache is often unrecognised and under treated.

ENDPOINTS FOR THE ASSESSMENT OF SYMPTOMATIC DRUG EFFICACY IN JUVENILE MIGRAINE: WHAT DO PATIENTS WANT?

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Primary headaches, and particularly migraine, cause serious disability in young subjects, with loss of social activities and worsening of scholastic results. For these reasons, symptomatic treatment is important as well as prophylactic treatment (when indicated), but clinical trials for the assessment of its action are very difficult to carry out. Symptomatic drugs do not show real efficacy, because the migraine attack in children and adolescents is of brief duration (1–2 hours), and there is a typical tendency to fall asleep. A great response can be

observed to placebo (up to 50%). To identify the characteristics of an ideal symptomatic drug for migraine required by young patients (<18 years old), we administered a questionnaire to those subjects examined in our Headache Centre, where they had to attribute a value, ranging from 0 (not important) to 3 (very important), to 8 parameters: absence of pain at 2 hours after taking the drug, reduction of pain from strong to light or medium, total efficacy during the 24 hours after taking the drug, absence of side effects, partially or totally recovering the capacity of performing normal activities, disappearance of symptoms accompanying migraine (nausea, vomiting, phono- and photophobia), desired pain-free interval after taking the drug. The study was conducted on 24 subjects, 14 females and 10 males, aged between 10 and 17 years (mean age 14.3). According to IHS 2004 criteria, 3 were affected by migraine with and without aura, 2 by migraine with aura, and 19 by migraine without aura. Results showed that young patients attributed most importance to recovery of normal capacities (mean 2.75), followed by absence of side effects and disappearance of phono- and photophobia (2.33), total efficacy in the 24 hours after taking the drug (2.25), absence of pain at 2 hours after drug intake (2.16), reduction of pain from strong to light or medium (2.00) and disappearance of nausea and vomiting (1.83). The mean desired pain-free interval after taking the drug was 28.75 minutes. We concluded that the characteristics of an ideal symptomatic drug required by young patients suffering from migraine were obtainable for the most part with triptans, so it is to be hoped that these drugs will soon have the scientific evidence for their approval for use in patients under 18 years old.

CASE REPORTS I

A PARTICULAR CASE OF PRIMARY STABBING HEADACHE WITH "SENSITIVE AURA"

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We describe the case of a 26-year-old woman who, about 8 months ago, presented with acute stabbing pains, lasting 10 to 15 seconds, located unilaterally in various parts of the head (anterior and posterior regions). The particular nature of this disturbance was due to the fact that the stabbing pain was always preceded by a sense of pins and needles in the centre of the back of the head, of 5 to 6 seconds duration, followed by a pain-free period lasting about 1 minute. Immediately thereafter, the pain returned localized in various regions unilaterally, with a right-sided preference. Early on, the attack frequency was very sporadic, but with time the frequency increased from weekly to almost daily after 50 days of attacks. The daily attacks consisted of 3 episodes at no particular time of the day. Pain intensity was scored at 8 on a scale of 1 to 10. The neurological and clinical records were normal. An MR angiography of the intracranial vessels showed reduced visibility of the right posterior cerebral artery; the ipsilateral anterior cerebral artery appeared reduced in diameter.
The administration of indomethacin (75 mg/die) for 5 days resulted in no improvement. More recently, the patient has been taking flunarizine, 5 mg tablet, for 30 days, and has noted during these last weeks a reduction in the number of episodes and in the intensity of pain.
This case is an example of a primary stabbing headache, with the exception that there were also stabs of pain in the posterior regions of the head. A characteristic of this case was the paresthesis present in the centre of the back of the head, which constantly preceded the stabs of pain; another unique feature was that for 50 days the stabbing pains presented almost daily.
Until now, this type of headache has been attributed, for its peculiarity, to a trigeminal neuralgia with neuronal stabbing. This singular case, with a "sensitive aura" invariably the same, which precedes the pain, could not only confirm this interpretation but also foresee the involvement of vascular structures.

KARTAGENER'S SYNDROME AND MIGRAINE: A CASE REPORT AND REVIEW OF THE LITERATURE

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Primary ciliary dyskinesia (PCD), also known as Kartagener's syndrome, is a human syndrome that results from ciliary dysfunction. This syndrome is characterized by recurrent respiratory infections, situs inversus and infertility. In some cases, neurological complications are also observed. The pathogenesis is a possible channelopathy.
Rapid progress in the complementary fields of molecular genetics and cellular electrophysiology has led to a better understanding of many disorders which are caused by ion channel dysfunction. These channelopathies may manifest in a multitude of ways depending on the tissue specificity of the channel that is affected. Several important general medical conditions are now known to be channelopathies but the neurological aspects are amongst the best characterized.
One such case is that of a young woman who presented with attacks of headache with visual aura and catamenial headache for some years. The evaluations of the diagnostic flow-chart for headaches were negative. The possible relationship between headache and Kartagener's syndrome with a common channelopathy-based pathogenesis is hypothesised.

Suggested readings

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HEMIPLEGIC MIGRAINE AND FAMILIAL EPISODIC ATAXIA TYPE 2

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Introduction Familial episodic ataxia is an unusual hereditary disorder caused by mutations in the gene encoding the Ca2+ channel subunits (gene CACNA1A) on chromosome 19 p 13.
Recently, different types of this mutation were shown to be involved in three human disorders: familial hemiplegic migraine, episodic ataxia, and chronic spinocerebellar ataxia type 6.
In addition, more evidence is showing that the same gene is also involved in the common form of migraine with and without aura.
Patients We describe the case of a 13-year-old female, with a symptomatology characterized by migraine without aura, right-sided hemiplegia and paraesthesia, gastralgia, vomiting, and aphasia lasting for 5 hours.
Materials and methods Haematologic tests were normal (including homocysteinemia); magnetic resonance imaging of the brain was normal.
Discussion We report this case because the mother and other members of her family are affected by familial episodic ataxia type 2. It is likely that our patient presents with different symptoms of the same channelopathy.

NUMMULAR HEADACHE: CASE REPORT AND FIRST THERAPEUTIC PROPOSAL

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Nummular headache (or coin-shaped cephalgia) is a distinctive type of head pain, first described by Pareja et al. in 2002. It is reported in the new IHS Classification (ICHD, 2004) in the Appendix (A13.7.1), which is intended to present research criteria for some novel headache entities that have not been sufficiently validated by scientific evidence. Nummular headache is described as pain in a small circumscribed area of the head in the absence of any lesion of the underlying structures. No therapy until now was reported as effective in this pain syndrome. We describe a case of a 55-year-old woman suffering for 1 year from continuous pain of moderate intensity, without autonomic associated symptoms, strictly localized to a small area of the left parietal region, partly responsive to NSAIDs, in accordance with previous observations of nummular headache. Cerebral MRI with contrast enhancement was essentially normal, showing only minimal unspecific alterations of deep white matter and asymmetry of the vertebral arteries. Gabapentin at the dose of 300 mg t.i.d. led to total disappearance of pain.

HEMICRANIA CONTINUA EVOLVING FROM MIGRAINE WITH AURA: A CASE REPORT

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Introduction Hemicrania continua (HC) is an uncommon primary headache disorder originally described in 1984 by Sjaastad and Spierings and characterised by a continuous, strictly unilateral headache of fluctuating intensity with exacerbations of more severe pain usually accompanied by autonomic disturbances, and with complete response to indomethacin. Even though migrainous features can be part of HC, its relationship with migraine with or without aura has not been clarified.
We report a case of remitting HC with absolute response to indomethacin evolving from migraine with aura.
Case report A 40-year-old woman had suffered from migraine with typical aura from the age of fifteen, with a range of attacks of three to six per year. The headaches, almost exclusively localised on the left side, were regularly preceded by ipsilateral visual scotoma and numbness and tingling in the left upper limb. Three months earlier the patient began to complain of daily, continuous, left-sided headache with superimposed exacerbations of more severe pain. These exacerbations were always preceded by paresthesias over the left hand and the left side of the mouth and tongue, lasting 5 to 15 minutes, and associated with nausea, eye redness and nasal congestion. Frequent short-lasting ipsilateral jabs and jolts were also reported. Common analgesics and NSAID administration resulted in little or no effect. Medical history and physical examination were normal. Brain magnetic resonance imaging (MRI) was normal as were blood cell count, ESR, autoimmunity, and coagulation tests.
A diagnosis of possible HC was made and the patient was administered indomethacin 75 mg daily, with a disappearance of symptoms by the third day. Indomethacin was gradually tapered after one month without recurrence of symptoms. The patient was still asymptomatic at the six month follow-up, with the exclusion of a single spell of usual migraine with aura.
Discussion The coexistence of HC with another form of primary headache is rarely reported in the literature. The clinical and pathogenic relationships between HC and migraine are poorly understood. The exact prevalence of migraine in patients suffering from HC is still unknown. The two clinical entities share common aspects such as migraine-like exacerbations associated with vegetative symptoms. Conversely, aura does not seem to be an exclusively migraine-dependent phenomenon.
Our patient's headache could represent a clinical and pathogenic continuum between migraine and HC. Further descriptions and more careful analysis of migraine aspects in HC patients are needed to better clarify the relationship between migraine and HC.

NEUROVASCULAR HEADACHE: EVIDENCE FOR A ROLE OF MIDBRAIN VASCULAR MALFORMATION IN ACUTE MIGRAINE-LIKE HEADACHE

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After the vascular theory, migraine seems to be increasingly a neurovascular disorder with a primary involvement of central subcortical sensitive structures, with a secondary neurovascular response. Functional neuroimaging techniques, confirm this hypothesis reinforced by the human model of secondary migraine-like symptoms related to brainstem pathology (Goadsby PJ et al., Cephalalgia, 2002; Afridi S et al., J Neurol Neurosurg Psychiatry, 2003).
We present the case of a young patient who came to our Emergency Department affected by a second-time headache, which started one week before, of moderate/severe intensity, described like a continuous throbbing right-sided pain, with severe aggravation by physical activity but without photophobia.
Following the pain, slight neurological symptoms appeared, such as allodynia in the area of the right greater occipital nerve, hypesthesia on the right side of the face, and hiccups. MRI scan of the midbrain and of the cervical medulla demonstrated a medial voluminous cavernous angioma that had recently bled, ranging from the distal part of the trigeminal nucleus to the level of C2. Resolution of part of the neurological symptoms (hypesthesia and hiccups) in the following days reduced the necessity of neurosurgical intervention. At follow-up visits 1, 3, and 6 months later, the patient presented with a continous reduction of headache and allodynia but with persistence in the right C2 dermatome of paroxysmal, jabbing electric-like pain (4–5/days) that disappeared with amitriptyline therapy. Neurophysiological tests (BAERS, Blink Reflexes, AEP, and ESP) were normal. No other episodes of migraine-like headache were registered during the follow-up period, confirming the secondary nature of these migraine-like symptoms.

CASE REPORTS II

MIGRAINE AND EPILEPSY: FOLLOW-UP OF A CHILD SUFFERING FROM CORTICAL DYSPLASIA

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Migraine and epilepsy are two different syndromes, which often show an overlapping of symptoms in childhood.
MS aged 16 years came to our observation affected by West syndrome since the age of 10 months. A familiarity with mental and language retardation was present in the maternal relatives. Therapy with synacthen and valproic acid resulted in remission of the crises after 3 months.
Brain magnetic resonance imaging (MRI) revealed polymicrogyric dysplasia of the left frontal parietal region, EEG revealed left-sided

temporal and occipital OP discharges until the age of 6. Antiepileptic therapy (valproate) was stopped at age 6. Neuropsychological assessment showed mental retardation (QI=70) with dyslexia and dyscalculia present until now. Neurological examination revealed motor clumsiness and incoordination of the right hand. At 7 years of age the boy suffered from headache diagnosed as migraine without aura (5 crises per year).
A new MRI showed the same cortical dysplasia and SPECT showed modification of the frontal and occipital areas. At age 15, he experienced an abrupt onset of two generalized tonic-clonic crises. EEG revealed OP discharges during light stimulation and hyperpnea. Therapy was started with oxcarbazepine stopping the seizures and migraine.
A relationship between epilepsy and migraine has been postulated. Migraine and epilepsy are highly comorbid, but the nature of their association remains unclear. ICHD-II codes in point 7.6 for headache attributed to epileptic seizure and defines migralepsy as epileptic seizures occurring between the migrainous aura and the headache phase of migraine. Exceptionally, reversible brain MRI abnormalities following migraine and seizures have been reported. There are few descriptions, however, of patients with brain MRI changes.

ASSOCIATION BETWEEN HYPNIC HEADACHE AND REM SLEEP: CASE REPORT

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A 68-year-old man presented a 3-month history of frontal, bilateral, dull, and sometimes pulsating headache, of mild severity, not associated with other symptoms, occurring exclusively during nocturnal sleep. These attacks occurred almost every night and awakened the patient an hour after he fell asleep and lasted about sixty minutes. The attacks usually recurred once or twice during the night. CT and NMR were negative, as was neurological examination.
A diagnosis of hypnic headache (HH) was made based on the above data.
Before starting prophylactic treatment, we performed a full-night polysomnography (PSG), using a portable device. EEG traces were acquired with electrodes positioned in accordance with the International 10–20 System. Other channels recorded ocular movements, EMG activity from mylohyoid and tibialis muscles, measurement of thoracic and abdominal efforts (by means of piezoelectric strain gauges), airflow (by means of thermocouples located at nostrils and mouth), snoring sounds (by means of a microphone), oxygen saturation level (pulse oxymeter with finger probe), body position, and heart rate.
The patient reported two headache attacks during that night. Both attacks aroused him from the rapid eye movement (REM) phase of sleep, respectively 15 and 14 minutes after REM onset. During that night we recorded another short REM phase (about 5 minutes), without any attack. No apnoeas or hypopnoeas were recorded.
After PSG, the patient started treatment with lithium carbonate 600 mg at bedtime, but we could not observe any beneficial effect; moreover the patient experienced typical lithium side effects (tremor and thyroid dysfunction). Then he was treated with flunarizine 5 mg at bedtime and the attacks completely disappeared within 60 days.
Although the first PSG analysis of a case of HH documented a relationship with REM sleep, subsequent studies did not always confirm this association. Until now, 17 HH attacks in 11 patients have been studied with PSG. Twelve of them occurred during REM phases and 5 started during non-REM period.
Our case suggests a relationship between HH and REM sleep. Moreover, HH attacks seem to not start immediately after REM sleep has begun, but rather when this period has lasted for some minutes.

CLINICAL AND RADIOLOGICAL FINDINGS IN A CASE OF PROBABLE CLUSTER-LIKE SYNDROME

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Cluster headache (CH) is the most frequent primary trigeminal autonomic cephalalgia.
Among the hypotheses, activation of the trigeminovascular system [1] and the role of the hypothalamus and brainstem are well established [2]. Furthermore, deep brain stimulation of the hypothalamus (inferior-posterior area) with successfully operated intractable chronic cluster headache patients [3] and biogenic amine metabolism alterations [4] supported the hypothesis that the pain of CH is generated directly from the brain.
In the literature few observations have been reported as cluster-like syndrome or symptomatic cluster headache associated with another neurological disease, such as pituitary adenoma, vascular loops, fungal sinusitis, or even a tumor.
The relationship between the two diseases is debated.
We describe a 48-year-old man who since June 2003 developed weekly episodic right-side periorbital headache with ipsilateral nasal congestion, lacrimation, and conjunctival injection. The pain occurred once a day around 9 a.m. and lasted 20–40 minutes. No nausea, vomiting, photophobia or phonophobia were reported.
For one month he was treated with verapamil 120 mg twice a day with improvement. When four months after the beginning of therapy, he stopped taking verapamil, the attacks immediately reappeared but disappeared after resuming verapamil.
In October 2003 and February 2004 magnetic resonance imaging was performed and revealed, on both occasions, a mild suprasellar mass with possible compression of the right paramedian hypothalamic region.
Serum hormone assays showed slightly elevated levels of growth hormone (GH).

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SUPERIOR SAGITTAL SINUS THROMBOSIS AND HEADACHE: CASE REPORT

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Introduction Cerebral venous thrombosis (CVT) is a rare disease associated with many etiological factors. At onset the clinical picture is characterized by a wide spectrum of non specific symptoms often leading to a delay in diagnosis. Headache may be, often, the only symptom in the early stage of the disease. We present a case of superior sagittal sinus thrombosis in a girl with headache, ethmoid sinusitis, and positive for lupus anticoagulant antibodies (LAC).
Patients and methods The patient was an 11-year-old girl with an uneventful personal history but with a family history of migraine. She was admitted to our department complaining of headache characterized by pulsating pain of severe intensity associated with vomiting, photo- and phonophobia, refractory to oral analgesics, lasting 4 days. Clinical examination revealed unsteady gait, dizziness, and ethmoid sinusitis; thus antibiotic and anti-inflammatory therapy was started. CT scan was unremarkable. Since the patient worsened 5 days later, an additional

CT scan was performed, showing thrombosis of the posterior and middle third of the superior sagittal sinus. Laboratory investigations regarding the hypercoagulable state detected lupus anticoagulant antibodies. The patient was placed on anticoagulant drugs which induced a slow and progressive improvement.

Discussion CVT is an uncommon cause of headache that is characterized by an equilibrium disturbance between endogenous, thrombogenic, and fibrinolytic factors. The causes and/or the predisposing conditions for CVT have been classified as infectious and non-infectious. It has been reported that congenital thrombophilia, autoimmune disorders, head injury, cardiac disease, cirrhosis, Crohn's disease, and ulcerative colitis may be non-infectious causes of CVT. The clinical features and the time course of CVT are usually related to the efficiency of venous collaterals. CVT may develop in association with a single risk factor for thrombosis, but additional risk factors should be sought, especially when thrombosis occurs in very young individuals. Our clinical data point out that a hypercoagulability disorder, masked by sinusitis, may be an unusual cause of CVT in children. Moreover, in our patient the first CT scan did not show any abnormality, suggesting that in the early stage of the disease it may be less sensitive than MRI. Therefore, the progressive clinical impairment should lead to more specific neuroradiological investigations because early recognition linked with appropriate treatment of CVT may result in improvement of awareness needs in symptomatic headache. Therefore, we believe that the hypercoagulable state be examined in the evaluation of children with severe and persistent headache.

INTERMITTENT ANGLE-CLOSURE GLAUCOMA IN THE PRESENCE OF A WHITE EYE, POSING AS VISUAL AURA

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We report a case of a 58-year-old woman with a history of migraine without aura since she was 18. The attacks were always located in the right periorbital region extending to the parietal-temporal zone. The intensity was moderate or severe; the pain pulsating, accompanied by nausea and/or vomiting, phono- and photophobia, and increased with physical activity. The frequency was of 2–3 attacks per month, the duration 12 hours. Followed elsewhere, the response to NSAID's was partially satisfactory, the use of oral sumatriptan 50 mg improved most of the attacks. Cranial and cervical column x-ray, EEG, and cerebral CT scan with contrast, all resulted normal**.** After the onset of menopause, the attacks became sporadic. At the age of 55, the patient was visited at the Emergency Room for a migraine attack with characteristics matching those described above, but preceded by a new visual disorder, referred as the sudden appearance of a "white flashing cloth in front of the right eye"; the duration of this visual disorder was approximately 20 minutes, with the painful attack beginning before its end. The patient's clinical examination by the Emergency Room doctor and later by the neurologist on call was normal; the painful symptomatology had a good response to the administration of indomethacin 1 fl i.m.. She was released with a diagnosis of migraine with aura. The attacks repeated with no variations in the following months, with an average frequency of two episodes per month. The only modification that evolved over time was the duration of the visual disorder that increased to approximately three hours, maintaining the same relationship with the onset of pain. One year later, following an attack of particular intensity and of visual disturbance in the right eye for approximately 8 hours, the patient went to the Emergency Room with a noticeable conjunctival injection. After a general and neurological examination, she was given an ophthalmologic examination with tonometry, which recorded an intraocular pressure of 60 mmHg. Iridectomy in the right eye for intermittent angle-closure glaucoma was performed. Since then, the patient has reported a complete resolution of the visual and painful symptomatology. This case underlines the necessity to carefully study the visual symptoms to establish a correct differential diagnosis, at times not simple, between a secondary or primary headache, especially when atypical features are present, such as the increasing duration of the supposed aura, exceeding the IHS diagnostic criteria.

A NEW CASE OF OPHTHALMOPLEGIC MIGRAINE SUGGESTING AN INFLAMMATORY CONDITION

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Ophthalmoplegic migraine is a rare headache disorder characterized by repeated attacks of headache associated with paresis of one or more ocular cranial nerves in the absence of a demonstrable intracranial lesion. The pathophysiology underlying this disorder may be due to an epiphenomenon of trigeminovascular activation, which is dependent on the unique oculomotor nerve anatomy and porous blood-nerve barrier at the emergence of the oculomotor nerves from the brainstem and on the sequelae of demyelination. The IHS classification 2004 includes it in chapter 13 (cranial neuralgias and central causes of facial pain) because of different hypotheses supporting the secondary nature of this rare headache disorder.

We describe the case of a 28-year-old male patient with recurrent episodes of headache associated with paresis of the third cranial nerve. The headache, of pulsating quality and moderate to severe intensity, located in the left frontal-temporal region, and associated with nausea and photo- and phonophobia, preceded the onset of fixed left-sided ptosis, associated with convergent strabismus and diplopia on central and right-sided gaze. Such episodes receded after steroidal therapy. The IgG-index (index of Link) was increased. Brain magnetic resonance imaging scan and angio-MRI were normal, and there was no contrast enhancement of the oculomotor nerves at their exit from the midbrain.

Recently, M.D. Ferrari [1] has described the case of a patient with ophthalmoplegic migraine with paresis of the third and fourth cranial nerves. MRI of the patient showed enhancement only of the fourth cranial nerve and an increased IgG-index. An inflammatory etiopathogenesis was hypothesized. In our case no alterations on MRI were noted as was reported in the case of a patient with ophthalmoplegic migraine in whom neurological deficits persisted [2].

The increase in the index of Link and the resolution of the symptoms after steroid treatment in our case supports the inflammatory nature of this disorder, whereas, the absence of alterations on MRI in our case confirms its peculiar nature and phenotypic variability.

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HEADACHE PATIENT DIAGNOSIS AND MANAGEMENT

HEADACHE MANAGEMENT IN PATIENTS REFERRING TO A HEADACHE CENTRE

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Objective Despite the progress in knowledge and treatment of headache disorders, their social burden is still high. We evaluated fac-

tors influencing headache treatment compliance in patients referring for a first visit to our Headache Centre.
Patients and methods Patients referring for a first visit to the L'Aquila Headache Centre, during the year 2002 were included in the study. Headache disorders were classified according to the International Headache Society Classification, first edition.
Results Data from 421 patients (328 women and 93 men; mean age 36.4±14.9 years) were available. One hundred and twenty-seven (30%) patients were from L'Aquila, 115 (27%) from the L'Aquila district, and 179 (43%) were from other districts. Three hundred and ten (74%) patients suffered from migraine without aura, 50 (12%) from migraine with aura, 13 (3%) from episodic tension-type headache, 21 (5%) from chronic tension-type headache, 1 (0.2%) from cluster headache, 13 (3%) from other headaches, and in 13 (3%) patients the diagnosis could not be performed during the first visit. In 155 (37%) patients an association of migraine without aura with episodic (19%) or chronic tension-type headache (16%) was found. Two hundred and forty (57%) patients were prescribed two or more preventive drugs, 122 (29%) were prescribed a single preventive drug, and 59 (14%) were not prescribed any drug; 349 (83%) were prescribed an acute treatment, while the remaining 72 (17%) were not prescribed any acute treatment. One or more paraclinical examinations were requested for 143 (34%) patients. One hundred and twenty-seven (30%) patients came back to the Headache Centre for follow-up within a year. One hundred and seven (85%) patients who underwent follow-up were compliant to the prescribed treatment. Factors predicting the request of a control visit were the lack of any prescribed preventive treatment ($p<0.0001$), the presence of two different headache types ($p=0.004$), and the request of a paraclinical examination ($p=0.021$); sex, headache type, prescription of acute treatment, and living outside of town did not favour a control visit.
Conclusions Although a low percentage of patients came to the Headache Centre for a second visit, compliance to treatment in patients who had a second visit was high. The second visit was mostly related to non adequate treatment of the headache disorder.

HEADACHE CENTRE IN AN EMERGENCY DEPARTMENT: THE EXPERIENCE OF A THREE-MONTH COLLABORATION

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Headache symptoms account for 1–3% of Emergency Department (ED) admissions. The overwhelming majority of patients who present to an ED with acute primary headache (PH) have migraine and very few of them until then have received a specific diagnosis and an appropriate treatment. Ten percent of patients who visit an ED for PH are repeaters [1] i.e., they have already been admitted for the same reason in the past. The aim of this study was to evaluate the epidemiological-clinical and economic impact on the collaboration between a headache centre (HC) and an ED regarding the diagnosis and treatment of migraine.
Patients with a discharge diagnosis of headache were visited immediately or within a maximum of 36h at our pain clinic where a headache specialist of the headache clinic section made a diagnosis of headache according to 1998 and 2004 IHS criteria.
In agreement with MIDAS we started specific therapy using a stratified approach.
Out of 237 patients admitted to our HC with a diagnosis of PH made in our ED, 190 (63M/127F; age 35±14 years) met IHS criteria for migraine or its complications (e.g. status migrainosus and/or chronic migraine), whereas 18 subjects were affected by cluster headache. Twenty patients, (8%) of the total, were affected by secondary headaches, and of these 9 patients were classified with psychiatric disorders. Only 14% of migraineurs reported having previously seen a headache specialist before the ED visit and 90% were triptan naïve prior to coming to the ED. The percentage of ED repeaters in the population was 10%, exclusively migraineurs.
Our data confirmed that migraine represents the most frequent PH observed in an ED and that it is an under-diagnosed and under-treated pathology. A strict collaboration between the HC and the ED, would improve health care of migraineurs and reduce direct and indirect cost of migraine.
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HEADACHE IN THE EMERGENCY DEPARTMENT: THE MOST APPROPRIATE MANAGEMENT

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In most cases, patients coming to the Emergency Department (ED) complain of headache. Headache has many potential causes but in 85% of the cases the physician can correctly diagnose primary headache disorder. However, even if less frequent, the remaining 15% of headaches may represent a potential life-threatening pathology, particularly, when headache is attributed to a cranial vascular disorder such as subarachnoid haemorrhage (SAH), resulting from a ruptured saccular aneurysm [1].
We report the case of a patient with SAH who went to the ED after suffering initially from acute retroorbital headache with brain CT that excluded the presence of bleeding. Neurological examination showed no abnormalities. The patient was dismissed even though she returned to the ED the day after, presenting ptosis in her right eye. This case illustrates how inadequate management might cause serious medical and legal consequences. It also proves that the presence of a first acute, unusual headache must always lead the physician to exclude secondary headaches [2]. In particular, we should always consider the possibility of SAH, which represents the most frequent cause of acute headache with abrupt onset, though the neurological examination and CT scan may not always reveal any abnormalities [3].
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HEADACHE IN THE PAEDIATRIC EMERGENCY DEPARTMENT

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Headache in the Emergency Department is the most frequently reported phenomenon of young children involving considerable economic loss, as well as an important worsening of the quality of life of those who suffer from it. Many tests are performed and a variety of therapies are used.

In the present study with the objective of evaluating the quality of primary care for acute headaches and the therapies utilized, we examined, retrospectively, 55000 patients with a complaint of headache who sought the Emergency Room of a paediatric hospital. Of these, 1.3% presented with headache.
The etiologies of the headaches secondary to neurological disorders corresponded to less than 10% of the cases of headache that did not require patient hospitalization and even in these cases the etiology was relatively benign. Of the hospitalized patients, 51.5% had headaches secondary to neurological disorders.

HEADACHE IN CHILDREN IN THE EMERGENCY DEPARTMENT

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Introduction The medical information of the family paediatrician and the collaboration between the hospital specialist physician and family physician represent the first approach to headache in children. In fact, the family physician should identify, at first consultation, a severe headache.
Objective The aim of this study was to investigate the rate of acute headache in children presenting to the Emergency Department of a general hospital, where there was a headache department dedicated to adults and children. The period of observation was one year, from April 2003 to April 2004. Among 1532 paediatric consultations in the Emergency Department of L'Aquila Hospital, headache was diagnosed in 31 patients. After paediatric consultation, 25 patients were treated in the hospital, 4 were hospitalised, and 2 were observed for 4 hours in the Emergency Room. The causes of hospital consultation were: fever (5 cases), vomiting (2), apistaxis (1), abdominal pain (2), sinusitis (2), loss of consciousness (2), and blurred vision (1). Three patients suffering from gastroesophageal reflux, haemophilia B, and ventriculoperitoneal shunt malfunction presented to the hospital because of headache and were admitted. Three children presented headache associated with head injury. Six children were evaluated by laboratory investigations, ophthalmologic and neurosurgical consultation. CT scan was performed on 1 child and EEG on another 2 children. The causes of headache were upper viral respiratory infection (11 children), streptococcal pharyngitis (4), meningitis (1), migraine (3), ventriculoperitoneal shunt infection (1), epileptic seizures (1), and posttraumatic headache (4). Etiological diagnosis of headache was made in 80.6% of the patients, while in 19.3%, the etiology remained unknown.
Conclusions The abrupt onset of headache represents 2% of all consultations in the Emergency Department of a general hospital, 12.8% of all headaches observed in one year in the Neuropaediatrics Department, and of these, 0.2% of hospitalisations. The correct approach to headache in children can be determined in only 3.9% of investigations and in only 1 case by neuroradiological examination.

HEADACHES IN THE EMERGENCY DEPARTMENT OF A PAEDIATRIC HOSPITAL

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Objective To describe and analyse the patients observed for headache in the Emergency Department of a paediatric hospital.
Methods We retrospectively evaluated the medical records of all children attending the Emergency Department with the symptom "headache" during a period of one year (1 May 2002 – 30 April 2003). We considered age, gender, associated symptoms, physical evaluation (in particular neurological examination), use of complementary diagnostic techniques, treatment received, and outcome. Patients with previous head trauma were excluded.
Results Two hundred and fifty-six patients (1.46% of all paediatric Emergency Department visits – total number 17488) presented to the Emergency Department with headache. Mean age was 7.9 years, range between 2 and 16 years with a distribution male / female=136 / 120 (52.5% vs 47.5%). In 81 subjects (31.6%) headache was the only complaint. Fever was associated in 100 patients, vomiting in 63, nausea in 28, abdominal pain in 15, and neurological symptoms in 15 (i.e., visual symptoms, vertigo, dysarthria, paraesthesia). Others symptoms (i.e., diarrhea, abdominal pain, otitis, etc.) were less frequent. Neurological evaluation was abnormal in 5 patients. Diagnostic techniques used were ophthalmoscopic examination in 20 patients, CT scan in 6, X-ray in 4, and MRI in 1. Ninety-four patients (36.7%) were treated with analgesic medications, including acetaminophen, ibuprofen, and acetaminophen plus codeine. Fifteen patients were admitted to the hospital for further evaluation and treatment: 5 of these patients had primary headache (i.e., migraine, tension-type headache, paroxysmal benign vertigo, abdominal migraine), 8 patients secondary headache (i.e., ventriculoperitoneal shunt malfunction in brain tumor, aseptic meningitis, systemic viral or bacterial infections, hypertension in nephropathy), and 2 patients unclassifiable headache. Of the total of 256 patients, 30 patients underwent further evaluation in the headache centre of our hospital. The headache type according to ICHD-II, 2004 was tension-type headache in 9 patients, migraine in 16 patients, abdominal migraine in 2, secondary headache in 2 (i.e., ventriculoperitoneal shunt malfunction in brain tumor, ocular disorder), and unclassifiable headache in 1 patient.
Conclusions Clinical diagnosis plays a key role in the evaluation of headache disorders in a paediatric Emergency Department. The majority of the headaches are secondary to concurrent illness, and are treated with minor analgesics and no diagnostic tests are required. In a small minority of patients hospitalisation is required to perform diagnostic tests to exclude serious diagnosis (i.e., intracranial space–occupying lesion, meningitis, and vascular abnormalities).

THERAPEUTIC ASPECTS I

MULTIPLE-ATTACK STUDY ON THE TRIPTANS AVAILABLE IN ITALY

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Objective The aim of the study was to evaluate the efficacy and tolerability of the 5 triptans commercially available in Italy (Zolmitriptan 2.5 mg, Rizatriptan 10 mg, Sumatriptan 100 mg, Almotriptan 12.5 mg and Eletriptan 40 mg) and compare them to one another and to placebo.
Materials and methods The study was conducted in single-blind and of 18 months duration. At the Headache Centre of the "Agostino Gemelli Polyclinic" in Rome we selected 42 patients, suffering from headache with and without aura (IHS, 1988), whose headache frequency was between 1 and 4 monthly crises. A different triptan and placebo were taken for every 5 consecutive crises up to a total of 30 crises. After 2 hours patients could take a rescue medication if they wished to do so. The study end-points were as follows: response at 2 hours, "pain free" at 2 hours and "sustained pain free" (at 24 hours). The intra-patient consistency and tolerability were also evaluated.
Results Thirty patients completed the study and statistical analysis was only applied to these patients. No substantial differences as regards to the efficacy of the triptans were noted (some of the differences could be due to pharmacokinetics); the 5 triptans resulted superior to placebo, also in the intra-patient treatment; all triptans were well tolerated.

Conclusions These results suggest the possibility of testing different triptans in the same patient in order to identify the ideal drug for every patient.

PREVALENCE, PATTERN AND PREDICTORS OF USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) IN MIGRAINE PATIENTS ATTENDING A HEADACHE CLINIC IN ITALY

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The use of complementary and alternative medicine (CAM) for migraine is a growing phenomenon about which little is known. This study was undertaken to evaluate the rates, pattern, and presence of predictors of CAM use in a clinical population of patients with different migraine subtypes. Four hundred and eighty-one migraineurs attending a headache clinic were asked to complete a questionnaire designed to gather information on CAM use. Past use of CAM therapies was reported by 30.9% of the patients surveyed, with 17.1% having used CAM in the previous year. CAM therapies were perceived as being beneficial by 39% of the patients who had used them. The most common source of recommendation for CAM was a friend or relative (52.9%). Most migraineurs used CAM treatment specifically for headache (89.3%). Approximately 61% of CAM users had not informed their medical doctors of CAM use. The most common reason for choosing to use a CAM therapy was "potential improvement in headache" (48.3%). The patients who used CAM treatments were: those with a diagnosis of transformed migraine; those who had consulted a large number of specialists and had completed a higher number of conventional lifetime visits; those with a psychiatric comorbid disorder; those with a high income; and those in whom the headache had been either misdiagnosed or not diagnosed at all. Our findings suggest that migraine patients, in their need and search for care, seek and explore both conventional and CAM therapies. Physicians should be made aware of this patient-induced climate change in medicine so as to prevent health-care resource misuse and better meet patients' needs.

VENLAFAXINE AS PROPHYLACTIC TREATMENT OF MIGRAINE: PRELIMINARY RESULTS OF A MULTICENTRE OPEN-LABEL PROSPECTIVE STUDY

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Objective The joint effect on serotonin and norepinephrine has been considered the major reason for the effectiveness of amitriptyline (a tricyclic antidepressant: TCA) in the prophylactic treatment of migraine. Venlafaxine is a selective serotonin-norepinephrine reuptake inhibitor but is better tolerated than TCA. A retrospective study by Adelman et al. [1] showed the efficacy of venlafaxine extended release in the preventive treatment of migraine.

On this basis, we planned an open-label prospective trial to investigate the efficacy and tolerability of Venlafaxine as preventive treatment for migraine.

Materials and methods The study was designed as a multicentre open-label prospective trial involving 10 Clinical Outpatient Centres in Sicily. We planned to include 100 patients meeting the following criteria: age range, 12 to 65 years; the diagnosis of migraine according to the International Headache Society criteria; and 3 to 12 migraine attacks per month, but with 15 or fewer headache days per month during a 4 week prospective baseline phase (run-in). Depressed patients with scores greater than 15 using the Hamilton Depression Rating Scale (HDRS) were excluded.

After run-in, patients (following 7 days titration at 37.5 mg/day) were treated with 75 mg/day of venlafaxine extended release for 12 weeks. The primary outcome measure was the change in attack frequency per month as compared to baseline (run-in). Secondary efficacy measures were responder rate (proportion of patients with 50% or more reduction in monthly migraine frequency) and reductions in mean number of monthly migraine days. Effects on mood and disability were assessed by HDRS and Impact Test (IT) given after run-in and at the end of treatment.

Results Twenty-five patients have now completed the study. Amongst which, venlafaxine treatment significantly reduced attack frequency per month and mean number of monthly migraine days, with a responder rate of about 75%. IT and HDRS scores were also significantly reduced. Treatment was well tolerated and no patient dropped out; the most frequently reported side-effects were loss of weight, nausea, and dizziness.

Conclusions If confirmed, these preliminary results could support the potential efficacy of venlafaxine in preventing migraine, which is worth exploring in further controlled trials.

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EFFICACY AND TOLERABILITY OF LEVETIRACETAM AS PROPHYLACTIC TREATMENT OF MIGRAINE WITH AURA: A PRELIMINARY OPEN-LABEL STUDY

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Objective Migraine with aura with high frequency of attacks could represent a very demanding therapeutic problem. D'Andrea et al. [1] reported efficacy of the antiepileptic drug lamotrigine for treatment of this form of migraine. Levetiracetam is a new antiepileptic drug with an excellent tolerability profile. Mechanisms of action of this drug remain largely unknown, but quite recently Lukyanetz et al. [2] showed that levetiracetam is able to exert inhibitory effects on N-type calcium channels. Inhibition of N-type calcium channels in experimental animals have been shown to block propagation of cortical spreading depression in experimental animals [3].

On such grounds we evaluated the efficacy of levetiracetam as prophylactic treatment for migraine with aura in patients with high frequency of attacks.

Materials and methods We carried out a small open-label trial treating 15 patients affected by migraine with aura with a high frequency of attacks (4 or more per month). Ten patients had previously undergone other preventive treatments that proved completely ineffective. A run-in period of 1 month preceded the treatment with levetiracetam that was given for 3 months at the dosage of 1000 mg/die. The number of attacks per month was considered the major outcome measure.

Results Levetiracetam was generally well tolerated and no relevant adverse effects or dropping out were recorded. Mean number of attacks per month was reduced from 7.1±5 during the run-in period to 2±1 at

the 3rd month of treatment ($p<0.00001$). In 7 out of 15 patients, the attacks were completely abolished after 3 months of treatment.
Discussion Our results show that Levetiracetam is well tolerated and could be effective in preventive treatment of migraine with aura.
Conclusion Levetiracetam could represent a new therapeutical option in migraine with aura. Controlled trials are needed to confirm the results.
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LEVETIRACETAM IN MIGRAINE NON-RESPONDERS: AN OPEN-LABEL STUDY OF EFFECTIVENESS AND TOLERABILITY

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Antiepileptic drugs are used in the prevention of migraine and other head pains, whereas their mechanisms of action are not still completely understood. Levetiracetam seems to affect nociception by modulating GABA-mediated neurotransmission.
This drug interferes with GABA metabolism and possibly inhibits sodium ion channels and modulates activity of the N-Type calcium ion channels. The prevention of migraine could be exerted through such mechanisms as modulating the biochemical phenomena of aura or acting on the nociceptive system.
Levetiracetam has been used for a variety of pain conditions, such as trigeminal neuralgia, migraine without aura (Drake, 2001; Kursz, 2002), and chronic daily migraine.
In an open-label study on 26 cases of migraine according to IHS (International Headache Society), patients were initially treated with levetiracetam at a dosage of 500 mg/die for seven days, then dosages were titrated up by 500 mg per week to a final dosage of 2000 mg/die. The therapy took three months.
The aims of treatment were the reduction in number of migraine attacks and of analgesic consumption.
These studies indicate that levetiracetam is well tolerated by patients, reduces migraine frequency and intensity, and use of symptomatic drugs. Levetiracetam seems to have a therapeutic action in the prophylactic treatment of migraine, but more clinical trials are necessary to prove the effectiveness of the drug in these indications.

FLUNARIZINE EFFECTS ON PROPHYLAXIS AND ON OXIDATIVE STRESS IN MIGRAINE

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Objectives The calcium-channel antagonist flunarizine is largely used in migraine prophylaxis because of its effectiveness in long-term reduction of frequency, severity, and duration of the migraine attack. The prophylactic action of flunarizine is linked to the modulation of cerebral vessel tone related to nitric oxide (NO) and oxygen free radicals activity and to its powerful antioxidant properties. In this study, we investigated the prophylactic efficacy of flunarizine and whether its anti-migraine action might be ascribed to its influence on NO and oxidative markers.
Materials and methods Twenty-five subjects suffering from migraine without aura were examined. Urine samples collected 24 h before and after 6-month treatment with flunarizine (5 mg orally per day) were assayed for NO stable metabolites (NO_x) and thiobarbituric acid reactive substances (TBARS). Migraine frequency, expressed as number of attacks per month, and mean pain severity score (0: no pain; 1: mild pain; 2: moderate pain; 3: severe pain) were counted and evaluated according to past medical history during the 6 months preceding prophylactic treatment and at the end of treatment.
Results Frequency (6.84±2.43 *vs* 3.36±1.96, $p<0.005$) and severity (2.03±0.40 *vs* 1.47±0.67, $p=0.001$) of migraine attacks during flunarizine prophylactic treatment decreased when compared to those observed before treatment. Urinary TBARS were decreased after flunarizine treatment with respect to levels measured before prophylaxis (0.35±0.07 vs 0.43±0.12 μmol/mmol creatinine; $p<0.05$). No differences were observed in NO_x values in migraine sufferers before and after treatment with flunarizine (0.72±0.15 vs 0.75±0.10 mmol/mmol creatinine; $p=0.413$).
Conclusions Our results suggest that flunarizine is clinically helpful in migraine prophylaxis and in decreasing the frequency and pain severity of attacks. Flunarizine is effective in limiting oxidative reactions in migraine sufferers although useless in preventing NO-mediated vasodilation.

THERAPEUTIC ASPECTS II

DEXAMETHASONE AND AMITRIPTYLINE IN THE DETOXIFICATION OF PATIENTS WITH CHRONIC DAILY HEADACHE AND MEDICATION OVERUSE

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Introduction Chronic daily headache (CDH) is a highly invalidating pathology which affects 4–5% of the general population and which significantly interferes with the professional activity, the social life and the family life of the people affected by it. Up to 80% of patients affected by CDH excessively overuse analgesic medication.
Methods Twenty-five patients affected by "chronic daily headache with medication overuse" (Silberstein and Lipton, 1996) were admitted to the "Agostino Gemelli" Hospital in Rome for 15 days to undergo a detoxification/"wash-out" period before starting prophylactic medication. During this period, we suspended the abused medication and administered dexamethasone i.v. and amitriptyline daily.
Results The headache frequency, which was daily, or near-daily, in all patients decreased significantly during the hospital stay.
Conclusions This therapeutic scheme has proven to be useful in interrupting the chronic pattern of daily headache and in offering patients immediate relief from pain.
Discussion The efficacy of this therapeutic scheme is probably due to the effect these drugs have on the mechanisms implicated in the genesis of acute and chronic pain.

GREATER OCCIPITAL NERVE BLOCKADE IN CHRONIC MIGRAINE WITH CERVICO-OCCIPITAL LOCALIZATION: PRELIMINARY RESULTS

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Introduction Physiological and pathophysiological data showed the convergence of trigeminal and cervical afferents on neurons in the

trigeminocervical complex of the brain stem. Convergence along with sensitization of central trigeminal neurons provides a physiologic basis for the clinical phenomenon of spread and referred pain by which pain originating from an affected tissue is perceived as originating from a distant receptive field. After strong noxious inputs, nociceptive second-order neurons in the spinal cord can be subjected to a transient or long-lasting hyperexcitability to afferent stimulation. Greater occipital nerve (GON) infiltration with local anesthetics and steroids was successfully used for diagnostic and therapeutic purpose in cervicogenic headache.
Objective The aim of the study was to evaluate in chronic migraine with cervico-occipital localization the efficacy of GON blockade in stopping pain and in incrementing efficacy of preventive therapy.
Materials and methods We enrolled consecutively 10 patients affected with chronic migraine according to IHS criteria 2004. These patients were refractory to principal preventive therapies for migraine. All patients suffered from bilateral cervico-occipital distribution of pain and were submitted, at T=0, to bilateral GON blockade using lidocaine 2% (8–10 ml) and betamethasone (4 mg). Follow-up visits were done at 1 (T=1), 3 (T=2) and 6 (T=3) months. Clinical data, numeric pain intensity scale (NPIS) and Migraine Disability Assessment Scale (MIDAS) were collected and administered at every step. Informed consent was obtained from all patients.
Results At baseline our patients showed the following characteristics: (1) headache frequency (days per month): 22±7; (2) pain-killer use: 35±10; (3) NPIS score: 8±1; (4) MIDAS score: 55±9. At T=1 follow-up visit we observed a significant reduction in all clinical parameters considered (p<0.05). At T=3 follow-up visit we did not observe any significant reduction of headache frequency, pain-killer use, NPIS or MIDAS score.
Conclusions These preliminary results pointed out that bilateral GON blockade in chronic migraine with cervico-occipital localization is strongly effective in reducing pain intensity, pain-killer use, disability, and headache frequency up to one month after injection. Otherwise, this positive effect disappears at the 6 month follow-up visit. A greater number of subjects and the homogeneity of the preventive therapy started after the bilateral GON blockade will be indispensable for an accurate evaluation of the efficacy of this technique.

TIME TO DAILY HEADACHE RESOLUTION IN MEDICATION OVERUSERS

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Objective Controlled trials and guidelines for the treatment of medication overuse headache are currently not available. The aim of the present study was the evaluation of the efficacy of a therapeutic regimen of detoxification to stop the daily headache in a large sample of medication overuse headache patients.
Methods One hundred and five daily analgesic abusers (P) admitted to an inpatient Headache Unit were treated by abrupt discontinuation of overused medication and intravenous hydrating and sedative therapy with benzodiazepines for an average of 10 days [SD 3]. Symptomatic and antiemetic drugs were used only in case of severe rebound headaches. The efficacy measure of the therapeutic regimen used was the time to daily headache resolution. Follow-up lasted three months.
Results The study included 93 females (88,6%), mean age 55 years [SD 12], and 12 males (11,4%), mean age 58 years [SD 16]. The initial headaches were migraine without aura (78 P), migraine without aura and tension-type headache (12 P), migraine with aura and migraine without aura (10 P), and tension-type headache (5 P). Medication overused were: combination analgesics, 43 cases (40,9%); simple analgesics, 39 cases (37,2%); triptans, 13 cases (12,4%); and ergotamine, 10 cases (9,5%). Average time to daily headache resolution was 8 days [SD 5]. Daily headache stopped more rapidly in triptan abusers (5 days [SD 2]) than in abusers of other medications (simple analgesics 10 days [SD 6], ergotamine 10 days [SD 4], or combination analgesics 8 days [SD 5]). No correlation was found between the time to daily headache resolution, the type of initial headache, the daily drug intake duration, and the number of daily drugs taken. At 3-month follow-up all patients had reverted to a pattern of less than 15 attacks/month.
Conclusion The time to daily headache resolution in medication abusers treated with detoxification as in-patients was remarkably shorter than that indicated by IHS (≤ two months). Positive results were obtained also in patients with a prolonged overuse period and high daily drug intake. A comparison among different therapeutic strategies for the treatment of medication overuse headache is warranted.

COMBINATION OF TIZANIDINE AND AMITRIPTYLINE IN THE PROPHYLAXIS OF CHRONIC TENSION-TYPE HEADACHE: EVALUATION OF EFFICACY AND IMPACT ON QUALITY OF LIFE

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Chronic tension-type headache (CTTH) is one of the most widespread types of chronic headache. It has a particularly strong impact in terms of the individual's "Quality of Life" (QOL) and socio-economic costs. We carried out an open-label randomized clinical trial on 20 adult patients with CTTH (diagnostic criteria IHC 2004), divided them into two groups of treatment, each of 10 patients, in order to compare the effectiveness and impact on QOL of two different schemes of pharmacological prophylaxis. The first consisted in the use of amitriptyline 20 mg/d over a 3 month period, while the second proposed to combine amitriptyline with tizanidine (4 mg/d), a molecule with a faster pharmacological effect, that recent studies have shown as a promising prophylactic adjunct for different forms of chronic headache in the first 3 weeks of treatment.
In our opinion, the in-combination therapy could guarantee an improvement in QOL even in the early stages of treatment, compared with the usual utilization of only amitriptyline. In fact, as is well-known, the efficacy of amitriptyline in the prophylaxis of CTTH may be observed only after 2–3 weeks of treatment, with consequent persistency, in the first phases of therapy, of the cephalalgia and its correlated negative impact on the individual's psycho-physical condition.
Outcome measures included frequency, pain intensity, duration of headache, and the Headache Impact Test (HIT) used as QOL measures. The in-combination therapy was effective from the first month of treatment, with a significant reduction (>50%), greater than the results obtained with amitriptyline alone, in terms of frequency (-52,3% vs. -40,7%; p<0,05), intensity (-59,51% vs. -20,39%; p<0,02), and duration (-53,17% vs. -36,16%; p<0,05) of the headache. This trend was confirmed by the pattern of HIT scores which are indicators of the impact on QOL (1st month: -18,6%vs. -12,8%; p<0,05/ 3rd month -22,10 vs. -23,20; p>0,05). At the end of the 90-day treatment period, however, there were no significant differences. Further, subjective reporting by the patients showed a total degree of satisfaction, higher on average, for the group treated with both medicines. Our data suggest that the combination of tizanidine and amitriptyline is effective in guaranteeing a more rapid improvement in the headache pattern and correlated QOL rather than the use of amitriptyline alone. We therefore propose it as a possible therapeutic option in the preventive treatment of CTTH.

STEROID TREATMENT AND NEUROIMAGING CORRELATIONS IN FIVE CASES OF PAINFUL OPHTHALMOPLEGIA (TOLOSA-HUNT SYNDROME)

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Objective To evaluate the correlations between clinical evolution, neuroimaging and steroid treatment in patients (pts) affected by Tolosa-Hunt syndrome (THS).
Materials and methods We report 5 pts (3 males, 2 females, age range: 35–65 years) affected by THS according to International Headache Society (IHS) inclusion criteria. All pts underwent general, neurological, and ophthalmologic examinations, routine blood tests, serum inflammatory and infectious disease tests, autoantibodies, angiotensin converting enzyme, tumor markers and gadolinium enhancement brain MRI. Cerebral angiography and cavernous sinus biopsy were performed in 1 pt, CSF examination was performed in 1 pt.
Results In 3 pts laboratory data and neuroimaging were normal at symptom onset; high dose steroid therapy was promptly started (deamethasone, 16 mg bid i.m., tapered over 4 weeks) within 5 days from onset of symptoms. Pain disappeared within 60 hours, ocular palsies within 5 days from onset of therapy. Two other pts had cavernous soft-tissue masses on gadolinium-enhanced brain MRI and slightly increased erythrocyte sedimentation rate. Cavernous sinus mass biopsy was performed in 1 case showing non-specific inflammatory abnormalities. These 2 pts underwent high dose steroid therapy after only 1 month from the onset of symptoms and showed slow improvement with complete recovery within 2 mouths. The cavernous sinus mass disappeared after 6 months on brain MRI. All pts did not show any clinical relapse during follow-up (from 3 to 10 years, mean 6 years).
Discussion THS is a rare painful ophthalmoplegia often due to non-specific granulomatous inflammation in the cavernous sinus or superior orbital fissure. Diagnostic criteria are based on oculomotor nerve involvement, steroid responsiveness and/or demonstration of granuloma by MRI or biopsy and exclusion of other causes (tumors, vasculitis, basal meningitis, sarcoidosis, aneurysm, diabetes, and ophthalmoplegic migraine), according to IHS 2004.
Conclusions Our report confirms that steroid treatment has to be started early during the course of the disease to obtain a more rapid resolution of symptoms and signs, possibly preventing anatomical damage. MRI could have a positive prognostic value predicting steroid efficacy and clinical outcome.

HEADACHES AND THE MARFAN SYNDROME

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Marfan syndrome is a genetically transmitted disease affecting 1 person in 5000–10000 people.
Two hundred twenty-four patients' charts with a confirmed diagnosis of Marfan were reviewed at the Centre for Marfan syndrome at the University of Florence, Careggi Hospital. The diagnosis of these patients was clinically positive and corroborated by echocardiogram, MRI, eye consultation and when in doubt, by genetic studies.
Twenty-one patients were interviewed in depth by a neurologist (PH). Ninety (40%) of the patients were found to have headaches, of these 75% were consistent with a migraine syndrome and the rest were of tension-type, 75% had common migraine, and 25% suffered from classic migraine with visual auras.
None had a TIA or stroke-like accompanying syndrome. The course of headaches was essentially benign over the years with gradual improvement in most patients. Mitral valve prolapse was present in 90% of Marfan patients. This high association may partly explain the impressive frequency of migraine in this syndrome. Other features affecting the Marfan patients, such as dural cysts of the sacral spinal cord, visual impairment (dislocated lenses, high myopia, etc.), and dissection of the aorta may also contribute to and\or aggravate the headaches in these patients.
The presence of migraine in morphologically characteristic patients should alert the neurologist and the headache specialist to proceed to a complete neurovascular check-up, since an early diagnosis of this condition may avert fatal complications, such as sudden dissection of the aorta (fatal in 50% of the cases).
Genetic counselling is indicated in all patients.

SOME NEW FINDINGS IN THE PATENT FORAMEN OVALE MIGRAINE SYNDROME

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This syndrome should be of great interest to neurologists since 20% of the general population is affected with patent foramen ovale (PFO) and 15% with migraine. An unknown number of this combined group has a right-to-left cardiac shunt.
A significant percentage of this group has psychiatric disturbances, general fatigue, lack of energy, and mild continuous headaches, in addition to the well known cerebrovascular accident (CVA)-migraine complications. The response of these symptoms to conventional medical treatment or after PFO closure has not been described.
The objective of this study was to review the response of migraine and related symptoms in patients following placement of the "Amplatzer" prosthesis, which closes the PFO and arrests the right-to-left shunt.
Patients and methods Thirty-two patients underwent the transcatheter endovenous "Amplatzer" procedure for closure of the PFO. The age range was 17–70 years; mean age 40 years, and 14 were females. Assessment of their post intervention condition was made by direct interview and/or telephone follow-up.
The original reason for referral was TIA/CVA in 88%. Seventy-five percent of the patients had headaches, 58% lack of energy and chronic fatigue, and 48% psychiatric symptoms. All patients had a transesophageal echocardiography (TEE) prior to prosthesis placement, which showed a right-to-left shunt in most, after Valsalva procedure.
Results Length of follow-up was one month to five years and mean follow-up was 26 months. There was improvement or disappearance of headaches in 50% of the patients, and of psychiatric symptoms in 36%. Fifty-five percent reported improvement in general fatigue and well-being. Except for one patient none reported worsening of symptoms. One-third did not experience any changes. There was no recurrent CVA/TIA after the "Amplatzer" procedure, A subgroup of 5 patients reported "miraculous" improvement. Transient atrial fibrillation occurring during PFO closure responded to medication in one and to cardioversion in two patients. About 65% of patients were still taking medications after PFO closure mostly for related conditions. The reason for improvement in headaches, psychiatric symptoms, and decrease of fatigue is conjectural and includes control of hyperradrenalism and improvement in cerebral ischemia/hypoxemia.
Conclusion PFO closure may join the therapeutic armamentarium for management of severe migraine, with right-to-left shunt, with additional benefits to the classical ones.