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Pharmacological therapies and beyond

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Proceedings

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

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PREFACE

I am proud to present the abstract book of the 26th Congress of the Italian Society for the Study of Headaches again in this year. This supplement contains over 100 abstracts sent spontaneously by Italian researchers in the headache field, whereas the abstracts of the invited speakers represent only a minor part of this volume. All the abstracts have been peered reviewd and ranked according to the originality of the study, methodology, relevance of the results and the appropriate conclusions. The best abstracts have been choosen and will be presented in the oral communication sessions.

The scientific contributions were divided into the following categories: Clinical Aspects, Case Reports, Comorbidity, Genetics, neurophysiology and neurochemistry, Neuroimaging, Therapeutics, and Children and adolescents.

In conclusion, even though the considerably diversity of the topics warrants more attention, I would like to emphasise the generous participation of young Italian scientists, which suggests a great interest towards this argument and a good level of preparation of the participants. This interest and the importance in Italy is well documented by the publication of headache studies by Italian authors in the international literature. The present international economic situation is draining funds from the research field, particularly in Italy, but the strong will of our scientists continues to be reflected in this abstract book. SISC, on its part, is determined to continue supporting young researchers through its awards, in particular the Franco Michele Puca Award and the Enrico Greppi Award - and the Congress poster prizes, which will be maintained also this year.

Luigi Alberto Pini
President
Italian Society for the Study of Headaches
XXVI National SISC Congress

ORAL PRESENTATIONS

Lectures

"Alessandro Agnoli" Lecture

Placebo analgesia

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Introduction The placebo effect has evolved from being thought of as a nuisance in clinical and pharmacological research to a biological phenomenon worthy of scientific investigation in its own right. The study of the placebo effect and of its negative counterpart, the nocebo effect, is basically the study of the psychosocial context around the treatment and the patient, and it plays a crucial role in the therapeutic outcome.
Methods In recent years, different types of placebo effects have been analyzed with sophisticated biological tools, such as neuropharmacology, neuroimaging, and single-neuron recording from awake subjects, that have uncovered specific mechanisms at the anatomical, physiological, biochemical and cellular level.
Results Most of our knowledge about the neurobiological mechanisms of the placebo effect comes from the field of pain, whereby different neurotransmitters have been found to be involved, such as endogenous opioids and endocannabinoids in placebo analgesia and cholecystokinin in nocebo hyperalgesia. In addition, dopamine has been found to play a role as well, with an activation of dopamine receptors in the nucleus accumbens in placebo analgesia and their de-activation in nocebo hyperalgesia. Recent findings suggest that some of these mechanisms are also present in other medical conditions, like Parkinson's disease, in which placebos induce dopamine release in the striatum and changes of neuronal activity in the thalamus, subthalamus and substantia nigra.
Conclusions This recent research has revealed that these placebo-induced biochemical and cellular changes in a patient's brain and body are very similar to the biochemical changes induced by drugs. This new way of thinking may have profound implications both for clinical trials and for medical practice.

"Giovanni Lanzi" Lecture

Pain and chronic pain: an anthropology of suffering as experience and as social condition

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Introduction The medical anthropology, for decades, has paid special attention to pain, especially chronic pain.
Discussion It is difficult to give an unambiguous definition of pain, because under this label are grouped different forms and experiences. In any case, it is evident that pain appears as something with which the different human groups, in different historical periods and social contexts, have had to cope with. Pain and its culturally coded expressions, and the ways through which it is counteracted, present a huge variety.
In recent years the debate has focused mainly on pain as a human experience and on how it is linked to the social order.
With regard to the first aspect, ethnographic examples from literature, have shown how the "construction of a world of pain" is the way that allows individuals to go beyond the unspoken and unutterableness of pain. Pain does not remain at the level of inarticulate and inexpressive language, but it takes on a cultural meaning and is given a sense in the existential trajectory of individuals. The construction of an illness narrative is pivotal in this process.
With regard to the second point, I will focus on how pain, just like every disease, is a form to inscribe the social order in the body. The experience of pain cannot be seen as a mere event that pertains to the individual suffering; it is instead a phenomenon that should be studied in its historical and social dimension. It has to be studied in its historicity, since the pain, seen as a cultural experience, is a historical experience. In its social dimension, because it is shaped by social relations. Pain is a form of embodying of the social inequalities.
Conclusions From an anthropological point of view, pain can be seen as a manifold and complex phenomenon which concerns, at the same time, the individual and the society. It can only be understood as a historical phenomenon only in its contextualization in wider cultural configurations

"Franco Michele Puca" Lectures

Familial aggregation of putative biomarkers of migraine: a family-based pilot study

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Background Migraine is a recurring, episodic neurovascular disorder characterized by painful headache, as well as neurological, gastrointestinal and other somatic symptoms. Currently, diagnosis of migraine is based solely on clinical history and neurological examination, while no biomarkers of the disease exist. Different approaches have been adopted to study migraine and migraine susceptibility. In particular, several studies have been conducted to assess biochemical, neurophysiological and psychological markers. Moreover, a clear genetic risk to develop migraine occurs within the family and we hypothesize that some traits could be segregated within migraine families. Our aim was to identify three markers of migraine: 1) Calcitonin gene-related peptide (CGRP); 2) Neurophysiological measurements; 3) Individual psychological traits.
Methods We studied 10 children with migraine without aura (MO) (mean age: 9.3 years; s.d. 2.5 years) and their parents referred to our Headache Centre. Neurophysiological recording was investigated studying the visual evoked potential (VEP) habituation. VEPs were recorded in six successive blocks to test the change in amplitude of N75-P100 from the first to the sixth block (habituation). The psychological profile was made according to the CBCL/6-18 for children, YSR 11/18 for patients 11-18 years old and ASR for parents. CGRP was measured in the saliva of subjects collected during the interictal period.
Results No significant difference was found in the group when we compared the Internalizing ($p = 0.5$), Externalizing ($p = 0.3$) and Total scales scores ($p = 0.1$). Habituation was significantly lower in both patients and migraineur parents (two-way ANOVA: $p = 0.000$), than in non-migraineur par-

ents. No difference between interictal CGRP levels was found between groups on the basis of their status of migraineurs. Conversely, differences were found when statistical analysis of familial aggregation was adopted resulting in a familial clustering of levels of CGRP.
Discussion and conclusions Our results suggest a familial influence in determinants of cortical information processing in migraineurs. Again biomarkers exploring genetic background in migraine susceptibility showed a strong familial aggregation.

Could cathodal transcranial Direct Current Stimulation (tDCS) normalize the abnormal activity of glutamatergic intracortical circuits in migraine with aura?

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Introduction There is a growing belief that to solve the migraine puzzle it is necessary to reinterpret several neurophysiological findings in light of the rules of homeostatic plasticity acting in the human cortex. We recently evaluated by means of brief trains of high-frequency repetitive transcranial magnetic stimulation (hf-rTMS) mechanisms of intracortical glutamatergic facilitation in migraine with aura (MA) patients, showing hyper- and hyporesponsivity respectively at lower and higher intensity of stimulation [1]. Thus, we hypothesized on the one hand cortical hyper-responsivity and, on the other, activation of inhibitory homeostatic mechanisms of glutamate release in response to higher intensity of stimulation. If so, we expect that reducing motor cortical excitability would normalize the response of migraineurs to the 5-Hz trains. To this aim we preconditioned rTMS trains with inhibitory cathodal transcranial direct current stimulation (tDCS).
Methods In the main experiment 14 patients affected by migraine with aura received brief trains of 5-Hz rTMS to the motor cortex at an intensity of 130% of the resting motor thresold (RMT), with recording of the EMG traces evoked by each stimulus of the train from the contralateral abductor pollicis brevis (APB) muscle. This interventional protocol was preconditioned by 15 min of cathodal tDCS delivered at 1.5 mA intensity. In three supplementary experiments we evaluated: 1) duration of the after-effects induced by cathodal tDCS; 2) effect of anodal tDCS on the motor cortical response to the rTMS trains; and 3) effect of cathodal tDCS on the motor cortical response to the rTMS trains given at 110% RMT intensity of stimulation.
Results Inhibitory cathodal tDCS was able to normalize the response of the migraine motor cortex to the hf-rTMS trains given both at low and high intensity of stimulation. Conversely, excitatory anodal tDCS preconditioning did not interfere with the inhibitory response seen in the baseline condition.
Discussion and conclusions These findings can be considered somewhat specular to those of a previous study in which we showed that in healthy subjects the normal facilitatory response to the hf-rTMS trains was turned into inhibition by anodal tDCS preconditioning [2]. They support the hypothesis that abnormal regulatory mechanisms of glutamate neurotransmission could be involved in migraine cortical hyper-responsivity and contextually play a role in the homeostatic inhibitory response to a high magnitude of stimulation. Such an interpretation could account for apparently conflicting results coming from a large number of neurophysiological studies in migraine where opposite interpretations, i.e., interictal hypo- and hyperexcitability, have been raised.
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Lecture

Cost of healthcare for patients with migraine in five European countries: results from the International Burden of Migraine Study (IBMS)

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Migraine is a disabling neurological disease that affects 14.7% of Europeans. Studies evaluating the economic impact of migraine are complex to conduct adequately and with time become outdated as healthcare systems evolve. This study sought to quantify and compare direct medical costs of chronic migraine (CM) and episodic migraine (EM) in five European countries. Cross-sectional data collected via a web-based survey were screened for migraine and classified as CM (≥15 headache days/month) or EM (<15 headache days/month), and included sociodemographics, resource use data and medication use. Unit cost data, gathered using publicly available sources, were analyzed for each type of service, stratified by migraine status. Univariate and multivariate log-normal regression models were used to examine the relationship between various factors and their impact on total healthcare costs. This economic analysis included data from respondents with migraine in the UK, France, Germany, Italy, and Spain. CM participants had higher level of disability and more prevalent psychiatric disorders compared to EM. CM participants had more provider visits, emergency department/hospital visits, and diagnostic tests; the medical costs were three times higher for CM than EM. Per patient annual costs were highest in the UK and Spain and lower in France and Germany. CM was associated with higher medical resource use and total costs compared to EM in all study countries, suggesting that treatments that reduce headache frequency could decrease the clinical and economic burden of migraine in Europe. Comparing patterns of care and outcomes among countries may facilitate the development of more cost-effective care, and bring greater recognition to patients affected by migraine.
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Lecture

Nummular headache & Co.: the epicranias

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The term "epicranias" was coined by Pareja in 2003 to identify a group of painful syndromes of the head characterised by a local lesion-type pain supposedly arising from extracranial, sensitive branches of the trigeminal nerve. Local lesion-type headache is described as continuous pain having a distinct maximum in a circumscribed area of 5 cm or less, but eventually spreading to the surroundings or referring to more distant areas. The painful area is restricted to either the cutaneous territory of a pericranial nerve or the involved tissues within a focal area. In addition, signs and symptoms of neuropathic pain, such as tenderness along the course of the nerve, hypoesthesia or dysesthesia are found, indicating nerve dysfunction. Otherwise, there may also be focal discomfort or tenderness on the tissues of the affected area. Head pain syndromes stemming from extracranial structures (epicranias) can be subdivided into epicranial headaches and epicranial neuralgias. The prototypic epicranial headache is nummular headache, first described in 2002. It is characterized by head pain exclusively felt in a rounded or elliptical area, typically 1 to 6 cm in diameter. The pain remains confined to the same symptomatic area, which does not change in shape or size with time. The pain is generally mild or moderate, commonly described as oppressive or stabbing, and lasting minutes, hours, or days, with a remitting or unremitting pattern. During and between symptomatic periods, the affected area may show variable combinations of hypoesthesia, dysesthesia, paresthesia, tenderness, and trophic changes. Other epicranial headaches are: epicrania fugax, primary stabbing headache, external compression headache, trochleitis, and mucosal contact point headache. Epicrania fugax, recently reported, consists in strictly unilateral, shooting pain paroxysms starting in a focal area of the posterior parietal or temporal region and rapidly spreading forward to the ipsilateral eye or nose along a lineal or zigzag trajectory, the complete sequence lasting 1–10 s. Trochleitis is a local inflammatory process of the trochlea-oblique muscle complex with pain felt in the inner angle of the orbit, frequently extended to the ipsilateral forehead. Mucosal contact point headache is an intermittent pain localised to the periorbital and medial canthal or temporozygomatic regions promptly abolished by topical application of local anaesthesia to the middle turbinate. The group of epicranial neuralgias includes: supraorbital neuralgia, supratrochlear neuralgia, nasal nerve neuralgia, greater occipital nerve neuralgia, lesser occipital nerve neuralgia, and auriculotemporal neuralgia.

Care pathways in the management of headaches

Alcmeone Project

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The aim of the Alcmeone Project was to create a multidisciplinary structure that could further the integration of the scientific experience of a southern group of Italian physicians working in the field of headache and other functional neurological diseases. From the start, the project was conceived as a network, pooling together the human and technological resources of some of the best southern Italian university and hospital centres. The objectives of the project are pursued through a policy of divulging scientific knowledge, organizing seminars, promoting and co-ordinating the activities of external investigators who collaborate with the university and hospital centres (University/Hospital of Bari, University of Palermo, IRCCS INRCA of Cosenza, IRCCS Neurolesi of Messina, Hospital of Catanzaro, Hospital of Caltanisetta). The Alcmeone Project contributes to advancement in technology, with the development of more and more sophisticated techniques, by drawing attention to the need for closer collaboration between various university/hospital centres, each equipped with facilities that are able to deal with common scientific issues, enabling them to adopt a different, multi – integrated approach; to submit and implement projects of basic, applied and goal-oriented research; and to provide support in the scientific and research activities of public institutions on headache management. The Headache Centre of the Hospital of Catanzaro was founded in 2008 as a tertiary outpatient headache clinic. Treatment involves a multidisciplinary approach. Additional in-patient treatment facilities are available for patients with medication overuse and severe psychiatric comorbidity. The Headache Centre and the Migraine Care Regional Project cooperate with a network of primary care physicians and secondary care headache specialists. All network partners are connected with the Regional Headache Centre by specifically designed online documentation. At the Regional Headache Centre of Catanzaro the guidelines of the European Headache Federation and the Italian Society for the Study of Headaches for the organization of headache clinics have been implemented by the Region of Calabria.

CephalAid: an integrated platform of services for the optimal clinical management of headache patients

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CephalAid is an innovative technological platform of services which provides efficient and effective support for the optimal clinical management of cephalalgic and migraine patients. CephalAid contributes in developing a collaborative and cooperative environment that provides an informative and decisional support system to all the end-users involved, through the advanced integration and processing of biomedical, clinical and health care data, information and knowledge. In this way, CephalAid induces the development of innovative clinical workflow and care programmes guaranteeing continuity of care, outpatient/in-patient integration, efficient use of health care resources, and reduction of economic costs.

CephalAid is based on a new business model and related set of services in supporting the integrated clinical management of cephalalgic and migraine patients. The model designs the architecture of a new integrated care programme by defining:

- relevant health care operators with their roles and responsibilities;
- services for sustaining collaborative and cooperative interactions among health care operators;
- services for supporting, planning and operative management of all the involved health care resources;
- services for supporting integrated clinical workflows among health care environments (mainly secondary and primary care).

On this basis, the CephalAid platform concretely allows:

- to manage and effectively support all the relevant health care operators and the patients themselves, during the evolution of the diseases through several integrated health care environments;
- to provide appropriate support to make all the processes related to the clinical management of cephalalgic patients more efficient and effective through the suitable integration of advanced processing of heterogeneous biomedical data and expert feedback and care, in closed-loop systems.

Generally, improving health care quality while reducing costs requires the elimination of unintended and unnecessary overhead in the entire care process (prevention – diagnosis – prognosis – therapy). To this end, eHealth technologies and applications can play an ever greater and crucial role. In fact, during the last years we have assisted in an increasing development of high technological effective solutions (such as Electronic Health Records and Clinical Decision Support System prototypes) to foster evidence-based medicine and best clinical practices. These solutions have the potential to help reduce unreliability and errors by improving effectiveness and efficiency. Within this general context, CephalAid provides an integrated and holistic approach, based on the continuity and personalization of patient care, by devising and developing optimal health care procedures and workflows based on scientific evidence and yet consistent with best clinical practice.

Headache and chronification

Mechanism of pain chronification

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There is evidence clarifying the origin of chronic pain. Now it is well known the existence of two different kind of persistent chronic pain: nociceptive/inflammatory pain and neuropathic pain. The first, inflammation associated, is caused by tissue damage. These fibres are responsible for sensitization, recruitment of nociceptors normally silent and ionic channels and membrane receptors activation.
The activation of the immune system has a main role in both peripheral and central abnormal sensory processing. Zuo et al [1] indicated that mast cells were activated in a model of partial sciatic nerve injury. Therefore, neutrophils could have an important role in the early stage of neuropathic pain development. Several lines of evidence indicate that macrophages had a key role in the development of allodynia or hyperalgesia. Not only immune cells but also cytokines play a role in the perception and transmission of pain, for example, TNFa IL-1, and IL-6 [2].
Damaged neuron cells lose their binding with target and show a different gene expression. Some damaged fibres A with a phenotypic change express molecules normally associated to nociceptors (substance P, BDNF).
Altered gene expression of afferent intact nerves could be explained by an increasing of NGF available. Moreover, substance P and VR1, abundant in intact fibres C, are regulated by NGF. A different expression of ionic channels could contribute to explain the mechanism of spontaneous neuronal firing. The latest revealed new nociceptive mechanisms, involving molecules receptors and a neuronal network in the spinal cord and in the brain, developed after peripheral nerve injury or nerve damage. During peripheral chronic inflammation, the continuous activation of fibres C results in gene transcription alteration in the DRG and in the posterior horn neurons. Following peripheral lesion, changes in the neuron excitability and in mRNA levels in sensory neurons are substrate for chronic pain. The prolonged activity of fibres C, even if with moderate frequency, is able to induce a synaptic conduction increase in dorsal root neurons. This central sensitization has been demonstrated in many experimental models of inflammatory pain.
The importance of glutamate, substance P, neurokinin, in central sensitization has been demonstrated for their ability to prevent depolarization using antagonist of NMDA receptors in particular not competitive antagonists of NMDA receptors, which reduce nociceptive behaviour formalin induced [3]. In our study we observed after formaldehyde injection in rat lip skin, an altered releasing of GABA in the spinal nucleus of trigeminus; moreover, NO synthesis mediates the increased releasing of amino acids in the same nucleus.
The strong evidence that nitric oxide is an important mediator of hyperalgesia is in the CNS, but evidence for a peripheral action is less clear. Nitric oxide is induced in tissues during inflammation, probably through both inducible and neuronal nitric oxide synthase (iNOS and nNOS). Nitric oxide donors can induce pain in humans and NOS inhibitors can reduce inflammatory hyperalgesia in PGE2 dependent manner. The central nervous system is obviously required for pain perception, and central plasticity certainly contributes to the chronitization pain, but it is generally agreed that reversing peripheral hyperexcitability could relieve or markedly attenuate many varieties of chronic pain.

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Emerging treatment for chronic migraine and refractory chronic migraine

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Introduction CM is a progressive and worsening evolution of episodic migraine. CM may affect 1.3% to 5.1% of the global population and is the most common disorder faced by experts in tertiary headache centres. When resistant to conventional medical treatment even with prophylactic medications, this condition is defined as refractory chronic migraine (RCM) and this clinical condition represents the major challenge in headache medicine.
Areas covered The ongoing and future treatments of chronic migraine include: OnabotulinumtoxinA, antiepileptic drugs (Levetiracetam, Magnesium valproate hydrate, Lacosamide, BGG-492), 5-HT agonists (Lasmiditan, NXN-188, novel delivery systems of Sumatriptan, a well-established drug treatment for acute migraine), CGRP receptor antagonists (BMS-927711), ML-1 agonists (Ramelteon), orexin receptor antagonist (MK-6096), plant derived compound (LLL-2011) and other multitarget drugs such as Tezampanel, Tonabersat, intranasal carbon dioxide and BOL-148.
Expert opinion Unfortunately, electrical neuromodulation seems to be promising for the management of the RCM. However, medication-overuse headache (MOH) represents a harmful of both chronic and refractory chronic migraine. Reduction of MOH represents the first step for evaluating the effectiveness of new preventative approaches. This condition will allow the use of innovative drugs for acute migraine with a more personalized medicine strategy.

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Headache, drugs and hormones

Neurobiology of medication-overuse headache

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Medication-overuse headache (MOH) is a condition characterized by an increase of headache frequency to a daily or near-daily pattern [1]. This chronic disorder is associated with overuse of analgesic drugs, triptans, nonsteroidal anti-inflammatory drugs (NSAIDs) or other acute headache compounds. Patients repeated attempts to solve pain may trigger overuse of medication, even in the presence of clear negative consequences. Patients with

MOH frequently fulfil criteria for dependence on acute symptomatic treatments for pain based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders.
Different neurotransmitters might be involved in MOH. Neurobiological mechanisms underlying drug addiction and reward system such as altered endocannabinoids, dopamine and orexin systems might be involved in MOH [2]. Moreover, glutamate is implicated in cortical spreading depression, trigeminovascular activation, central sensitization, and might be linked to migraine chronification.
A dopaminergic hypothesis of migraine has been postulated and a hypothalamic involvement with a possible hyperdopaminergic state was found indeed in patients with chronic migraine overusing analgesic drugs.
The endocannabinoid system plays a role in modulating pain including headache and this system is involved in the common neurobiological mechanism underlying drug addiction and reward system mainly interacting with dopamine. An involvement of the endocannabinoid system in MOH has been outlined in clinical and experimental studies.
The orexins (hypocretins), hypothalamic neuropeptides, play a crucial role in arousal, feeding and reward. Orexin A is able to inhibit neurogenic dural vasodilation via activation of the OX1 receptor, resulting in inhibition of prejunctional release of CGRP from trigeminal neurons. Moreover, orexins could be involved in the abnormalities of feeding, sleep, and neuroendocrine functions often observed in some chronic headaches.
Finally, a possible involvement of the serotoninergic system in MOH has also been supported by clinical studies measuring serotonin content in platelets.
Both experimental and clinical studies suggest that multiple neurotransmitter systems, resembling those described in the neurobiology of drug dependence, play a role in MOH.

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Relevant issues in the classification of chronic headaches

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With respect to the International Classification of Headache Disorders (ICHD-I) 1988, the ICHD-II introduced relevant changes concerning the diagnosis of chronic forms of headache but revealed several limitations that were only partially overcome by its revised version ICHD-IIR [1, 2].
In particular, from the publication of the classification in 2004, the diagnostic criteria established by the ICHD-II for chronic migraine (CM) appeared to be ambiguous and scarcely realistic and this prompted the committee to formulate new criteria in the ICHD-IIR version. At the moment these criteria are the standard reference but still present several limitations.
The first concerns the severity gradient in CM which, in clinical practice, is so wide that there is a risk of including heterogeneous cases under ICHD-IIR diagnosis for CM. Patients who, for 3 months, have had 8 days of migraine and at least 7 days of headache with tension-type characteristics are different from patients suffering from migraine-like headache every day for years. If the former group of patients has a potential chance of improving after an adequate preventive treatment, the latter patient group in general do not respond satisfactorily to standard prophylactic therapies and need a customized, more complex treatment approach.
The minimum time limit fixed in the ICHD-IIR for the diagnosis of CM (15 days in a month for 3 months) also appears to be too short to allow its inclusion among complications of migraine. This is for example the case of migraine with a transient increase in its frequency or a transient association of medium-frequency migraine with tension-type headache as frequently observed in the natural history of patients with migraine.
The second relevant question in the ICHD-II classification is the symptomatic medication overuse, affecting the majority of patients with CM. Patients with CM who did not use drugs to block or at least relieve pain report medication overuse as a consequence of pain are in fact relatively rare. One of the main problems which needs to be resolved is to define if medication should exist as a single entity or should be more appropriately viewed as a risk factor for chronification.
The ICHD-II diagnostic criteria have been revised twice in the past few years on this issue, and those currently recognized in the ICHD-IIR for the diagnosis of medication-overuse headache (MOH) no longer require the resolution or reverting of headache to its previous patterns within 2 months after the discontinuation of overused drugs [2].
According to the ICHD-IIR, patients with a form of migraine that has progressed over the years evolving into daily or near-daily headache, with a daily or near-daily use of symptomatic drugs, should receive both the diagnoses of medication-overuse headache and probable chronic migraine.
Instead of a dual diagnosis of medication-overuse headache and probable chronic migraine, a single diagnosis of CM with medication overuse should be preferred until the patient is free of the overused drugs.
The ICHD-III, which is expected to be completed in 2013, should integrate the ICHD-IIR diagnostic criteria for CM and MOH. Some issues however need to be resolved. In particular the term of chronic attributed to migraine which is criticized because it is used in three different meanings in the ICHD-II.
The term "transformed migraine" could be preferred because less ambiguous and more indicative of such type of patients. A minimum time period for daily or near-daily headache pattern should be established. The 3-month period now used as a reference seems too short to distinguish transformed migraine from a migraine that has only a transient worsening. A 1-year period seems more appropriate.
The quantification of daily and of near-daily pattern of headache as 15 days or more also appears to be oversimplified. A more accurate statement should consider headache for 20 days or more per month, with the specification that it should be never more than 5 consecutive headache-free days. At the moment MOH is a largely arbitrary entity, and its very existence appears questionable for certain subtypes. Thus, it remains to be established if MOH should be placed in the Appendix with alternative diagnostic criteria [3].

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Drugs and progression from episodic to chronic migraine

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To prevent progression from episodic to chronic migraine with analgesic overuse it is recommended that migraine patients with severe and frequent attacks receive: 1) an effective acute treatment, and 2) early initiation of prophylaxis [1]. Unfortunately, available drugs for acute and prophylactic treatments of migraine have, just in more severe patients, limited efficacy. Twenty percent of migraine women experience migraine attacks in at least two thirds of their menstrual cycles. These attacks are more impairing, longer lasting,

and have more associated symptoms, greater severity, susceptibility to relapse, and resistance to treatment than nonmenstrual episodes. Severe and prolonged attacks are associated with the risk of becoming chronic. It follows that many of the women with chronic migraine and medication overuse who presented to headache centres suffered from menstrual episodic migraine at the onset. The strong impact of menstrual migraine on chronification is demonstrated by the fact that its improvement by hormonal therapy is related with either the conversion of chronic migraine to an episodic pattern or a significant reduction of medication overuse [2]. Yet, for this so common and serious disorder there is no specific highly effective pharmacological therapy. With prophylactic treatments only 50-65% of patients can expect a reduction of 50% of attacks. Prophylactic drugs do not significantly change the severity and length of the attacks. In addition, the choice among the drugs recommended is empirical. After a physician has prescribed, by trial and error, the third or fourth prophylactic drug without benefits, it may be too late: migraine may have become chronic and complicated by medication overuse. Actually, patients with chronic headache have a higher prevalence of the use of migraine prophylactic medications compared to those with episodic headache. Therefore, even if the advances achieved in the treatment of migraine in the last 20 years are to be appreciated, they are not yet sufficient. If they were decisive, the prevalence of chronic headache and analgesic overuse would probably decrease over time. It remains instead stable. Overall, these data indicate that more effective acute and prophylactic treatments are needed and markers of response must be identified, to allow choosing the optimal drug for the individual patient sooner. It has been suggested that chronic migraine with medication overuse is a marker of refractory. Maybe, in many patients medication overuse is a signal of the limitations of currently available drugs to treat more severe migraine.

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Migraine and hormones

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The International Headache Society (IHS) criteria describe a new entity classified as hormonally associated headaches. Serious diagnostic inconsistencies and clinical variabilities are evident, as a consequence of not well-proven scientific findings. To fulfill the criteria for exogenous hormone-induced headache, headache should begin or "markedly worsen" within 3 months of beginning exogenous hormones and "revolve or revert to its previous pattern" within 3 months of stopping exogenous hormones. On the other hand, to fulfill the criteria of estrogen-withdrawal headache, headache should develop at least within 5 days of discontinuation of estrogen used for at least 21 days and should resolve within 3 days. Such a temporal association is, however, based on anecdotal and personal beliefs and it does not take into account many variables related to reproductive biology that may be relevant to a better understanding of the role of exogenous sex hormones in migraine both during fertile life and throughout menopausal transition. In addition, the variety of hormonal products and the significant changes over time of the type and dose of molecules, as well as the availability of new routes of administration, have to be taken into account when establishing diagnostic criteria. Indeed, even though headache is the most common side effect reported in studies conducted on hormonal contraception, a clear impact of estrogen-progestin association on the course of migraine has been reported only in women referring to headache centres, especially when neurological symptoms (i.e., aura) occurred. Nevertheless, data are now available suggesting that the reduction of the estrogen-free interval (from 7 to 4 days) or the use of an extended/continuous regimen may represent successful strategies to reduce frequency and severity of migraine. On the other hand, progestogen-only contraception has been proven effective in those women presenting absolute or relative contraindications to the use of estrogen-progestin compounds, such may be the case in women with migraine, especially with aura. Finally, the transdermal route of estrogen administration at the lowest effective dose and possibly in a continuous combined regimen with progestogens may represent a suitable option to avoid exacerbation of migraine in highly symptomatic menopausal women.

Therapies "Beyond": the scientific data

Occipital nerve stimulation in chronic headache

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Neurostimulation is a branch of neuromodulation which concerns the processes and technologies of applying electrical currents of varying parameters by means of implanted electrodes in order to achieve functional activation or inhibition of specific neuronal groups, pathways or networks.
In the headache field occipital nerve stimulation (ONS) is an emerging and promising neurostimulation procedure to treat pain while improving both physical and emotional functioning of the individual. ONS procedure is used when other treatments have failed to provide long-term pain relief and the headache severely compromises the patient's quality of life since head pain is chronic and medical intractable. The mechanism of action of ONS is poorly understood. ONS is usually implanted bilaterally and transversely into the subcutaneous space nominally at or just above the level of C1. When the stimulation is turned on, sub-cutaneous tissue can conduct and propagate electrical impulses in a dermatomal and/or myotomal distribution of one or more peripheral nerves without direct nerve contact producing pain relief in the region of the electrically induced local paresthesias. However, central modulatory effects of ONS were observed both in the animal and human models: it increases metabolic activity in trigeminal nucleus caudalis and other brain areas belonging to the pain matrix. ONS was proved to be effective in chronic migraine, intractable chronic cluster headache, and hemicrania continua, reporting improvement in frequency and severity of attacks. These benefits increase with longer duration of stimulation.
In general, since its side effects profile is modest, ONS should be considered prior to any destructive procedures, such as, for instance, deep brain stimulation. Although the available data are promising, improvement of patients' selection criteria and placebo controlled trials are mandatory.

The techniques of non-invasive brain stimulation in the study and treatment of headache disorders: potentials and limitations

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Recently, neuronal mechanisms underlying cortical excitability and activation have been suggested to be dysfunctional in migraine, playing a critical role in the

pathophysiology of the disease. Together with neurophysiological studies in animal experimental models of migraine, in the last years, non-invasive brain stimulation techniques have been shown to be safe and effective tools to explore the issue of cortical excitability, activation and plasticity directly in migraine patients. Two different neurostimulation approaches are now available: one based on magnetic fields (transcranial magnetic stimulation: TMS) and the other one lying on direct electrical currents (transcranial direct current stimulation: tDCS). Moreover, TMS given in repeated pulse, repetitive TMS (rTMS) and tDCS due to their ability to perform effective modulation of cortical activity with plastic, persistent effects, have also been investigated as potential therapeutic approaches, opening an interesting perspective for both symptomatic and preventive treatment of migraine and other headache forms.

Manual therapy as a possible treatment for primary headaches

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The therapeutic management of patients with head pain is going toward a multidisciplinary approach which includes both pharmacological and non-pharmacological treatments. The reason why non-pharmacological tools have been sought resides in the limitation of drug therapies that require the risk/benefit acceptance that means biological costs, possible poor efficacy, and side effects. Unfortunately, the need for "other than pill" options has induced a certain degree of creativity leading to a wide variety of unconventional modalities to approach head pain, in the lack of controlled methods and reliable results. The multidisciplinary approach should include several types of therapies, given that there is evidence for the use for each one of them. Recent literature reports better efficacy of multimodal treatment including physical, psychological and pharmacological tools compared to pharmacological treatment alone [1]. According to the EFNS (European Federation of Neurological Societies) guidelines, manual therapy (MT) may be an effective treatment in headaches, particularly in tension-type headache [2]. Nowadays, MT, as well as other complementary therapies, is a part of the Ministry of Health programme for treating patients with several types of chronic pain.
MT is intended for maintaining the integrity of structure and functions of muscles, bones and joints, being either of them the primary location of pain or the final target [3]. It is necessary to consider MT as a possible treatment choice, alone or in association with others, after careful examination of the patient and wherever the muscle-skeletal components and functions are diagnosed as the proper sites for specific treatment. MT alone, or in association with pharmacological and psychological therapy may induce benefits on pain, if properly administered, and it should not be chosen without an adequate clinical background.
As a rehabilitation hospital, the IRCCS Fondazione Santa Lucia in order to comply with its mission, started a clinical trial to test the efficacy of non-pharmacological rehabilitation treatment, namely Osteopathy Treatment (OT), in primary headaches as an open pilot study. Up to now, among patients attending the Headache Centre, a group of patients affected by high frequency migraine without aura and receiving preventive pharmacological treatment has been enrolled for OT. Patients receive OT on a weekly basis for 5 weeks. Prior to and after OT, patients are also evaluated for psychiatric disorders in order to evaluate the role of such disorders in modulating pain.

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"Complementary and alternative" medicine in headache patients

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The attention to "complementary and alternative" medicine (CAM) has increased during the past decade both among patients and physicians. Although the attitude of the general population is often favourable, the effectiveness of these therapies remains controversial. Different CAM techniques have been applied in almost the entire domain of medicine, from pain therapy to psychiatric affections. The definition of CAM has been debated in recent years. The US National Centre for Complementary and Alternative Medicine (NCCAM) classifies CAM into five categories: mind-body medicine; natural product based therapies; manipulative and body-based practices; energy medicine; whole medical systems. There is a growing body of literature supporting the usefulness of CAM as an unconventional approach for acute and prophylactic management of headache attacks. However, what is its quality? Are we able to say that the real efficacy of CAM is established? Mind-body therapies are the most frequently used CAM techniques. Further research is needed to establish the uselfulness of CAM treatments in adults with migraine and other primary headaches and their possible role in the clinical practice.

Migraine and diet: from debunking myths to possible transitional therapy

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A close relationship between migraine and dietary aspects has been proposed by authors and patients observations, however no definitive data are available to state the existence of that relation and to understand in which way food intake could influence migraine pathogenesis. It is a matter of fact that some foods could act as triggers for migraine, but associations between certain dietary factors and the triggering of migraines are limited by the lack of prospective studies with clear experimental designs. Indeed not all migraineurs recognize the same trigger factors for their attacks: it is, for example, the case of tyramine, chocolate, alcohol or vasoactive amines.
On the other hand, a dietary restriction in migraineurs, in the context of a weight loss programme, could help them to improve their headache. Dietary restriction could interfere with some neuroendocrine parameters directly or indirectly related to migraine pathogenesis, such as serotonin or insulin release, or could improve metabolic performances by reduction of weight that indirectly improves breathing performances, heart activity, dyslipidemia and proinflammatory diathesis. Moreover, different authors proposed a relationship between migraine and binge eating disorder.
As a consequence, weight control may be very helpful in migraineurs. Recently, among different dietary strategies, the use of ketogenic diets to achieve a rapid weight loss has been proposed. This kind of diet is liable to a preferential loss of fat mass, in despite of muscle that is preserved. Irrespective to weight loss, ketogenic diets were proposed since the first decades of the last century as effective in some neurological conditions, such as, epilepsy or migraine. In fact, ketone bodies seem to improve energetic brain metabolism and modulate cortical excitability. More recently it was observed that ketone bodies could reduce progression of the cortical spreading depression and could act as neuroinflammatory modulators, inhibiting inflammation.
In the last three years, our group has acquired great experience on the clini-

cal usefulness of ketogenic diet in migraine, observing a close relationship between migraine improvement and ketogenesis instauration, but we have also ascertained the uselessness of ketogenic diet on headache improvement of overweight patients affected by chronic tension-type, cervicogenic and post-traumatic headache.
Our experience has led us to conclude that the positive effect of ketone bodies on headache is still limited to migraine.

What guidelines say

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Non-pharmacological treatments of primary headaches are useful and too often underestimated options to pharmacological treatments. Patients generally show a marked preference toward these forms of treatments, since in the majority of cases they prefer to avoid more traditional drugs.
Many different techniques can be used as non-pharmacological treatments for primary headaches, some of them belonging to traditional medicine (i.e., behavioural therapy, physiotherapy, surgery), while others to alternative medicine (i.e., acupuncture, osteopathy, chiropractic). Unfortunately, the majority of them are not supported by any demonstration of efficacy, having only been published in anedoctal reports.
The evaluation of the efficacy of all these techniques is extremely difficult for many different reasons, mainly because for the majority of them very few scientifically valid papers are available, and in any case they are extremely eterogenous, so that meta-analysis is almost impossible to be conducted on them.
Non-pharmacological treatments are described both for symptomatic and prophylactic therapy of almost every form of primary headache; they can be used alone or combined with a pharmacological therapy, a possibility that should definitely be pursued more, as the combination of the two kinds of treatments enhances the effects of the other [1].
According to the recently published Italian Guidelines for the Diagnosis and the Therapy of Primary Headaches [2], sure demonstrations of efficacy of most non-pharmacologic symptomatic treatments of primary headaches are not yet available. Transcranial magnetic stimulation was only classified for symptomatic therapy at the level of evidence B, but the large-scale use of the devices needed for it is impossible.
On the other hand, among prophylactic therapies of both migraine and tension-type headache, acupuncture and biofeedback only reached a level of evidence A. All the others techniques including surgical ones, specifically used for chronic migraine, were classified at level of evidence B or even C. In many cases because there were not enough papers to establish their efficacy. In patients with chronic cluster headache, surgical treatments may be the only worthy alternatives when medical therapy is ineffective, impossible for contraindications, or poorly tolerated. Occipital nerve and deep brain stimulation are the techniques that showed the best results, but their efficacy is still uncertain.
It is important to point out that in the last 18 months many well conducted papers on the use of different non-pharmacological treatments for the prophylaxis of primary headaches have been published, so probably in the near future the level of evidence of some of these techniques will change and it will be possible to give better indications for their use in the prophylaxis of primary headaches.

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JOINT SESSIONS

SISC-SIR: Fibromyalgia a common syndrome: diagnosis and treatment

Therapeutic approach to Fibromyalgia Syndrome

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Fibromyalgia (FM) is a chronic syndrome affecting up to 6% of the general population. It is characterized by diffuse musculoskeletal pain and tenderness, frequently associated with sleep disorder, fatigue, headache, other functional somatic syndromes, mental and physical disorders, disability and diminished quality of life. FM treatment still lacks a precise standardization, reflecting an incomplete knowledge about its pathophysiology. The most credited hypothesis about its mechanisms remains that of central sensitization, with enhanced pain transmission in the sensory compartment of the central nervous system and impaired pain descending inhibitory controls, secondary to the imbalance of various neurotransmitters (e.g., serotonin, norepinephrine, dopamine). EULAR (European League Against Rheumatism) guidelines recommend a multidisciplinary approach to treatment, including a combination of pharmacologic and non-pharmacologic interventions [2]. After discussion with the patient, treatment should be tailored based on pain intensity, function, and associated features. Tramadol is recommended for pharmacologic management of acute pain episodes (flares). Other symptomatic options may include simple analgesics (e.g., paracetamol), but corticosteroids, strong opioids and non-steroidal anti-inflammatory drugs are not recommended. For preventative treatment, antidepressants are recommended because they decrease pain and often improve function, i.e., tricyclics (especially amitriptyline), but also selective serotonin reuptake inhibitors (e.g., fluoxetine), or serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine or duloxetine). Pregabalin is the drug of choice among antiepileptics. Recommended non-pharmacologic measures include heated pool treatment, with or without exercise, and in some cases also individually tailored exercise programmes (aerobic exercise, strength training). Cognitive behavioural therapy may prove beneficial in certain patients. Based on the specific needs of the FM sufferer, also relaxation, rehabilitation, physiotherapy and psychological support can be of help. Not yet included in official guidelines, but gaining increasingly more importance in the international literature, is treatment of the so-called "peripheral or additional pain generators". FM patients who also have sources of nociceptive pain in their somatic periphery (e.g., myofascial trigger points, painful joints), or comorbid pain conditions (such as headache or visceral pains) typically present an exacerbation of their fibromyalgia pain. The phenomenon probably occurs because of an enhancement of the level of central neuronal excitability, due to the nociceptive input from the additionally affected areas. Recent studies have indeed shown that proper identification and effective treatment of these comorbid pain conditions can significantly decrease FM symptoms, allowing a dose reduction of the specific drugs to be employed for fibromyalgia treatment [1].

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Fibromyalgia and chronic headaches: biochemical evidence of shared pathophysiological mechanisms

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Fibromyalgia syndrome (FMS) is a common chronic pain condition characterized by chronic widespread pain, decreased pain threshold tenderness to palpation of tender point areas, hyperalgesia and allodynia. Comorbid conditions include fatigue, morning stiffness, non-restorative sleep, mood disturbance, irritable bowel syndrome and headache. In particular the prevalence of headache in patients with FM is high (35-88%), with migraine being the most frequent type. Furthermore chronic forms of migraine and tension-type headache show a high frequency of FM comorbidity [1].

FMS and chronic headaches share the same pathopysiological mechanisms. Central sensitization has been associated with both FMS and chronic headache (especially chronic migraine) involving dorsal horn and trigeminal nociceptive neurons and leading to transmission of altered nociceptive information to the brain. It can be maintained and also negatively influenced by behavioural, psychological, and environmental mechanisms [2].

Evidence is available in the literature which provides the biochemical basis of central sensitization in both chronic pain conditions.

A similar increase in glutamate levels in the cerebro spinal fluid (CSF) has been demonstrated in chronic migraine and FMS patients supporting the involvement of this excitatory amino acid in altered nociceptive responses underlying sustained central sensitization. Significantly higher levels of both neurotrophins and glutamate were also found in the CSF of these patients which are significantly related to glutamate levels suggesting the possibility of a NGF-mediated up-regulation of brain-derived neurotrophic factor (BDNF) associated to long-term neuroplastic changes in these two persistent chronic painful conditions. Nerve growth factor (NGF) might indirectly exert its effect through enhancing glutamatergic transmission via BDNF.

Levels of glial derived neurotrophic factor (GDNF) and somatostatin were also significantly reduced in the CSF of patients with chronic migraine and FMS. The failure of both antinociceptive regulatory molecules may favour the prevalence of NGF-mediated nociceptive effects. Furthermore reduced levels of somatostatin may be an indirect expression of impairment of the stress system in both pathological conditions.

Intrathecal elevation of cytokines and chemokines in patients affected by FMS has been interpreted by glial cell activation in response to pain mechanisms. A similar increase could be present in chronic migraine but no data are available up to now in this regard and should be investigated in future research.

Recent findings also support the involvement of a mitochondrial dysfunction and oxidative stress in the headache symptoms associated with FM.

Current pharmacological strategies are based on the emerging evidence that pain in FMS and chronic headaches is primarily related to central pain sensitization. The knowledge of pathophysiologic mechanisms underlying nociceptive and antinociceptive system abnormalities may furnish the basis for the development of new molecules which could be valuable additional tools in the treatment of these chronic pain disorders.

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SISC – SINC: The role of the neurophysiologist in cranio-facial neuropathic pain and headache

Laboratory tools for assessing cranio-facial pains

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Brainstem reflexes The International Federation of Clinical Neurophysiology and the European Federation of Neurological Societies, both recommend trigeminal reflex testing as the most useful and reliable procedure in the laboratory diagnosis of trigeminal pains [1]. The trigeminal reflexes consist of a series of reflex responses (R1 and R2 components of the blink reflex after electrical stimulation of the ophthalmic division, SP1 and SP2 components of the masseter inhibitory reflex after electrical stimulation of the maxillary or mandibular division, and the jaw jerk to chin taps) that assess function of the trigeminal afferents from all trigeminal territories, as well as the trigeminal central circuits in the midbrain, pons, and medulla. In all patients with pain secondary to a documented disease, including symptomatic trigeminal neuralgia, postherpetic neuralgia, benign tumours of the cerebello-pontine angle and multiple sclerosis, even in those patients who have no clinical signs or complaints other than pain, trigeminal reflex testing invariably demonstrates trigeminal dysfunction [2].

Laser evoked potentials The best tool for assessing nociceptive pathway function is laser stimulation. Laser-generated radiant heat pulses selectively excite free nerve endings in the superficial skin layers, activate Aδ and C mechanothermal nociceptors, and evoke scalp potentials generated by the operculoinsular cortex and cingulated gyrus. Aδ (evoking pinprick sensations) or C receptors (evoking warmth or burning sensations) can be preferentially excited by varying the area of the irradiated spot and the stimulus intensity.

The trigeminal territory is particularly advantageous for laser evoked potential (LEP) recording because of the short conduction distance and high receptor density. Trigeminal-LEPs are of higher amplitude and are recorded more easily than LEPs after limb stimulation. Trigeminal-LEPs have recently been studied in Wallenberg syndrome, classical and symptomatic trigeminal neuralgia, trigeminal sensory neuropathy, postherpetic neuralgia, temporomandibular disorders, and headache [3].

In general, in conditions that engender structural damage, such as herpes zoster, compression by tumours, or multiple sclerosis, LEPs are abnormal. In temporo-mandibular disorders, tension-type headache, or migraine, the LEP latency - though other types of abnormalities may be found - is always normal.

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The role of clinical neurophysiology in headaches: how important it is in studying their pathophysiologies

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In the past fifty years many efforts have been made to improve knowledge on primary headaches pathophysiologies. At the present these efforts, although not able to totally define all the headache facets, provide satisfactory hypotheses able to explain many aspects of these diseases. To this aim, neurophysiological techniques played a pivotal role: in migraine they helped to identify a neurophysiological behaviour common to each patient, such as the identification of reduced brain response habituation to repetitive stimuli. This behaviour was identified not only for different sensory modalities, but also at different CNS levels, as present also in stimulating both cephalic and extra-

cephalic nociceptive pathways. Other methods, such as transcranial magnetic stimulation (TMS), gave conflicting results, possibly suggesting a higher instability of cortical excitability in migraineurs than in controls. The use of both single pulse and repetitive TMS (rTMS) has been proposed to be of some help in migraine treatment.
Neurophysiological methods were used also in testing aspects of tension-type headache, leading to the hypothesis that central modulation of pain may be defective in patients affected. In cluster headache some neurophysiological studies were conducted particularly on trigeminal reflexes, but a leading role was played in refractory cluster headache treatment by neurostimulation.
In conclusion, the methods of clinical neurophysiology still offer the unique opportunity, on the one hand, to improve atraumatically our knowledge of the pathophysiologies of headaches, and to provide novel ways to treat them, on the other.

The role of clinical neurophysiology in headache: unveiling the mechanisms of drugs

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While the role of the neurophysiological techniques in differential diagnosis of primary headaches is limited, the present knowledge about the pathophysiological mechanisms has received a great contribution by clinical neurophysiology. Especially in migraine, neurophysiological examinations have also been used to understand the mechanisms of action of drugs effective in headache treatment. A few studies measured some neurophysiological parameters, such as the amplitude of the contingent negative variation (CNV), before and after triptan administration, but they did not provide definitive results. On the contrary, a higher number of studies tried to investigate the mechanisms of action of drugs used for migraine prophylaxis. The most commonly used drugs, such as beta-blockers (metoprolol), calcium-antagonists (flunarizine), antiepileptics (levetiracetam and topiramate), have been shown to improve some neurophysiological abnormalities found in migraine patients. In particular, a relationship between normalization of the brain excitability and reduction of headache attack frequency has often been described after prophylactic treatment. Unfortunately, no neurophysiological measure has been identified to discriminate the patients who respond to a prophylactic treatment from the non-responders. Future studies will have to be addressed to search for neurophysiological parameters able to predict the clinical response to a certain prophylactic drug.

SISC – SIF: The future of Italian research in headache

TRPA1 channel and activation of the trigeminovascular system

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Migraine and cluster headache have been related to the activation of specific brain areas and the trigeminovascular system, with release of calcitonin gene-related peptide (CGRP) seemingly playing a prominent role. Indeed, CGRP levels are increased in the cranial circulation during migraine and cluster headache attacks, and intravenous administration of CGRP triggers migraine attacks in migraineurs. CGRP is mainly expressed by peripheral neurons and exerts remarkable cardiovascular effects and profound arterial vasodilatation. CGRP release from sensory nerve terminals results from the activation of multiple mechanisms, including some members of the transient receptor potential (TRP) family of channels.
Peptidergic neurons are characterized by the expression of the capsaicin-sensitive vanilloid 1 (TRPV1) channel, and the mustard oil-sensitive ankyrin 1 (TRPA1) channel [1]. TRPA1 is also stimulated by cold temperatures, by a series of chemically diverse and highly reactive environmental agents and by various electrophilic natural products that covalently modify cysteine residues of the channel. This unusual activation is produced also by some endogenous mediators generated at sites of inflammation and tissue injury.
TRPA1-expressing sensory neurons release neuropeptides, including tachykinins and CGRP, from their central and peripheral terminals. In peripheral tissues, including extra- and intracranial vessels, tachykinins and CGRP produce neurogenic inflammation, which is mainly represented by plasma protein extravasation in post-capillary venules and arterial vasodilatation. The original hypothesis that neurogenic inflammation could be the main contributing factor to migraine mechanism has been strengthened by the paramount observation that two chemically unrelated CGRP receptor antagonists have shown clinical efficacy in migraine.
Recently, we demonstrated that Umbellulone, the major volatile constituent of the leaves of Umbellularia californica also known as “headache tree”, activates through a TRPA 1-dependent mechanism, the trigeminovascular system, thereby causing nocioceptive responses and CGRP release [2]. This observation is consistent with the recent report that the intranasal delivery of TRPA1 agonists, mustard oil or acrolein results in meningeal vasodilatation via a TRPA1-dependent mechanism. These findings are also consistent with the epidemiological observation that a series of agents, recently identified as TRPA1 agonists, including formaldehyde, chlorine, ammonium chloride, cigarette smoke and others, have long been known to be triggers of migraine attacks in susceptible individuals.
A similar pathway may represent the underlying mechanism responsible for headache crises triggered in sensitive people by a series of compounds present in environmental pollutants and botanical perfumes/odours.

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Cortical spreading depression: a role for CGRP receptors

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Introduction Cortical spreading depression (CSD) is a key pathogenetic step of migraine with aura. Dysfunctions of voltage-dependent and receptor-operated channels have been implicated in the generation of CSD and in the pathophysiology of migraine. Although a correlation exists between migraine and release of the calcitonin gene-related peptide (CGRP), the possibility that CGRP is involved in CSD has never been addressed. We have analysed the pharmacological mechanisms underlying CSD and investigated the possibility that endogenous CGRP contributes to this phenomenon.
Methods CSD was analysed in rat neocortical slices by imaging of intrinsic optical signal (IOS). CSD was evaluated as percentage of the maximal surface of cortical slice covered by the propagation of IOS changes during an induction episode. Reproducible CSD episodes were induced by repetitively elevating the extracellular potassium concentration.

Results AMPA glutamate receptor antagonism did not inhibit CSD, whereas NMDA antagonism reduced it. Blockade of voltage-dependent sodium channels by tetrodotoxin reduced CSD. This event was also decreased by the antiepileptic drug (AED) topiramate but not by carbamazepine. Interestingly, MK-8825, a novel CGRP-R antagonist, exerted a dose-dependent inhibition of CSD.
Discussion Our findings show that both glutamate NMDA receptors and voltage-dependent sodium channels play a role in CSD. Moreover, this phenomenon is modulated only by AEDs effective in migraine prevention such as topiramate. As a novel finding we demonstrate that CGRP antagonism reduces CSD supporting the possible use of drugs targeting central CGRP receptors as anti-migraine agents.
Conclusions This model might represent a good tool for the study of the mechanisms underlying migraine and in helping to develop preventive drugs.

Spinal Cord Stimulation (SCS) for refractory chronic pain

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Neuromodulation is an evidence-based invasive, reversible treatment which delivers an adjustable blockade to modify pain pathways and ultimately manipulate physiological function. Used routinely in chronic pain, it may be applied to virtually any neural structure including the spinal cord, deep brain structures, motor cortex and peripheral nerves. When applied as Occipital Nerve Stimulation (ONS), neuromodulation has shown to be an effective treatment for patients suffering from multiple primary chronic headaches which do not respond to conventional medical treatments.
However, the application of this technology to the severe headache patient population has still several unresolved issues which the existing published data fail to address. Previous studies have been impeded by an unacceptably high rate of technical failures, poor patient selection and lack of blinding of patients and investigators to active treatment.
The fact that a specific common neuroanatomical pathway for all cephalic afferents exists suggests that there may be a potential benefit in stimulating additional or different neural structures to enhance the efficacy of neuromodulation in chronic primary headaches. The functional continuum of the cervical extensions of the trigeminal nucleus into the dorsal horn of the high cervical region offers an operative target to neuromodulate, in a retrograde fashion, the trigemino-cervical complex. In fact, stimulation of the upper cervical spinal cord (SCS) has been recently reported as a successful treatment in patients affected by cervicogenic headache and cluster headache. With the technology available today, spinal cord stimulation seems to be less prone to lead migration or breakage compared to occipital nerve stimulation, and may decrease the high complication rate reported by previous ONS trials.
Novel technologies (different frequencies, waveforms and electrode arrangements) are also worthy of consideration. The sensation of paraesthesia produced with conventional stimulation has been a confounding factor in trials of efficacy as it prevents "blinding" to treatment. In an open-label, prospective study in patients suffering from failed back surgery syndrome, a novel high frequency spinal cord stimulation has been proven to be clinically effective without producing any paresthesia sensation, and similar results have been anecdotally reported in chronic migraine patients.

CHRNA5 polymorphism and nicotine dependence in patients with cluster headache

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Introduction Up to 90% of cluster headache (CH) patients have a prolonged history of cigarette smoking prior to headache onset. A genetic link has been suggested between CH and nicotine addiction and, also, that agents found in cigarette smoke have a direct effect on the hypothalamus, a pivotal area for the pathogenesis of CH [1].
Case-control and genome-wide association studies have reported links between single nucleotide polymorphisms (SNPs) in the alpha-5 nicotinic acetylcholine receptor subunit (CHRNA5) genes and cigarettes smoked per day (CPD).
In particular, *in vivo* studies have demonstrated that α5 subunit is involved in controlling nicotine intake, in mediating nicotine withdrawal symptoms and in affecting anxiety-related behaviour [2].
Objective To compare the presence of CHRNA5 SNP in smoking patients with CH to non-smoking patients with CH and healthy patients (control group) without a history of smoking status, all selected on the basis of sex and age.
Methods Up to date a total of 70 smoking patients (60 male, 10 female; mean age ± SD: 47 ± 11 years; male/female ratio 6:1) with cluster headache, diagnosed according to the criteria of ICHD-II, seen at the Headache and Drug Abuse Interdepartmental Research Centre and Anti-smoking Centre of Modena, underwent blood tests, after having signed a written informed consent. The samples were compared with those of non-smokers with CH and those of a control group for the research of CHRNA5 SNP.
The DNA was extracted from whole blood and polymorphism of the CHRNA5 gene was analyzed using the PCR-based restriction fragment length polymorphism method.
Results and conclusions The results are currently being processed. What we expect to find is a close correlation between CHRNA5 SNP and longer duration of the active phase of the cluster in smoking patients.
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Phenotypes of headache and facial pain

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During my experience in an internationally-recognized Headache Centre (University of California, San Francisco – Head: Prof. Peter Goadsby) I had the privilege to see unusual phenotypes of head and facial pain. I also had the opportunity to gain new perspectives on things I already knew [1]. While the latter aspect was at first more bewildering, later I also realized the importance of studying unusual cases of head/facial pain. Indeed I found the opportunity to delve deeply into these particular cases for quite distinct reasons. First, they stimulated me to draw a very detailed description of the phenotype. This aspect of practice can become impoverished by routine daily-activity and/or by an excessive confidence in the impression that we obtain from the first "picture" of the patient. Secondly, it pushed me to review the literature relating similar cases, confronting my findings and considering those of other eminent authors. Thirdly, it inspired me to formulate questions - the more fascinating part of clinical science. Indeed those questions can bring us to a better understanding of the pathophysiological mechanism of the disease -

that means to know the disease. Beside, deepening the knowledge of what is happening in the central nervous systems (CNS), unusual cases can bring us to better understand how the CNS works, also in much more common conditions - I would say "*to study the exception to prove the rule"*. To describe facial pain in a case of Parry Romberg Syndrome led me to a deeper understanding of general concepts of trigeminal neuropathic pain and trigeminal neuralgia [2], such as describing headaches in three cases of Harlequin Syndrome led me to a better comprehension of the cranial autonomic nervous system. This aspect of my experience abroad taught me that this approach – drawing a very detailed description of the phenotype keeping an eye pointed on the possible pathophysiological mechanisms of what we are observing – it is very precious and it should be always followed with every patient we encounter along our daily practice. I adopted this attitude also in the projects I have been working on: pharmacogenetics studies in migraine. Indeed I started to clinically classify the patients not just into responders and non-responders, but also into different endophenotypes (i.e., those with dopaminergic premonitory symptoms or autonomic cranial signs). I think this would be a step forward in the study of association between genotype and phenotype, clearly multifaceted and heterogeneous in the migraine population.

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COMOESTAS Symposium: Computer technology applied to chronic headache with overuse of symptomatic drugs

COMOESTAS: The project and its rationale

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The acronym COMOESTAS stands for "COntinuous MOnitoring of Medication-Overuse Headache in Europe and Latin America: development and STandardization of an Alert and decision support System" and it is the name of a project on Advanced ICT (Information and Communication Technology) for Risk Assessment and Patient Safety of the 7th Framework Programme of the European Community, with a specific aim for the transfer of European standards and technologies to Latin American countries. The project started in 2008 and it was inspired by the idea that appropriate delivery of quality healthcare requires constant monitoring of the patient during the follow-up phase, particularly in the presence of chronic diseases. This approach can be further improved if leading edge tools supporting diagnosis, as well as prediction, identification and monitoring of adverse events are available. The target chronic disease of the COMOESTAS project was medication-overuse headache (MOH) a curable disorder with a high risk of relapse [1]. During the project we developed and tested an innovative ICT system that allows MOH patients to receive continuous and personalized treatment in the post-detoxification phase [2]. The whole system is based on an advanced, "all-in-one" Alerting and Decision Support System associated with an electronic diary that follows patients from the diagnosis and supports the physician in managing the therapy, controlling relevant events impacting on patient safety and activating specific procedures if selected thresholds are exceeded. A strength of the project idea was represented by the attempt to transform the patients into a key node in the entire process (Patient-centric Health Care System), involving and empowering them in the management of their condition [3]. The research was accomplished by a Latin American-European consortium that incorporated ICT units located in Italy and Argentina, along with top-level centres for headache and pain management located in Italy, Denmark, Germany, Spain, Argentina and Chile. The project's sustainability resides in the appropriate transfer of innovative processes and the underlying technology, along with the uptake of European standards in Latin America, thanks to the adoption of the most innovative health electronic records available on the market. The ultimate goal of the COMOESTAS project is to grant the delivery of a better healthcare quality to MOH patients with an improved cost-effectiveness in this specific field.

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The results

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COMOESTAS is the acronym of an e-health project funded by the European Commission and conceived with the aim of offering an innovative approach

for the management of medication-overuse headache (MOH), a chronic and disabling disease, based on a closer electronic monitoring aid of patients. The objective of the study is to demonstrate that the proposed system may improve the management and outcome of MOH.
Using an electronic headache diary associated with an assisted diagnosis feature and an alert system we compared the Comoestas approach vs. the traditional approach.
Six hundred and sixty-three MOH patients (521 female and 142 males) were enrolled in the classic or in the Comoestas arm (365 and 298, respectively). The mean duration of chronic headache and of drug overuse was 5.25 ± 6.8 years and 4.5 ± 5.9, respectively. The majority (76.6%) of patients underwent an outpatient detoxification programme. Ninety-nine patients were lost at the follow-up visits (65 in the traditional approach and 34 in the Comoestas approach).
The primary outcomes were the number of relapses over a 6-month period and the number of cured subjects at the end of the study.
In the traditional arm the percentage of cured was 62% and of relapses was 10.6%. By contrast, in the Comoestas arm, we found, respectively, 74.3% (p 0.001) and 6.2% (p 0.05).
At months 2 and 4 after the detoxification, the number of headache days was reduced both in the traditional and in the Comoestas groups. The number of drug days was significantly lower in the group of patients that underwent the Comoestas protocol both at visit 2 (p 0.001) and at visit 3 (p 0.001).
The overall impact on daily life (evaluated with MIDAS), psychiatric comorbidity (evaluated by the Hospital Anxiety and Depression Scale) and Quality of Life (evaluated by the WQoL scale) improved after detoxification in both groups but it is noteworthy that the score reduction in MIDAS, from baseline to the final follow-up visit was in favour of the Comoestas arm (p 0.002).
Conclusions Detoxification in MOH is associated with a high rate of success: headache frequency, drugs intake and drugs days were significantly reduced in both arms. The percentage of patients cured was significantly higher in the Comoestas group with a low rate of relapse.
The constant monitoring, based on the electronic diary and on the alert system (Comoestas strategy) permits, favouring a better interaction between patient and physician, a further improvement of the MOH management.
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Italian-Lebanese Workshop

Tension-type headache pharmacological and/or non pharmacological therapy

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Tension-type headache (TTH), along with migraine and cluster headache and other trigeminal autonomic cephalalgias, is a primary headache that can occur alone or in combination with other primary headaches. The diagnosis is mandatory for any single headache since acute and preventive treatment have to be chosen accordingly. TTH is classified into three subtypes according to headache frequency: infrequent episodic TTH (<1 day of headache per month), frequent episodic TTH (1–14 days of headache per month) and chronic TTH (≥15 days per month) [1]. For all of them distinction is also made between TTH associated or not to pericranial tenderness. Treatment choice of TTH depends upon the above parameters, given that infrequent TTH events can be successfully treated with acute therapy, whereas frequent or chronic TTH calls for preventive treatments. It is crucial to avoid frequent and excessive use of analgesics to prevent the development of medication-overuse headache. Although clinical diagnosis of TTH is not difficult when the headache satisfies the recommended criteria (being also possible to make a probability diagnosis, as coded in the ICHD classification), the most difficult part of the story is represented by the need of accurate characterization of the patient (not only of the headache features) according to other conditions that may underlie, contribute, sustain or aggravate TTH. Mood disorders, anxiety, sleep disorders, muscle contraction, pericranial tender points need to be carefully sought and examined to provide the best treatment option to reduce the burden of those concomitant favouring conditions as well as head pain and interrupt the vicious circle that often stands behind TTH disability. According to treatment guidelines, in particular, the ones of the Italian Society for the Study of Headaches (Società Italiana per lo Studio delle Cefalee) being the most recently published [2], pharmacological preventive treatment is represented by antidepressants, benzodiazepines and muscle-relaxants with different levels of efficacy that should be followed as recommended by official guidelines, although patient pharmacological history and compliance should be taken into consideration before prescribing any compound. Non-pharmacological therapies are also useful alone or in combination with pharmacological preventive treatment, although scientific evidence and adequate clinical trials are not sufficient for scoring most of them as highly recommended. However, non-drug management should always be considered although the scientific basis is limited. Information, reassurance and identification of trigger factors may be rewarding. Electromyographic biofeedback has a documented effect in TTH, whilst cognitive-behavioural therapy and relaxation training most likely are effective. Physical therapy and acupuncture may be valuable options for patients with frequent TTH, but there is no robust scientific evidence for efficacy. Evidence for the use of spinal manipulation as an isolated intervention for patients with tension-type headache remains equivocal. No good evidence exists for efficacy of Botulinum Neurotoxin-A (BoNT-A) in the treatment of chronic TTH (CTTH), although it seems that the parameter efficacy should be evaluated on a long-term observation period, where it seems that BoNT-A have higher efficacy than placebo in CTTH.

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Remove mistakes for a handy diagnosis and treatment in cluster headache

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Trigeminal autonomic cephalalgias (TACs) are relatively rare but clinically well-defined primary headaches. Despite the current clear-cut diagnostic criteria (2nd edition of the International Classification for Headache Disorders - ICHD-II) and several therapeutic guidelines, errors in work-up and treatment are frequently encountered in clinical practice. Cluster headache is the most frequent headache seen in daily clinical practice in this chapter. The aim of the present contribution is to investigate all published data (English language) and case history collected by the authors in outpatient clinic with evident mistakes in diagnosis and treatment of cluster headache. Pubmed search identified 21 reports in this respect. The most frequent errors described in the management of patients with cluster headache are the following: referral errors, diagnostic delay, misdiagnosis and mismanagement using treatment without overt indication. Migraine with/without aura, trigeminal neuralgia, sinus headache, dental pain and temporomandibular dysfunction are the most frequent disorders overdiagnosed. Although facing a clear-cut clinical picture, cluster headache is frequently not recognized and/or misdiagnosed with other disorders, not only by general physicians, but also by neurologists and headache specialists. This is mostly due to the limited knowledge of specific characteristics and pos-

sible variants of cluster headache that leads to the prescription of ineffective and sometimes invasive treatments with heavy consequences on the outcome for the patients. Increasing the knowledge and the education concerning cluster headache both in primary care physicians and in headache specialists could contribute to achieving a correct diagnosis/treatment and improving the quality of life in cluster headache patients.

Drug abuse withdrawal: in-patient or outpatient protocols

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Medication-overuse headache is often difficult to treat, as successful management entails successful detoxification from analgesic drugs. This is a primary point because, even if some studies seem not to agree, preventative treatment may not be effective during medication overuse. Some protocols have been proposed, where patients should be simply advised to interrupt medication overuse in an outpatient setting, and to start a prophylactic treatment only after detoxification. In other protocols, however, some investigators proposed to immediately start a prophylactic programme during detoxification, while others suggested best outcomes for patients treated for detoxification in an in-patient setting. At the present, no evidence has been provided that one programme works better than the other in obtaining patient detoxification and in avoiding relapses; only for patients overusing opioids benzodiazepine, or barbiturates is an in-patient withdrawal therapy recommended.

ORAL COMMUNICATIONS

Preferential occurrence of migraine attacks during night sleep and/or upon awakening negatively affects migraine clinical presentation

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Introduction It is well known that migraine attacks can preferentially emerge during nocturnal sleep and/or upon awakening, requiring, like all morning headaches, an extensive and complex differential diagnosis. However, the possible implications on migraine clinical presentation still remain poorly investigated. This study was carried out in order to assess the possible implications of sleep related migraine (i.e., ≥ 75% of migraine attacks occurring during night sleep and/or upon awakening) on migraine clinical presentation (i.e., migraine related disability, severity of the attacks, consumption of symptomatic drugs), subjective sleep quality and finally excessive daily sleepiness and fatigue.
Materials and methods Two hundred consecutive patients, fulfilling ICHD-II criteria for the diagnosis of migraine without aura (2004), were enrolled at the Headache Centre of the University of Pisa. Inclusion criteria were the following: less than four migraine attacks/month in the previous 3 months, absence of any comorbid/coexisting medical condition and/or chronic medication use. Migraine related disability was assessed by means of MIDAS (Migraine Disability Assessment Score); the mean frequency of attacks per month, severity of attacks (patients had to choose the severity level of each attack using a ten-point scale) and consumption of symptomatic drugs per month were obtained according to headache diaries of the previous three months. Subjective sleep quality, excessive daily sleepiness and fatigue were evaluated by means of the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale, and the Fatigue Severity Scale, respectively.
Results Sleep related migraine was diagnosed in 78 migraine patients (39% of the total sample of migraineurs). Concerning migraine clinical parameters, monthly occurrence of migraine attacks did not significantly differ between patients with or without sleep related migraine, whereas migraine related disability ($p < 0.0001$), mean severity of attacks ($p < 0.0001$) and consumption of symptomatic drugs per month ($p < 0.0001$) were significantly higher in patients with sleep related migraine. Subjective sleep quality and excessive daily sleepiness did not significantly differ between the two groups. On the contrary, fatigue was significantly more represented in patients with sleep related migraine ($p < 0.0001$).
Discussion The results of the present study showed that patients with sleep related migraine had higher migraine related disability, severity of attacks, consumption of symptomatic drugs and higher degree of fatigue, compared to patients without sleep related migraine, supporting the hypothesis that patients with sleep related migraine represent a subset of individuals with more disabling-severe migraine attacks and with a greater impairment in terms of daily functioning, as suggested by the higher degree of fatigue.

Evaluation of a possible relationship between medication-overuse headache and potential renal dysfunctions by a proteomic study on urine samples

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Introduction Medication-overuse headache (MOH) is a chronic disorder that results from the overuse of analgesics drugs, triptans, or other acute headache compounds. Although the exact mechanisms underlying MOH remain still unknown, several studies suggest that it may be associated with the development of "central sensitization", which may cause cutaneous allodynia (CA). Moreover, the epidemiology of drug-induced disorders suggests that medication overuse could lead to nephrotoxicity, particularly in chronic patients. The aim of this study was to confirm and extend the results obtained from a previous study [1], in which we analyzed the urinary proteome of MOH patients in comparison with non-abusers, and to discover new characteristic proteomic profiles associated with MOH condition.
Materials and methods MOH patients overusing non-steroidal anti-inflammatory drugs (NSAIDs), triptans and mixtures (containing indomethacin, prochlorperazine and caffeine) were recruited by the Headache and Drug Abuse Centre of the University-Hospital of Modena and Reggio Emilia. Healthy volunteers, with a history of normal renal function, were also enrolled and used as controls. In this study we increased the number of patients and controls, and we employed further specialized proteomic techniques, namely two-dimensional gel electrophoresis (2-DE) coupled with mass spectrometry (MS), and the innovative and sensitive Surface-Enhanced Laser Desorption/Ionization Time-of-Flight mass spectrometry (SELDI-TOF-MS).
Results Urinary proteins were first separated by 2-DE and then identified by a Quadrupole-TOF Liquid Chromatography/mass spectrometer (Q-TOF LC/MS). Quantifying the protein spot intensity by the PDQuest software, we found a total of 23 differently abundant proteins in MOH patients compared to controls. Interestingly, 5 proteins (UROM, ITIH4, AMBP, RNAS2, CYTC) that were identified as differentially expressed in our previous study [1], were confirmed in this study. In addition, several novel significant changes in protein expression were revealed, such as the up-regulation in MOH patients of the Prostaglandin-H2-D-isomerase, a protein involved in the induction of CA. Furthermore, urine protein profiles were generated by SELDI-TOF-MS analysis, obtaining different and characteristic spectrum and a significantly higher number of low-MW protein peaks in patients vs. controls.
Discussion This proteomic study confirms the previous finding of alterations in urinary proteins excreted in MOH patients. Some of these proteins, identified as over-expressed particularly in NSAIDs abusers, were related to different renal dysfunctions and, probably in the development of CA.
Conclusions Proteomic analysis of urine proteins by the combination of 2-DE and MS could improve the knowledge of the pathophysiology of the MOH condition and identify early biomarkers to prevent the potential drug overuse-induced nephrotoxicity.
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The boundary between cluster headache and migraine: how to classify the patients with symptoms overlapping both disorders?

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Introduction Cluster headache (CH) is a well defined primary headache. When the attacks fulfil all but one of the criteria A-D for CH, established by the International Classification of Headache Disorders (ICHD) – 2nd edition [1], probable CH should be diagnosed. This entity requires one of the following conditions: 1) attacks lasting >180 minutes, 2) attacks without local autonomic signs or restlessness, 3) sporadic (less than one every other day) attacks. In the past "cluster-migraine" was considered an atypical variant of CH, but this entity was never categorized, not being sufficiently validated.
Materials and methods For the last 16 years we have observed 251 patients suffering from CH. Out of these cases, 33 (19 males and 14 females) could not fulfil all the criteria for CH. All the patients have been followed-up for at least 5 years.
Results In this population we could distinguish 4 different subgroups. Three subgroups could be diagnosed with CH except for: 1) duration > 3 hours, ranging 4-8 hours (6 cases), 2) absence of local autonomic signs or restlessness (5 cases), and 3) sporadic attacks, with no cluster periodicity (10 cases). We could also identify a fourth subgroup of 12 patients without cluster pattern and attacks' duration borderline between CH and migraine without aura (MO), usually lasting 3-5 hours. Moreover, the coexistence of MO and CH was noted in 8 cases.
Discussion The first subgroup overlaps with probable MO. Criteria are not fully met and patients are labelled as probable MO or probable CH, either of which could have features of the other. The second and third subgroups met criteria for probable CH. The fourth subgroup did not fulfil criteria for either probable CH or probable MO, therefore the old definition of "cluster-migraine" may be still appropriate, even if this term might be considered a regression to the time when CH was considered a variant of migraine [2]. Interestingly, 3 patients in the third subgroup evolved over time into a typical CH.
Conclusions Patients sometimes present with clinical scenarios having characteristics of both MO and CH, but either do not fully meet ICHD-II criteria for either disorder or have no sufficient symptoms and signs to allow both diagnoses to be present. These occasions provide diagnostic challenges and account for the controversial form of cluster-migraine. Patients with symptoms overlapping CH and MO likely reflect the inherent clinical variability in each of these two disorders, rather than distinct diagnostic entities.

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Acetylsalicylic acid in the prophylaxis of migraine with aura

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Objective Our study aimed to assess efficacy and tolerability of acetylsalicylic acid (ASA) in migraine with aura (MA) management, in a sample afferent to the Headache Centre of San Giovanni Battista University-Hospital of Turin.
Materials and methods For this purpose, we analyzed the medical records of 1,946 patients, consecutively presenting to our Centre in the period 1995-2007 and receiving a prophylactic treatment. The patients were divided into two groups: those who received ASA (90) and those who were treated with other therapies (106). Primary endpoint was to evaluate the improvement in MA crisis frequency in the two groups. A binary logistic regression model was used to identify possible factors associated with the positive response to treatment.
Results The mean age was 32.1 (± 9.9) in the ASA group and 36.8 (± 14.9) in the no-ASA group. Positive response to treatment (measured as a reduction of at least 50% of crises with aura) was reported by 85.6% of patients in the ASA group and 51.9% in the control group ($p < 0.001$). Multivariate analysis showed ASA, as the only variable related with a positive response to treatment (ASA Group: OR 6.26, $p = 0.006$), while there were no relationships with gender, age or type of aura.
Discussion In the past, other studies compared the effectiveness of ASA in migraine versus other prophylactic therapies, but they often considered very small samples, mixing MA and migraine without aura together. In those setting ASA appeared to be mildly effective. Our results show a large positive response to the treatment with acetylsalicylic acid, whose probability of success was about six times greater than the one associated with other therapies.
Conclusions According to our results, ASA is not only effective in the majority of MA cases, but the response is usually evident in a short time. A double-blind study with a larger sample is needed to ascertain these findings.

Nerve blocks in the treatment of chronic migraine

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Background and objectives In some people, headache is characterized by increased crisis frequency and in some of them the pattern is that of a chronic daily headache (CDH). According to the ICHD-II criteria, it could be caused by either chronic migraine (CM) or medication-overuse headache (MOH). A disorder in the head region may provoke pain in the areas innervated by the trigeminal and upper cervical nerves due to convergence of the afferent fibres of the three superior cervical roots on the neurones of the trigeminal nerve spinal nucleus. The therapeutic effectiveness of the greater occipital and supraorbital nerve blockade in chronic migraine patients with abuse of symptomatic migraine pain medication was investigated.
Methods and results Sixty-three patients (48 females, 15 males) affected by chronic migraine according to the ICHD-II criteria, were given repeated daily anesthetic blocks (once or twice a day for a five-day period). Perineural injections of 0.5 to 1.0 ml of 0.5% bupivacaine were carried out at the epicranial emergence points of the nerves in relation to the distribution of the cephalic pain only if nerves were conspicuously pain sensitive to pressure. Each patient kept a daily record of the frequency and severity of headache during the month preceding treatment, during, and at least one month after treatment. The efficacy of treatment was evaluated by the number of total migraine attacks per month, analgesic consumption per month, and the Pain Total Index (PTI), an integrated expression of the intensity and duration of the headache attacks over a month. Patients were considered responsive when the PTI decreased by ≥ 50% in the first month after treatment. Statistical analysis utilized the "one-tailed within subject *t*-test" with $p \geq 0.01$ on the PTI, on the number of the severe migraine attacks, and the number of analgesic doses. Sixty-three patients were screened, 55 were included while 8 patients were excluded. Every patient showed a significant reduction in the PTI 1 month after therapy (from 581.82 to 149.71 $p \geq 0.01$). The number of total migraine attacks per month and the consumption of analgesics per month decreased significantly as well. The treatment was without side effects in all cases [1].
Discussion and conclusions Therapeutic blockade of the greater occipital and supraorbital nerves may have resulted in inhibition of the constant trigeminal hyperexcitability characterizing headache not only by blocking the conduction of noxious stimuli, but also by blocking the antidromic flow of substance P and CGRP, mediators of the axonal reflexes that underpin

perivascular neurogenic inflammation. The consequent vasodilatation and extravasation of these peptides, local reinforcing factors of the algogenic stimulation, may have been interrupted by the anesthetic, resulting in normalization of the response threshold to the nociceptive stimuli. Inhibition of axonal transport by local anesthetic is well documented. Repeated anesthetic blocks could produce a long-lasting hypostimulation of the peripheral nociceptors, rebalancing their activation threshold and consequently arresting induction of the neuroplastic mechanism of central hypersensitization that may clinically produce chronic pain. Repeated anesthetic nerve blockade would modulate the trigeminal nociceptive onset which takes a (meaningful) part in the migraine crisis. In conclusion, the absence of side effects and the easy administration of this tecnique support the hypothesis that it may be an effective tool for the non-pharmacological treatment of chronic migraine. This clinical experience, together with a correct neurophysiological study, may be useful also in clarifying some pathogenic aspects of migraine [2].

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A CB1 agonist in the treatment of medication-overuse headache: a possible therapeutic strategy

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Backround Medication-overuse headache (MOH) is a severe burden to sufferers and its treatment has few evidence-based indications [1].
Objectives To evaluate efficacy and safety of CB1 agonist (nabilone) in reducing pain and frequency of headache, the number of analgesic intake and in increasing the quality of life of patients with long-standing intractable MOH [2].
Methods Thirty subjects were enrolled in a randomized, double-blind, active-controlled, crossover study comparing nabilone 0.5 mg/day and ibuprofen 400 mg/day, conducted at the University of Modena's Interdepartmental Centre for Research on Headache and Drug Abuse (Italy), between February 2009 and May 2010. Subjects received each treatment orally for eight weeks (first nabilone and then ibuprofen or vice versa), with one week wash-out between them. Randomization and allocation (ratio 1:1) were carried out by an independent pharmacy through a central computer system. Participants, care givers, and those assessing the outcomes were blinded to treatment sequence.
Results Twenty-six subjects completed the study. Improvements from baseline were observed with both treatments; nabilone, however, was more effective than ibuprofen in reducing the intensity of pain and the daily analgesic intake ($p < 0.05$). Moreover, it was the only drug able to reduce the level of medication dependence (-41%, $p < 0.01$) and improve quality of life scale scores ($p < 0.05$).
Conclusions Nabilone, a cannabinoid 1-receptor agonist would appear beneficial for patients suffering from MOH, primarily in reducing the intensity of pain and analgesic intake. Side effects were infrequent, of mild intensity and disappeared after discontinuation of the treatment. This is the first randomised, controlled, trial in which nabilone appeared to be safe, although larger-scale studies are required to confirm and identify the optimum treatment for these patients with intractable headache.

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Utilities of non-monothematic therapeutic approach in chronic headaches

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Objective In the therapeutic management of chronic headache [chronic tension-type headache (CTTH), hemicrania continua (HC), medication-overuse headache (MOH)], medical CAM techniques are perfectly integrated with conventional medicine in an holistic therapeutic framework.
Materials and methods Fifty patients suffering from chronic headaches from 25 to 70 years of age (47.5 +/- 21) were selected, (70% women). They were assessed using the following study criteria: average VAS > 7; NRS mean 7.12 +/- 1.55; HIT36 70 +/- 8; SAS 55 + / -7; SDS 20 +/- 6. These tests were repeated at T60 and after one year. Of these 50 patients, 25 underwent therapeutic CAM techniques only, which consisted in 10 sessions of reflexotherapy with dry needle [1] in the trigger points (TP) [2], biofeedback associated with cognitive behavioural therapy, chiropractic techniques, and posture exercises associated with an education programme to learn stretching exercises. The remaining 25 patients were treated with both CAM techniques and conventional medicine, using the same efficacy evaluation parameters. Protocol consisted of: discontinuation of drug abuse; prophylaxis with an antiepileptic drug (topiramate) to block neuronal fire; spheno-palatine ganglion block to control parasympathetic activities.
Results At T60, the group treated with CAM techniques presented a reduction of about 50% for migraine, and 60% for CTTH. The initial parameters were modified as follows: VAS 4.10; NRS 4.12 +/- 1.55; HIT36 35 +/- 8; SAS 28 +/- 7; SDS 10 +/- 6; ($p < 0.05$).
In the group treated with the integrated approach, after topiramate titration, the perceived efficacy increased from 50 to 75% with a consequent improvement of the values of the parameters: VAS 2.3; NRS 2.7 +/- 1.55; HIT36 23 +/- 8; SAS 18 +/-7; SDS 6 +/- 3; ($p < 0.03$).
Conclusions Both approaches appeared to be efficacious with the better results in favour of the integrated therapeutic approach, in terms of a reduction in headache frequency (4/month), intensity, duration, lower consumption of analgesics and a quicker drug response to the attack.
The integrated therapeutic approach disrupted the pain chronification and reversed back to an episodic pattern of headache. The effects remain unchanged after 1 year, if the therapeutic programme was respected.

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tDCs treatment: first experience in drug resistant migrainous patients with and without aura

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Introduction Transcranial direct current stimulation (tDCS), a non-invasive, neuroplasticity-generating brain stimulation tool, is increasingly used for therapeutic purposes in neurological and psychiatric diseases with pathological alterations of cortical excitability and activity such as epilepsy, stroke, migraine and depression [1].
Materials and methods Sixty randomized patients with chronic migraine, between 18 and 50 years of age were recruited from the Headache Centre of

the Istituto Clinico Città di Brescia. All the patients took topiramate 50 mg bid for four months. We excluded patients with a history of acute neurological, psychiatric or medical disease, family history of epilepsy, pregnancy, cardiac pacemaker and previous surgery involving implants in the head. In 40 of them, within 20 days after initiation of therapy, electrical (n = 20) or sham (n = 20) stimulations were performed, 20 minutes a day for 5 days.
Current stimulation was applied in accordance to the Gottingen protocols including the use of relatively large wet sponges with size nominally 25-35 cm_2 and currents of 1-2 mA applied for a duration of up to 20 minutes (resulting in charge densities of 345-960 C/m_2). Reproduction of these protocols across a wide range of applications and subjects has resulted in only isolated published reports of injury, limited to acute skin irritation under the sponges. The study included a follow-up at 30, 60, 90 and 120 days. For each patient crisis frequency, duration and intensity (VAS), headache days per month and the response to symptomatic therapy were evaluated; a list of the 5 main precipitating factors was also collected.
Results At the moment no results are available. The primary endpoint was the reduction for each patient of at least 50% of the parametres evaluated (frequency, intensity, duration and response to symptomatic therapy). Secondary endpoint was assessment of plausible decreasing threshold of cortical excitability by evaluating response to triggers.
Discussion There is increasing evidence that brainstem as well as cortical dysfunction is basically involved in the complex pathophysiology of migraine. Modified neuronal excitability may be one explanation of the effect of both pharmacological treatment and tDCS treatment [2].
Conclusions tDCS has been introduced as a non-invasive tool to guide neuroplasticity and modulate cortical function by tonic stimulation with weak direct currents. Studies involving patients affected by chronic pain confirm that five-day sessions of tDCs can produce long-lasting pain relief and our purpose is to investigate this also in patients with chronic migraine.
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High doses of methylprednisolone and verapamil in chronic cluster headache. A case report

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Introduction A short course of corticosteroids is considered the most fast acting prophylactic therapy for cluster headache (CH), rapidly suppressing attacks during the time required for the preventative agents, such as verapamil, to have effect. However, it is common experience that the current use of both drugs is often unsatisfactory. We present the case of a 62-year-old woman, affected by chronic cluster headache (CCH) (ICHD-II criteria), successfully treated with high doses of iv corticosteroids along with verapamil per os.
Case report The patient, a smoker, housewife with an unremarkable personal history, in June 2006 had an isolated cluster of 40 days duration, with 3 nocturnal and 1 daylight attacks/24 h, lasting about 60 min with circadian rhythmicity, unresponsive to NSAIDs. Headache was excruciating, stabbing, with a strictly unilateral distribution in the right supraorbital-temporal area and associated with ipsilateral ptosis, lacrimation, rhinorrhea. After 2 years, in July 2008, our patient had a second cluster. General and neurological examinations as well as brain MR with MR angiography, ECG, echocardiogram were unremarkable. Attacks were fully responsive to 6 mg sc sumatriptan; oxygen inhalation (7L/min/15 min) was ineffective. The patient was successfully treated, with complete remission within 5 days, with verapamil 240 mg/day and prednisone 50 mg/day per os for 7 days with progressive tapering over a 30-day period. In January 2009, she presented a new active phase, that became chronic with 2-8 attacks/24 h, not responsive to oral verapamil 320 mg/day neither in association with a course of prednisone administered following the schedule above. Treatments with lithium carbonate (750 mg/day) for 2 months, and then with valproic acid (1000 mg/day) for 45 days were ineffective. In June 2011 the patient was treated with prednisone 8 mg iv/day for 3 days, then 4 mg/day for 2 days, with a temporary disappearance of the attacks, which lasted 15 days. At the time of our evaluation, at the end of August 2011, she suffered 5 attacks/24 h (3 nocturnal), lasting about 20 minutes, despite taking verapamil per os 320 mg/day. The patient was admitted to DH and, upon her informed consent, was administered methylprednisolone 500 mg iv/day for 2 days, then 250 mg for 3 days, followed by prednisone 25 mg per os for 2 days with successive progressive tapering over an 8-day period. Verapamil was increased gradually to 600 mg/day. Both treatments had no relevant undesired effects. From the third day, during the following month the patient did not complain of any attack. At the end of September, she presented 1-3 nocturnal attacks/24 h of mild intensity, lasting about 15 minutes and well responsive to oxygen inhalation 7L/min/15 min. Verapamil was increased to 680 mg/day with complete disappearance of attacks in about a week. At the end of November 2011, verapamil was slowly reduced to 600 mg: the subsequent 6 days, she presented an attack every other day, of very mild intensity, lasting about 5 minutes and not requiring symptomatic therapy. During the following months, verapamil dosage was further decreased to 560 mg/day in January, to 360 in February, and to 320 since March. The patient had 3 isolated attacks like the last ones in January, one in February. At follow-up (May 21) no attacks have been reported since.
Conclusions To the best of our knowledge this is the first report about intravenous high doses of methylprednisolone associated with high doses of verapamil per os being effective in CCH. If confirmed, our finding warrants the reevaluation of the doses and timing of these drugs with appropriate clinical trials.

Cervical musculoskeletal disorders and neck pain in cervicogenic headache, tension-type headache and migraine: a diagnostic-rehabilitative pathway

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Introduction Cervical spine (CS) disorders can be correlated to different forms of headache.
Objective The aim of this study was to define a physiotherapy protocol assessment of CS musculoskeletal disorders, to verify the presence of these alterations in different types of headache so as to develop an individualized rehabilitation programme [1].
Materials and methods A bibliography research through the PubMed database was made to define the evidence of functional evaluation of CS disorders in patients with headache. We sought to establish the musculoskeletal disorders that are present in cervicogenic headache (CeH), tension-type headache (TTH) and migraine (M), with the aim to define a physiotherapy protocol assessment. This protocol included medical history, physical examination and Neck Pain and Disability Scale (NPDS-I).
The study involved the evaluation of patients with CeH, TTH and M with the defined protocol. There were two different blinded evaluations: the first one was carried out by a neurologist for headache diagnosis and the second by a physiotherapist, to establish the functional disorder of the neck. Exclusion

criteria were: pregnancy; serious mental illness; other serious illness (trauma, tumour, infectious disease); patient undergoing physical therapy; under 18 years of age; patients with multiple headaches or with modified headache; and pharmacological treatment in the last 3 months. Inclusion criteria were: patients with CeH, TTH or M who were not taking a pharmacological or prophylactic treatment in the last 3 months.
The neurological diagnosis was not revealed until after the first physiotherapy assessment to ensure blinded assessment. A control group without headache was also included.
All subjects signed a written informed consent.
Discussion Fifty-one of 54 patients with headache had cervical musculoskeletal disorders (CMD): 44 subjects had neck pain and the other 7 had CMD without pain. There were limitations in the range of motion in every type of headache. Seventy percent of patients with M presented weakness in neck muscle strength. The percentage of patients with headache who tested positive for flexion-rotation test was even higher [2]. Weakness of the deep neck flexor emerged in all patients with headache, especially in M. NPDS-I indicated the presence of disabilities from mild to severe in 68.5% of patients with migraine.
Conclusions A physiotherapy protocol assessment has been defined and tested to highlight CMD in patients with CeH, TTH and M. Patients are undergoing, as a non-pharmacologic prophylactic treatment, an individualized rehabilitative intervention trial according to the CMD identified.
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Impact of primary headaches: results from a population-based study conducted in Pavia

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Introduction Headache disorders, including migraine (M) and tension-type headache (TTH), are very common in the general population, causing personal and social disability. Notwithstanding their impact, they are underestimated, under-recognized and under-treated worldwide, while there is very little recognition of their public health impact [1]. In Italy, there are relatively few studies on the prevalence of primary headaches. We present the results of a survey conducted in the population of the Pavia province, in Italy. This study is a part of a global project conducted at the European Union level, the Eurolight Project (www.eurolight-online.eu), to analyse and measure the impact of headache disorders using a validated tool (the Eurolight questionnaire) [2].
Materials and methods The Eurolight questionnaire was distributed to a stratified sample (n = 3500) of the adult inhabitants of the Pavia province in Northern Italy, randomly selected in cooperation with the Azienda Sanitaria Locale (ASL). Of these questionnaires, 500 were returned completed correctly. The Eurolight questionnaire is divided into 103 items, including demographic and socio-economic information, diagnostic questions based on the ICHD-II criteria to identify M, TTH and medication-overuse headache (MOH), data related to treatment and management of headaches, the disability assessment, evaluation of quality of life and anxiety and depression status.
Results A total of 487 questionnaires were considered for the analysis (51% by women and 49% by men). Nearly 80% of our study population reported to suffer from headaches in their life and 91.7% had episodic headaches in the last year. MOH was diagnosed in 1.9% and up to 80% of responders suffering from headache never received a diagnosis by a doctor. About 15% had received professional advice in the last year (usually from headache specialists and primary care doctors). Only 2.4% of headache sufferers were taking preventative medication.
Almost 12% of headache sufferers reported a moderate or severe impact of headache in life, with interference of the disease in many aspects of their life (education, career and earnings, family planning and management).
Headache influenced the mood state and there was a correlation between the monthly headache frequency and anxiety or depression symptoms. In MOH patients the presence of anxiety and depression disorders was indeed very high.
Conclusions Despite primary headaches have a high prevalence in the Italian adult population, a large majority (about 80%) of affected people are primarily self-treating without receiving the advice of health professionals. Education of patients and health carers should be a high priority issue in public health.
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Case report: migraine or secondary headache?

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Case report F.G.F., a 49-year-old male, came to our attention for a neurological examination because of a pulsating headache (high-medium intensity) in the occipital region. For 20 days the headache had been daily and resistent to the most common drugs used to control symptoms (FANS and triptans).
His medical history consisted in the removal of neurinoma C5-C6 and the removal of neurofibroma (supraspinatus muscle). In 2000 he was admitted in a Neurological Department for occipital pulsating headache episodes, sometimes associated with vomiting. During hospitalization he underwent brain MR and angioMR (normal), rhachis MR (outcomes from bilateral laminectomy C3-C6; posterior discal protrusion C6-C7) and EEG (rare spike-shaped abnormalities with unspecific meaning). He was discharged with the diagnosis of "migraine", and was treated with amitriptyline for 6 months.
At neurological examination: walking with large support, mild nape rigidity. He underwent brain MR and angioMR that showed superficial siderosis in particular in the superior gutters of vermis cerebellaris and in the posterior peripons-mesencephalic area, due to previous bleeding. The patient underwent a cerebral angiography (vertebral artery aneurismatic ectasia (V4) just before the origin of the left posterior inferior cerebellar artery) and embolization of left posterior inferior cerebellar artery aneurism, occlusion of left vertebral artery, endovenous fibrinolysis of basilar artery. The patient continued complaining of a pulsating headache and was given amitriptyline with good results. After two years, he complained of a daily bilateral headache, in the parietal-occipital area, with high intensity pain, associated with vomiting and with an episode of loss of consciousness with slime and face cyanosis.

The patient underwent brain MR and angioMR again (same results of post embolization images, with cerebellar ischemic lesions). He started therapy with topiramate.
Conclusions Diagnosis of primary headaches does not have to foreclose further diagnostic exams, if they are necessary. Precautionary therapy has to be defined according to the patient's clinical and symptomatic conditions.

Epilepsy and migraine: data from the Headache Centre of Perugia

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Background Both migraine and epilepsy are chronic disorders characterized by transient and recurrent neurological symptoms. These two diseases often occur together and have a partial clinical-therapeutic overlapping. Although still incompletely clarified, the possibile existence of a link between migraine and epilepsy was for a long time under debate. Therefore, to evaluate the comorbility between migraine and epilepsy, we studied all consecutive patients attending for the first time our Headache Centre in the last year.
Methods We collected the clinical-anamnestic characteristics of migraine patients (sex, age of migraine onset, family history of migraine, subtype of migraine with or without aura - according to ICHD-II criteria [1] - subtype of aura, use of antiepileptic drugs as migraine prophylactic therapy and their effectiveness), as well as their clinical history and that of the members of the family for febrile seizures or epilepsy. Furthermore, we investigated the preictal, ictal and postictal headache [2] in epileptic migraine patients.
Results Out of 1,056 consecutive patients (79% women) 86% had migraine without aura, 5% migraine with aura (visual aura in 93% of cases) and 10% both migraine with and without aura. Febrile convulsions were referred in 2% of patients with migraine wheares a diagnosis of epilepsy was present in 4% of them. Furthermore, we found that 13% of patients had preictal haedache, while 3% had ictal haedache and 3% postictal haedache.
Discussion Our data confirm the findings of Haut et al [3] indicating that the prevalence of epilepsy in migraine patients ranges from 1 to 17% with a mean of 5.9% which is significantly higher than in the general population. In particular, the evidence of this comorbidity, does not support the hypothesis of a simple casual association but suggests a possible common pathogenic mechanism of both disorders. Ottman and Lipton proposed three alternative models to explain this comorbidity: the first is based on a simple unidirectional causal relationship, the second one takes into account the common environmental risk factors and the third one concerns common genetic risk factors. Furthermore, they proposed that a state of increased excitability of the brain may increase the risk for both migraine and epilepsy. This hypothesis is further supported by the efficacy of some antiepileptic drugs also in migraine.
Conclusions Migraine and epilepsy share several characteristics, including specific clinical features, overlapping therapeutic options and similar pathophysiological mechanisms. Both epilepsy and migraine are the most prevalent disorders seen not only by neurologists, but also by general practitioners. The latter must therefore be aware of the migraine/epilepsy comorbidity, its clinical spectrum, and its treatment.
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Psychiatric comorbidity and its relation with accompanying symptoms in headache patients

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Objective Previous personal studies have shown that in migraine patients the prevalence of generalized anxiety disorder (GAD) and depression increases when headache becomes chronic and that it is associated with an increased tenderness of the cranio-cervical-facial muscles and with an increased burden of accompanying symptoms [1, 2]. Our purpose was to evaluate the prevalence of psychiatric comorbidity, muscle tenderness and other accompanying symptoms along with headache, neck and shoulder pain in a working community and to assess the effectiveness of a cognitive behavioural programme on these variables.
Methods In 661 employees a psychological assessment was performed to investigate the prevalence of GAD and depression, muscle palpation of pericranial muscles was carried out and a Muscle Tenderness Score (range 0-3) was calculated. Furthermore, the presence of behavioural or somatic symptoms, was investigated with a semi-structured interview, using a checklist of 21 items. All subjects were given a diary for the day-by-day recording of presence and severity of headache and/or of neck and shoulder pain. The subjects were divided into two groups: a study group and a control group. After two months from baseline the study group received a physical and educational intervention, consisting of relaxation and posture exercises and use of visual feedback. Differences between groups at the baseline and after six months were statistically evaluated (Student's *t* and logistic models).
Results At the baseline and after six months the prevalence of GAD in the study group was 25.5 and 21.3%, respectively, and in the control group 25.0 and 28.0%. The prevalence of depression in the study group was 15.1 and 11.2% and in the control group 14.1 and 13.8%. At the baseline and after six months mean Muscle Tenderness Score in the study group was 0.45 and 0.31, in the control group 0.48 and 0.58 ($p < 0.001$). After six months the probability of the presence of psychosomatic symptoms was significantly lower in the study group (OR 0.69, 95% CI 0.56-0.85) with respect to the control group. After six months headache of any type and cervical pain were significantly reduced in the study group but not in the control group.
Conclusions In a large, unselected, working population with headache and/or cervical pain the prevalence of psychiatric comorbidity, GAD in particular, is relatively high and is frequently associated with increased muscle tenderness and a high number of physical and psychological accompanying symptoms. A cognitive behavioural programme is effective in reducing the burden of these problems.
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Headache and fibromyalgia: a relevant factor for treatment efficacy?

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Introduction Primary headache patients frequently present with fibromyalgia (FM) [1], a chronic widespread pain syndrome [2]. Chronic tension-type headache and chronic migraine are the headache types most involved in FM comorbidity, characterized by pericranial tenderness, sleep disorders, anxiety and poor quality of life [1].
Objective The aim of the present study was to evaluate the outcome of preventive therapies for primary headaches in light of fibromyalgia comorbidity in a large cohort of headache patients observed in 9 headache centres located in the Puglia region.
Methods The study design was based on the inclusion of outpatients with primary headaches, diagnosed according to the International Headache Society criteria, in a database located in a reserved area included in a public website (www.cefaleepugliabasilicata.it). All cases were evaluated, according to criteria in de Tommaso et al [1]. Patients reporting an average headache frequency ≥ 4 days/headache/month were assigned to preventive treatment, according to most validated guidelines. In addition, complementary treatments with vitamins PP and B6 and L-tryptophan were suggested when patients did not give their consent to preventive drug taking.
Results A total of 430 patients were included, starting from February 2011 up to April 30th 2012. One hundred and forty-one patients were also evaluated after three months of preventive treatment. They were 54 patients suffering from migraine without aura (MO), 3 patients suffering from migraine with aura (MA), 14 from both migraine types (MA+MO), 40 with chronic migraine (CM), 20 with chronic tension-type headache, and 10 with episodic tension-type headache. Thirty-six of these patients shared FM comorbidity. Propranolol was used in 20 patients, flunarizine in 27 patients, topiramate in 40 patients, valproate in 20 patients, amitriptyline in 20 patients, complementary treatment in the remainder of the patients. Independently from diagnosis and the drug used, FM patients presented with a poorer outcome after three months of preventive treatment, with 15 ± 9.3% of headache frequency reduction, compared with 42 ± 12.3% in non FM patients. In particular, the headache frequency reduction rate in FM patients was negatively correlated with fibromyalgia severity and pain at tender points
Discussion These preliminary results may suggest that FM exerts a negative effect on the efficacy of preventive treatments in primary headaches. The assessment of symptoms of widespread pain may potentially improve therapeutical management, verifying the best options for this invalidating associated syndrome.
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Prevalence of headache in an elderly population. Data from a pain centre

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Introduction Although the incidence and prevalence of headaches generally show a decrease in the elderly, headache still represents a diagnostic and therapeutic problem related to several factors. In fact, comorbidity and secondary types represent about 34% of headaches in the elderly, while primary types account for 66% of cases [1]. In this study we report the prevalence of headaches in a sample of patients over 65 years of age, who visited our Centre for pain management from 2003 to 2012.
Materials and methods We retrospectively analyzed medical records of 438 patients over 65 years of age, who visited our Centre from 2003 to 2012. Diagnosis was made according to ICHD-II criteria.
Results From 2003 to 2012, 2,294 patients with headache come to our Centre. Of these, 438 (19.1%) were ≥ 65, 70.7% were female. Primary headaches affected 50.2% of the patients, secondary forms 43%, and unclassifiable forms represented 6.8% of cases. Among primary forms, chronic headache (25%) showed the highest prevalence, followed by infrequent and frequent episodic tension-type headache and migraine without aura (both 15%). Essential trigeminal neuralgia represented 13% of cases. The remaining 30% of cases consisted in migraine with aura, chronic migraine, tension-type chronic headache + chronic migraine, hypnic, TACs and atypical facial pain (all with 5% prevalence). Among secondary forms the most frequent was the cervicogenic headache (30%), followed by the trigeminal neuralgia (12% due to neurovascular conflicts, 7% due to post – herpetic neuralgia); central pain cases were very frequent (11%) (due to peripheral, post – ischemic events, etc.). Temporal arteritis headache and headache due to abuse of drugs showed the same prevalence (8%). The remaining 24% consisted in: intracranial neoplasms (7%), from an adverse drug reaction (5%), systemic diseases (7%), other neuralgias 4%, post-dural neuralgias (3%), and sinusitis (1%). Unclassified forms represent 6.8% of all cases.

Total Headache

Diagnosis	Patients		Mean age
Primary	220	(50.2%)	71.2 ± 5.6
Secondary	188	(43%)	76.1 ± 6.4
n. c.	30	(6.8%)	81.4 ± 4.6

Discussion In our sample, secondary headaches showed a higher prevalence (43%) compared to that found in other studies [2]. This is probably due to the medical setting under study: a geriatric pain management centre, with elderly patients frequently suffering from chronic and/or neuropathic pain.
Among primary headaches, prevalence of chronic headaches (tension or tension and migraine together) was outstanding. Most of them occurred before 45 years of age, and then became chronic; moreover, 70% of chronic headaches were related to other issues, such as mood disorders, fibromyalgia, hip arthropathy, and cognitive disorders. Trigeminal neuralgia showed almost the same prevalence observed in other studies representing the most frequent type in elderly. The number of unclassified headaches was high (6.8%).
Conclusions Headaches in the elderly are certainly still a diagnostic and therapeutic issue for many and obvious reasons. Difficulty in constructing a temporal pattern of headache, polytherapy, comorbidity, difficulties in keeping a headache diary, failure to decribe symptoms, are just some of the reasons contributing to this issue. For these reasons a multidisciplinary, multimodal approach would be useful.
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Prevalence of KCNK18 (TRESK) gene mutations in a population of Italian migraine with aura patients

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Introduction Migraine with aura (MA) is a debilitating neurovascular disorder characterized by recurrent headache attacks associated with transient and reversible focal neurological symptoms. Recently, a frameshift mutation (F139Wfsx24) in the *KCNK18* gene, segregating perfectly with typical MA

phenotype, was reported in a large multigenerational pedigree [1]. *KCNK18* gene codes for TRESK, a member of the two-pore domain (K2P) family of potassium channels involved in the control of cellular electrical excitability. Functional analysis revealed that the F139Wfsx24 mutation causes a complete loss of TRESK function. This therefore highlighted *KCNK18* as a potentially important candidate gene and suggested that TRESK dysfunction might play a possible role in the pathogenesis of migraine with aura. Additional screening for *KCNK18* mutations in unrelated sporadic migraine patients also identified a number of other missense *KCNK18* gene variants (R10G, A34V, C110R, S231P and A233V). These mutations, however, showed different effects on TRESK function [2]. The purpose of this study was to evaluate the frequency of *KCNK18* gene variants in a large dataset of Italian migraine with aura patients.

Materials and methods We collected DNA samples from a group of 265 MA patients (80 men, 185 women, mean age ± SD: 38.34 ± 13.16 yrs) recruited at the Headache Centres of the Department of Neurology of the University of Turin and Istituto Clinico Città di Brescia. Diagnosis of MA was performed according to ICHD-II criteria. We analyzed the *KCNK18* (10q25.3) gene by direct genomic sequencing of all three coding exons and intronic-exonic boundaries.

Results We identified five genetic variants (G10R, C110R, Y163Y, S231P, F372L) in the coding regions and one genetic variant (c352 + 24 C>T) in the intronic region of the *KCNK18* gene in 13 MA patients. Three of these variants have already been published while three are new. *In silico* analysis suggested a pathogenetic role for two of these variants.

Discussion and conclusions Our study confirmed the presence of *KCNK18* gene mutations in migraine with aura patients. Genetic variants in the examined gene were present in approximately 5% of our dataset. In addition, we extended the list of genetic variants found in migraine with aura patients reporting two new mutations. However, the significance of the observed mutations in the *KCNK18* gene and the effects on TRESK function deserve additional studies.

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Cross-modal, sound-induced flash illusions are reduced in migraine and can be restored by cathodal inhibitory direct currents stimulation of occipital cortex: pathophysiological implications

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Introduction "Sound-induced flash illusion" represents one of the most powerful examples of cross-modal illusory phenomenon highlighting the role of modulation and interaction of sensory modalities in the generation of multisensorial percepts [1]. When a single flash is accompanied by two auditory beeps, the single flash is perceived as two flashes ('fission' illusion), on the other hand a "fusion" illusion occurs when a single beep causes the fusion of a double flash stimulus. Mechanisms underpinning such illusory perception are still unknown, but through the technique of transcranial direct current stimulation (tDCS), they have been shown to critically depend on the excitability level of the visual and temporal cortices: indeed anodal activating tDCS over occipital cortex and cathodal inhibitory tDCS of temporal cortex can disrupt the illusion [2]. In a previous study we observed that patients with migraine (with and without aura) examined both during attack and interictally showed reduced ability to perceive the illusions and we interpreted these results as due to a condition of visual hyperexcitability. On such basis, in the present study, we explored the idea that if reducing cortical excitability through cathodal tDCS over occipital cortex could normalize perception of sound induced flash illusion in migraineurs.

Methods Patients: 18 (14 F; mean age 32.11 ± 11.65 years) migraine patients [9 without aura (MO) and 9 with aura (MA)] were examined in the interictal phase and compared with 24 neurologically unimpaired, age- and sex-matched participants. The experimental paradigm for studying the illusion consisted of 1-to-4 or white filled circles presented in the centre of a black screen in isolation, or preceded by 1 to 4 beeps in different combinations [2]. It was performed at baseline and after real and sham cathodal tDCS stimulation with the following parameter (site: occipital cortex; intensity: 2 mA; duration: 10 min)

Results MO and MA patients showed less illusion with respect to healthy controls at baseline; after real cathodal stimulation but not after sham and occipital tDCS, a significant increase of illusory phenomena was observed in MA but not in MO patients.

Conclusions MA and MO patients perceive less illusions, similarly to what was observed by Bolognini et al [2], after increasing visual cortical excitability (through anodal tDCS) in healthy controls. Cross modal illusion can be restored in MA patients reducing excitability by cathodal tDCS. Taken together these findings suggest a condition of increased ictal and interictal visual cortical excitability in migraine that could be reverted by cathodal tDCS, at least in MA.

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Childhood periodic syndrome and headache

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Introduction The association between periodic syndrome (PS) and primary headache disorders has long been known, and should be considered, in its various forms, a chapter of migraine [1]. The presence of PS was found to influence the clinical course in young patients suffering from headache.

Materials and methods Three hundred and sixty-six headache patients, aged between 3 and 16 years, 169 M and 197 M, represent the study sample. The presence of PS and the diagnosis of headache were formulated according to the ICHD-II criteria. For each patient features of the crises, headache intensity, frequency and use of drugs were evaluated. A family history for headache and psychiatric disorders were considered. The Child Behaviour Checklist and Youth Self-report questionnaires were administrated.

Results One hundred and seventy-nine patients (48.9%) appeared to have migraine without aura (MO) (90 M and 89 F), 91 (24.8%) frequent episodic tension-type headache (FETTH) (43 M and 48 F), 49 (13.4%) migraine with aura (27 M and 22 F), and 47 (12.8%) chronic daily headache (CDH) (12 M and 35 F). Patients with PS were 313 (85.5%) without significant differences between male and female. RAP is the symptom most often depicted in the PS (54.6%), especially in the group of MO and FETTH. Family history of headache was present in 87.1% with predominance in the patients with PS. Family history of psychiatric disorders was higher in patients with PS (36 vs.

15% of patients without PS) and was prevalent in the CDH and FETTH (45.3 and 40.3%). Intensity and frequency of headache crises were reported very high in the sample of children without PS: the intensity of pain was medium-high in 79.8% of patients with PS complaints vs. 73.5% of children without PS. Monthly frequency of headache was prevalent (35.8%) in PS, meanwhile it was mainly multi-week (38%) in children without PS. Patients with PS (37.2%) had a positive score for internalizing and externalizing disorders, in comparison with patients without PS (20%). In children older than 11 years this positivity decreased to 22.5%.

Discussion The presence of PS influences the diagnosis of headache and the characteristics of the headache crises. The different trend of familiarity for headache and psychiatric disorders in patients with PS is noteworthy, as if the PS could represent an additional risk factor in individuals who already have a genetic imprinting [2].

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Medication-overuse headache in children and adolescents: a study in a clinical population

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Introduction Studies on medication-overuse headache (MOH) regarding adults are increasing in the literature, but still few consider children and adolescents. Our study intended to establish the prevalence of MOH in children and adolescents seen in our Centre, given that, to the best of our knowledge, there are no published papers examining this topic in the Italian population.

Materials and methods We collected data from all 118 children and adolescents consecutively seen for the first time in our third level Child Neuropsychiatry Unit for headache in 2011.

We studied correlations between age of onset, sex, age at first contact, headache type, presence of chronic daily headache (CDH), pain frequency and severity, and presence of MOH according to diagnostic criteria defined by Olesen et al [1]. Data were analyzed using SPSS 15 for Windows. Student's *t*-test, Pearson's Chi Square and Mann-Whitney's test (with a stepwise approach to reduce the risk of Type I errors due to the number of tests performed) were used to assess statistical correlations as appropriate.

Results Criteria for a diagnosis of CDH were fulfilled by 53 patients (44.9% of the whole sample). The prevalence of medication overuse in this subgroup was 20.8%. After drug withdrawal, at a 2-month follow-up, 5 out of 11 patients (45.4%) reported a significant improvement: they had a more than 50% reduction of headache frequency.

No statistically significant correlation was found between the presence of MOH and age of onset, sex, age at first contact, headache type, pain frequency, and severity.

Discussion and conclusions Our data showed that up to 20.8% of children with a highly frequent headache are at risk of getting worse due to inadequate treatment, resulting in medication overuse. This is surprising considering that previous studies did not show a role for medication overuse in the etiopathogenesis of CDH in children and adolescents [2]. Our study showed that a significant number of children and adolescents overuse medication for headache; this implies that their physicians should be aware of this possibility. Detailed information on drugs taken, including frequency of use, is mandatory; if one suspects overuse, a proper and specialized intervention should be started. More studies are needed, however, to define a specific treatment protocol.

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Migraine with aura in children: a retrospective analysis

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Introduction Many authors believe that migraine with aura and migraine without aura are different disease entities due to genetic, epidemiological, clinical and pathophysiological differences. Few studies are reported about migraine with aura in the pediatric population [1].

Materials and methods We retrospectively analyzed charts of children affected by headache referred to the Headache Centre of Bambino Gesù Pediatric Hospital between 2000 and 2011. Those diagnosed as migraine with aura according to ICHD-II criteria were selected. We analyzed the clinical features of headache. Moreover, we analyzed aura characteristics such as type of aura, duration of aura symptoms, timing of onset of aura. Descriptive statistics as well as non parametric analysis (chi-squared) were performed.

Results One hundred and sixty-six patients (36.7% males and 63.3% females) were included in the study. The mean age of headache onset was 9.5 years. Pain side was frontal (43.9%), temporal (34.1%), orbital (10.6%) and diffuse (3.3%), parietal (2.4%), vertex (4.9%) and occipital (0.9%). Headache duration was comprised between 1 and 2 hours in 38.9% of the patients, between 2 and 4 hours in 18.9%, between 5 and 30 minutes in 17.8%, between 30 minutes and 1 hour in 8.9%, less than 5 minutes in 8.9%, more than 24 h in 5.6% and between 4 and 24 hours in 1.1%. Familiarity for migraine was reported in 84% of patients, only 10.8% for migraine with aura in first-degree relatives. Aura symptoms were visual (86.6%), sensitive (12.7%) including aphasic disturbance, motor (0.7%) or a combination of them. Furthermore, aura was classified in preictal (67.3%), ictal (22.7%) or pre and ictal (10%) as regards to headache onset. Aura duration lasted from 5 to 10 minutes in 32.7% of cases, from 10 to 30 minutes in 34.5% of cases, and from 30 to 60 minutes in 13.7%; we also recorded aura duration shorter than 5 minutes in 15.5% and longer than 2 hours in 3.6%.

We found that the lower was the aura duration, the lower was the attack frequency ($p < 0.05$). Moreover, duration of aura was negatively correlated with the throbbing character of headache pain ($p < 0.001$) and it was shorter in the youngest children ($p < 0.001$). Visual aura was frequently associated with photo- and phonophobia ($p < 0.05$), and rarely with vomiting ($p < 0.05$). Visual aura with positive symptoms (scintillating scotoma) showed a significant correlation with a shorter duration of the migraine attack.

Conclusions There is a lack of information about migraine with aura in children. Indeed, many features of migraine with aura reported in children show some peculiarities which need to be further investigated. Our study, although retrospective, may be useful to improve our current knowledge of migraine with aura in children.

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Epileptic headache: a case in a 9-year-old child, with video-EEG recording during the accesses

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Introduction The terms "Epileptic headache" or "Ictal epileptic headache (IEH)" refer to a headache which occurs as a sole (or strongly prevalent) manifestation of an epileptic seizure. It is a rare condition, of which only 9 cases have been described in the literature, 5 of the 9 cases have been reported from 2010 [1, 2], it was probably underreported in the past. We present a child with IEH and the first video-EEG recording.
Case report A 9-year-old girl was admitted to our clinic for the presence of headache which started about 5 months before, with episodes of not more than 2-3 minutes duration, characterized by severe frontal pain, without accompanying symptoms except hypersensibility to noise. Before the hospitalization, the episodes began to be much more frequent, up to 10 episodes a day. During a video-EEG registration she complained of a sudden and rapidly increasing severe frontal headache, associated with what she successively described as "loud noises" inside her head. She was conscious, could understand the questions of the physician, but avoided answering, to not increase the head pain. In concomitance with the headache, the EEG showed the onset of spikes and high slow-waves beginning in the right temporal area and diffusing bilaterally in a few seconds (video-EEG). The headache lasted less than 2 minutes, and with the cessation of pain the EEG became normal. No EEG alterations were present out of the headache episode; however, in the following weeks, rare slow and sharp waves began to appear in the right temporal area. Other episodes were registered, until a year later, and all showed the same features. A MRI showed the presence of a dysplasic lesion in the right temporal cortex, anterior to the amygdala. The accesses of headache subsided for months with carbamazepine plus clobazam, then they returned, and had a transitory improvement with topiramate; due to progressive worsening, the surgeon performed an anterior temporal lobectomy. The histology confirmed a dysplasia type IIa. At follow-up the girl was doing well and did not report further episodes.
Discussion Distinctive features of this case are the brief duration of the headache attacks with minimal accompanying symptoms, the focal onset with recruiting spikes and slow waves followed by diffusion, with initially normal interictal EEG, and the absence of other types of seizures. This case underscores the ictal EEG as the main diagnostic tool for similar conditions, that, although rare, require a differential diagnosis from other kinds of headache.
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Italian multicentric study about the prevalence of nocturnal enuresis in child headache: preliminary data

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Introduction Several reports suggest the existence of a possible comorbidity between sleep disorders and headache, linked to probably common pathophysiological substrates. The details of this relationship are still not clearly understood, but it is known that sleep is related to the occurrence of some headache syndromes while headache may cause or sustain various degrees of sleep disturbance (i.e., parasomnias, sleep breathing disorders, sleep-wake transition disorders).
Nocturnal enuresis is a heterogeneous complex multifactorial problem arising from a mismatch between overnight urine production, bladder storage ability and impaired arousal with overall prevalence in different age groups, greatly varying in different countries, ranging from 2.3% to 25% [1].
The study was aimed to assess the prevalence of nocturnal enuresis in Italian children affected by primary headache.
Design: This was a multicentric prospective study.
Methods The study population was composed of 416 school aged, headache children enrolled consecutivelly in 5 Italian Childhood Headache Centres from October 2011 to April 2012. Headache diagnosis was performed according to the ICHD-II classification criteria.
In order to determine the prevalence of enuresis in the headache population, the presence of enuresis was investigated in all the sample. According to DSM-IV criteria primary nocturnal enuresis and secondary nocturnal enuresis were defined.
Results Our sample result was composed of 416 headache subjects (210 M) (mean age: 10.02 ± 2.98). According to the ICHD-II classification criteria, headache prevalence was the following: CTTH 33.41%, CH 2.64%, HNC 1.68%, ETTH 5.76%, MO 46.39%, and MA 10.09%. The prevalence of enuresis was 20.19%, 18.02% as primary nocturnal enuresis and in 2.16% as secondary nocturnal enuresis.
Conclusions According to our findings nocturnal enuresis and headache seem to be linked. The possible consequences of these preliminary results are that the presence of nocturnal enuresis could be investigated in children affected by headache [2].
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Dizziness in children with headache: one-year outpatient experience

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Introduction Dizziness is unusual in childhood, but is frequently associated with headache. Benign paroxysmal vertigo in childhood is represented by dizziness preceding headache and is considered among childhood periodic syndromes, which are commonly precursors of migraine [1].
Objective To perform a retrospective cohort study on the children presenting for the first time at our Juvenile Headache Centre at the Regina Margherita Children's Hospital in Turin, Italy, in a 1-year time period.
Materials and methods Two hundred and fifty-three outpatient children (119 males and 134 females; mean age: 10.5 years) were referred for the first time to our Centre between October 2010 and September 2011. Eighteen percent of the children were diagnosed with migraine without aura, 4% migraine with aura, 12% possible migraine, 49% tension-type headache and

17% were unclassifiable because clinical features did not permit a diagnosis according to the ICHD-II criteria. Thirty patients (11.8%; 8 males and 22 females; mean age: 11.2 years) presented dizziness. Benign paroxysmal vertigo of childhood was diagnosed in 28 of them (93%); one was affected by vestibular neuritis and one by vasovagal syncope. Among them, 4 patients underwent vestibular function tests: 3 proved negative and 1 was pathologic, which was normal later on a second examination. Brain MRI was performed in 8 patients and proved negative in all cases but one, in which Arnold-Chiari malformation was observed and neurosurgical follow-up was started.

Discussion Benign paroxysmal vertigo of childhood is a frequent cause of pediatric dizziness and is classified among periodic syndromes (ICHD-II, code 1.3.3). The diagnosis is pretty clinical and is made when almost 5 attacks occur, each represented by multiple, severe, unexpected dizzy episodes lasting minutes to hours and recovering spontaneously. No neurological impairment was detected on physical examination; audiometric and vestibular functions were normal between the attacks, even if vestibular function tests are difficult to perform and poorly reliable in children. Prepubertal females are more often affected, reflecting the trend reported for migraine incidence. The attacks usually decrease in frequency with aging, and can precede migraine onset or coexist. Other causes of dizziness (otitis media, labyrinthitis, head injuries, brain tumours in the posterior cranial fossa, psychiatric disorders) must be excluded [2]. In most cases of vertiginous syndrome of childhood, accurate history, physical examination and neurological assessment allow us to identify the causative factor. Further investigation could be considered for each single case.

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Migraine and metacognition in children and adolescents with migraine

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Introduction Metacognition refers to one's knowledge concerning one's own cognitive processes or anything related to them, e.g. the learning-relevant properties of information or data.

Some aspects of metacognition are related to anxiety and or depressive disorders. It is well known that migraine could be related to both but very little has been studied on the role that metacognitive aspects play in this. The Metacognitions Questionnaire for Children (MCQ-C) is a questionnaire that analyzes four main components in children and adolescents: positive meta-worry, negative meta-worry, superstitious, punishment and responsibility (SPR) beliefs, and cognitive monitoring.

Objectives Aims of the study were: 1) to validate the questionnaire in Italy and associate it with the presence of anxiety (A), depression (D) and obsessive compulsive disorder (OCD); 2) to analyze the possible relationship between migraine and metacognitive problems; 3) to evaluate the influence that such difficulties could have on psychiatric comorbidity.

Materials and methods The sample was composed of 65 (43.1%) migrainous children and adolescents and a control group of 82 (56.9%) (12.5; d.s. 2.8; 43.8% M and 56.2% F). The first group was composed of consecutive patients of our Headache Centre, the second of children and adolescents of a primary and secondary school of Rome randomly chosen.

Instruments used were: Metacognitions Questionnaire for Children (MCQ-C) [1] $\alpha = .74$; SAFA for A, D, and OCD; OCD Impact Scale, for OCD. Factorial Analysis and Linear Regression were performed.

Results Three factors, positive meta-worry, cognitive monitoring and SPR beliefs (negative meta-worry and superstitious, punishment and responsibility) [$c^2(218) = 378.65$, $p < .01$; RMSEA = .076; NNFI = .95; CFI = .95] gave us interesting results: positive meta-worry was associated to D ($\beta = .29$; $p < .01$) and OCD ($\beta = .44$; $p < .01$); negative meta-worry and SPR beliefs were associated to A ($\beta = .28$; $p < .01$), D ($\beta = .39$; $p < .01$) and OCD ($\beta = .33$; $p < .01$). Conversely, cognitive monitoring was not associated to any of the scales of SAFA or OCD Impact Scale.

Conclusions Even if the sample size was small, the results suggest a direct involvement of the metacognitive processes in psychiatric comorbidity associated to migraine in childern and adolescents.

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Migraine and epilepsy in pediatric age: from differential diagnosis to comorbidity

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Migraine and epilepsy are both common neurological disorders, although migraine is more frequent. Despite the similarities, migraine and epilepsy are distinct disorders with important differences and peculiarities.

The possible relationships between headache, particularly migraine, and epilepsy include: 1) differential diagnosis: headache and epilepsy may have some common clinical manifestations but can be distinguished taking into account the peculiarities of both diseases and also by EEG; 2) headache may be a symptom temporally associated with a seizure, as in these three possible conditions: peri-ictal headache, hemicrania epileptica, migralepsy; 3) headache and epilepsy may coexist in the same subject, this situation is called comorbidity; 4) headache and seizures secondary to neurological diseases.

In the International Classification of Headache Disorders (ICHD-II, 2004) these clinical entities are included: 1) postictal headache (code 7.6.2); 2) migralepsy (code 1.5.5); 3) hemicrania epileptica (code 7.6.1) [1].

An association between migraine and epilepsy was demonstrated in several studies, mainly based on adults affected by epilepsy, while in children data are even more conflicting and studies have been limited by the small numbers of patients and by the lack of clearly stated diagnostic criteria of childhood migraine. Recently, comorbidity between headache and epilepsy was studied on a large series of children with headache (1,795) [2]. Fifty-six cases (3.1%) suffered from idiopathic headache and idiopathic or cryptogenic epilepsy or unprovoked seizures. There was a strong association between migraine and epilepsy: in migraineurs (46/56) the risk of epilepsy was 3.2 times higher when compared with tension-type headache, without significant difference between migraine with and without aura ($p = 0.89$); children with epilepsy had a 4.5-fold increased risk of developing migraine than tension-type headache. In cases with comorbidity, focal epilepsies prevailed (43/56, 76.8%) [2].

The knowledge of the possible relationships between headache and epilepsy is essential for a correct diagnosis of these conditions when they have to be distinguished, as in the differential diagnosis, or when they both are present simultaneously in the same subject. It is necessary that the International Classification of both Headache Disorders and of Epilepsies include common diagnostic criteria for these entities in order to compare the results of the different studies, to identify groups of patients with more homogeneous phenotypes, and for genetic studies needed to clarify the pathophysiological mechanisms underlying the two diseases, in particular when they are associated in the same subject. This will also improve therapeutic strategies for both diseases, especially in cases of comorbidity.

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Efficacy and tolerability of a combination product with L-Tryptophan, Griffonia simplicifolia, Vitamin PP and Vitamin B6 in pediatric migraine prophylaxis: an open study

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Objective The aim of this study was to evaluate the efficacy and tolerability of the combination product with L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 in prophylaxis therapy of pediatric migraine.
Materials and methods Forty outpatients (26 F, 14 M), mean age 11.6 years (SD 5.2), range 4-18 years, suffering from migraine without aura (ICHD-II criteria) were enrolled. The mean duration of disease was 2.7 (SD 1.5) years, range 1-4 years. At baseline the mean frequency of attacks was 8.6/month (SD 3.1), range 4-12; the mean number of drug consumption for acute attacks was 7.1 tablets/month (SD 1.8).
During the 6-month evaluation period the combination product with L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 was administered (at the dosage 100 mg, 480 mg, 18 mg and 1 mg/die, respectively). All patients filled in a headache diary during the evaluation.
Results The basal frequency of attack was 8.6 (SD 3.1) and 4.6 (SD 2.2), 4.1 (SD 2.5), 2.7 (SD 2.9), after 1, 3 and 6 months respectively ($p < .01$; $p < .01$; $p < .01$). The basal value of drug consumption for acute attacks was 7.1 (SD 1.8) and 2.3 (SD 2.2), 2.1 (SD 1.8), 1.6 (SD 2.4) after 1, 3 and 6 months respectively ($p < .01$; $p < .01$; $p < .1$) (t-test analysis). The combination product with L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 was well tolerated (11 patients complained of somnolence, diarrhea and gastralgia but none withdrew from the study).
Discussion and conclusions These data showed a good efficacy in the reduction of frequency and intensity of headache attacks, a good tolerability and a very good reduction of drug consumption for acute attacks. Our study suggests that the combination of L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 could be an alternative therapy for pediatric migraine prophylaxis.

POSTERS

Clinical aspects and management of headache

Evidence of an increased restless legs syndrome occurrence in chronic and highly disabling migraine

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Introduction The existence of a clinical association between migraine and restless legs syndrome (RLS) has recently been reported, although the possible implications on migraine clinical presentation still remain poorly understood. The objectives of this study were to determine RLS frequency in a population of migraineurs compared to healthy subjects and to assess RLS occurrence in episodic versus chronic migraine patients; the relationship between migraine related disability and RLS comorbidity was also evaluated.
Materials and methods Two hundred and seventy-seven consecutive patients, fulfilling ICHD-II criteria (2004) for migraine with or without aura, were enrolled at the Headache Centre of the University of Pisa and compared to 200 healthy subjects. Patients with comorbid medical or psychiatric conditions, medication-overuse headache or in treatment with migraine preventive drugs, antidepressants, dopamine antagonists or gabaergic drugs were excluded. RLS, a sensorimotor neurological disorder, was diagnosed according to the four essential criteria of the International Restless Legs Syndrome Study Group (2003). Chronic migraine was diagnosed according to the presence of headaches for ≥ 15 days per month for at least 3 months, of which ≥ 8 days met criteria outlined for episodic migraine or were treated with an acute migraine specific medication; migraine was episodic in 175 patients and chronic in 102 patients. Migraine associated disability was assessed by means of MIDAS (Migraine Disability Assessment Score).
Results RLS occurrence was significantly greater in migraineurs compared to controls (22.7% migraineurs vs. 7.5% healthy subjects, $p < 0.0001$). RLS occurrence was 16% in episodic and 34.3% in chronic migraine patients, respectively, and the statistical analysis documented a significant association between RLS diagnosis and chronic migraine, compared to episodic patients ($p = 0.0006$). Concerning migraine related disability the existence of a significant association between moderate-severe migraine related disability and RLS comorbidity was also documented ($p = 0.0003$).
Discussion The results of the present study showed an increased occurrence of RLS in an homogeneous sample of migraineurs, especially in patients with chronic and highly disabling migraine. These data further emphasize the need to verify the presence of RLS in all migraineurs, but mainly in chronic patients and in subjects with moderate-severe migraine related disability; the identification, together with the adequate treatment, of RLS comorbidity in migraine patients, could immediately contribute to improve patient's quality of life and, hypothetically, in a lifetime-perspective, it could contribute to reduce the risk of migraine transformation from episodic to chronic.

From "Migralepsy" to "Ictal epileptic headache" concept: a long and winding road

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Introduction To date, the International Classification of Headache Disorders (ICHD-II) describes "migraine-triggered seizure" (migralepsy), coded among "complications of migraine", at 1.5.5, as a rare event in which a seizure happens during migrainous aura, whereas, the International League against Epilepsy (ILAE) does not mention this entity at all. Neither the International Headache Society (IHS) nor the ILAE mention that headache/migraine may rarely be the sole ictal epileptic manifestation.
Materials and methods Thus, we recently proposed to add a new entity, "Ictal epileptic headache" (IEH), to classify the events in which headache represents the sole ictal epileptic manifestation [1]. Cortical spreading depression (CSD) is considered to be the primary cause of the activation of the trigeminovascular system which in turn, seems to be involved in the pathophysiology of both migraine with and without aura. In addition, there is emerging evidence from both, basic and clinical neurosciences, suggesting that CSD and an epileptic focus are able to facilitate each other, although with a different degree of efficiency [2]. Indeed, since the 1950s German, English and Italian literature have described cases suggesting that headache could just be "an epileptic headache", and that it could even be the only clinical manifestation of idiopathic epilepsy.
Discussion We would like to stress the "long and winding road" that has been followed since the 1950s when the so-called "migralepsy" concept (a badly defined nosologic entity) was initially brought forth to the new emerging pathophysiological aspects and clinical EEG evidence suggesting the ictal epileptic headache concept. Taking this into consideration, we propose new IEH criteria:

Proposed criteria for ictal epileptic headache (IEH)
Diagnostic criteria A-D should all be fulfilled in order to make the diagnosis of "IEH"

A. Headache* lasting seconds, minutes, hours or days
B. Headache is ipsilateral or contralateral to lateralised ictal epileptiform EEG discharges (if EEG discharges are lateralised)
C. Evidence of epileptiform (localised**, lateralised or generalised) discharges on scalp EEG synchronous to headache complaints; different types of EEG anomalies may be observed (generalized spike-and-wave or polyspike-and-wave, focal or generalised rhythmic activity or focal subcontinuous spikes or theta activity intermingle or not with sharp waves) with or without photoparoxysmal response (PPRs)
D. Headache resolves immediately after i.v. antiepileptic medication

* A specific headache pattern is not required (migraine with or without aura, or tension-type headache are all admitted).
** Any localisation (frontal, temporal, parietal, occipital) is admitted.

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Psychiatric and personality profile disorders as predictive factors of chronic headache

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Background The mechanism that causes transformation of migraine attacks from episodic to chronic is unclear. Studies have investigated comorbidity between migraine and psychiatric disorders. Hypochondriasis, anxiety and depression, cyclotimic disorders have been reported to be most prevalent personality features in migraine patients.
Objectives To investigate comorbidity between chronic migraine and psychiatric disorders trait in the transformation from episodic migraine to chronic migraine.
Methods Our study sample consisted of 186 consecutive new patients, (148 females, 38 males; mean age 42 years; range 18-65 years; 132 episodic migraine, 54 chronic migraine) attending headache day service in the period 2010-2011 at the Headache Centre of the Hospital of Catanzaro. We applied ICHD-II classification criteria for the headache diagnosis and DSM-IV-TR criteria for the evalutation of personality and psychiatric disorders. Data were collected and analysed by using the statistic package STATA 8.
Results We found an increase of generalised anxiety (p = 0.03), major depression (p = 0.02), social isolation (p = 0.015), cyclotimic disorders (p = 0.035), family problems (p = 0.05); a responsiveness to pharmacological treatment in chronic migraine in comparison to episodic migraine (p = 0.017).
Conclusions The present study demonstrates that mood depression disorders, and generalised anxiety are risk factors for the chronification of migraine. In addition, these comorbidities predict unresponsiveness to pharmacological treatment. There is evidence that psychiatric comorbidity is higher in transformed migraine than in episodic migraine. Furthermore, a published study demonstrated that anxiety and major depression may constitute risk factors for the evolution of migraine into MOH. Subjects with migraine should be carefully screened for depression and anxiety, which should be managed to prevent the transformation of migraine, so as to improve the quality of life and to reach a higher level of success with migraine therapies.

Weekend migraine: myth or reality?

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Introduction The term weekend migraine (WM) is commonly used to define a type of headache that occurs only or almost exclusively on weekends. Several aspects of WM are still unclear, which explains why this headache has not been included in the International Headache Society classification, and its very existence is still being questioned [1]. Migraineurs are physiologically and psychologically hyperresponsive to a variety of internal and external stimuli, including chronobiologic factors.
Materials and methods We retrospectively evaluated the clinical records of 3,515 patients diagnosed with migraine without aura (MO), migraine with aura (MA) and tension-type headache (TTH), referred to our Headache Centre from 2005 to 2011. We studied the patients whose attacks occurred almost exclusively on weekends and we followed them up to 2 years.
Results We identified 172 patients (90 males and 82 females), constituting 4.9% of the total population, who complained of attacks occurring essentially on weekends. The patients' mean age was 36.4 ± 9.8 years (range 12-70). This group of headache sufferers consisted of 149 patients with MO, 9 with MO + TTH, 8 with MO + MA, 4 with TTH, and 2 with MA. The headaches occurred almost exclusively (> 90% of total attacks, at least three attacks per month) on weekends in 89 cases (51.7%); all these patients suffered from MO. For the remaining 83 cases (48.3%) the weekend attacks were clearly prominent, representing > 50% (at least two attacks per month) of all attacks occurring over a month. Interestingly, 14 women (17.1% of female group) reported attacks occurring exclusively both on weekends and in perimenstrual phase.
Discussion WM was found in almost 5% of all migraineurs. In contrast with the significantly higher prevalence of migraine in women, we found a preponderance of males in WM patients. The occurrence of this headache seems to be variable, irregular, unpredictable over time, but in most cases the relationship with weekend remains fixed. The most likely pathophysiology of WM seems to be related to sudden changes in stress levels and life-style (known as "let-up phenomenon") in susceptible patients [2].
Conclusions WM exists, either as a predominant form of migraine or as a subtype of migraine triggered by weekends. The mean age of WM patients corresponds to the peak of migraine prevalence in population-based studies, an age when the productivity in life starts being maximum. The role of WM therefore appears to be relevant, both due to its prevalence and its burden.
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Role of alcoholic drinks as a trigger factor of primary headaches

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Introduction About one-third of patients with migraine without aura (MO) reported alcoholic drinks (AD) as a trigger factor, even if some prospective studies limit considerably their importance [1]. Some studies show that AD are triggers also of tension-type headache (TTH), and recently some Danish studies reported that AD are triggers of migraine with aura (MA) and familial hemiplegic migraine in about the same percentage found in MO [2]. This study was aimed at evaluating the role of AD as a trigger of the more frequent types of primary headaches and alcohol habits in patients presenting to a Headache Centre.
Materials and methods Patients presenting to a Headache Centre, with diagnosis based on IHS classification criteria for MO, MA, chronic migraine (CM), episodic and chronic tension-type headache, were asked if their headache was precipitated by AD and their alcohol habits. We selected only patients with pure TTH, that is, without migraine attacks or other types of headaches. In abstainers the reasons for non-consumption were requested, that is, if headache, triggered by AD on previous occasions, was the reason for the abstinence.
Results Out of 448 patients (337 F, 111 M), only 22 (4.9%) reported AD as a trigger factors: 17 with MO, 3 with CM and 2 with both MO and MA. In the two patients with both MO and MA, alcohol was a trigger only for MO attacks. Considering all migraine patients, only 5.4% (8% of those consuming AD) referred that AD could precipitate their headache. None of the 44 patients with MA and 47 patients with pure TTH reported that AD precipitated their headache. Forty-nine percent of the headache population were abstainers (that is, they had not drunk any AD, at least, in the last 12 months), 17.6% regular consumers (one or more AD/week), 32.5% occasional consumers (less than one AD/week). A higher percentage of abstainers was found in CM (72%) in comparison with episodic MO (46%). Only a few migraine patients (3%) were abstainers and did not consume AD because they triggered their headache.
Conclusions Our study showed that AD are trigger factors only in a small percentage of migraine patients, and that, unlike results in previous studies,

they do not trigger MA and TTH attacks. The possible reasons for the variability of alcohol as a trigger factor may be partly due to methods of data collection and to different alcohol habits in various countries. Moreover, the percentage of abstainers in the headache population was higher in comparison to the general population.

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Medical messages about headaches in the traditional media. A history of glorification of high-tech therapeutic approaches and miseducation

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Background Thirty-one percent of EU citizens consider medicine as the most interesting news related issue and 64% of Italians declare to be interested in being informed on scientific research. Traditional media are the most popular media for medical information (61% of EU citizens regularly or occasionally watch TV programmes about health and science - Eurobarometer 2007). Media reports about medical issues may influence the general public, policy makers and health professionals. No study has investigated how traditional media informs about headaches.

Objective Alleanza Cefalalgici (Al.Ce.), a lay association working towards improving the awareness about headache disorders, founded a Media Observatory (MO), a multidisciplinary team including headache specialists, patients and journalists with the aim to study and analyze the information about headache released by traditional media.

Methods The MO monitored the 4 main Italian newspapers and the 6 national traditional TV stations searching for information regarding headaches. In addition, all the members of Al.Ce. were invited to inform the MO about info/news on headaches released by other sources. For every piece of information the MO evaluated: a) the form of presentation; b) the topic of the news; and its c) relevance/usefulness; d) reliability/accuracy; e) correctness/objectivity; and f) comprehensibility. The study lasted six months and was completed in November 2010.

Results Forty pieces of information were identified in the study period (80% from journals and 20% from television). The information was presented as short news in 72.5% of the cases and 20% as in-depth news. Forty percent of the pieces analyzed by the MO were released by journalists, 27.5% were integrated by interviews with specialists and 23% consisted only in interviews with specialists. The majority of the media information was about "new therapies" (50%), followed by "general information" (13%), "basic research data" (13%), and "patographies" (13%). The relevance, accuracy and correctness of media information about headaches was rated as poor/very poor in 35%, 43% and 55% of the pieces, respectively. The comprehensibility was almost always considered as good.

Discussion Traditional media information about headache is essentially limited to a sensationalistic and poorly objective glorification of high-tech therapies creating unrealistic expectations in headache sufferers.

A systematic review of common diagnostic/therapeutic errors in trigeminal autonomic cephalalgias and hemicrania continua

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Introduction Trigeminal autonomic cephalalgias (TACs) and hemicrania continua (HC) are relatively rare but clinically well-defined primary headaches. Despite the current clear-cut diagnostic criteria (ICHD-II classification) and several therapeutic guidelines, errors in work-up and treatment are frequently encountered in clinical practice [1, 2]. The aim of the present study was to investigate all published data dealing with mismanagement of patients affected by TACs and HC in order to understand and avoid the causes of such behaviours.

Methods We reviewed all the English language literature related to this particular topic.

Results The search strategy identified 65 published studies, 21 of which were relevant. The most frequent errors described in the management of patients with TACs and HC are the following: referral errors, diagnostic delay, misdiagnosis and the mismanagement in using treatment without overt indication. Migraine with and without aura, trigeminal neuralgia, sinus infection, dental pain and temporomandibular dysfunction are the most frequently disorders overdiagnosed.

Discussion Although facing a clear-cut clinical picture, TACs and HC are frequently not recognized and/or misdiagnosed with other disorders, not only by general physicians, but also by neurologists and headache specialists. This is mostly related to the limited knowledge of specific characteristics and variants of the disorders and it leads to the prescription of ineffective and sometimes invasive treatments, that may turn into heavy consequences for the patients. Increasing the knowledge and the education concerning these disorders both in primary care physicians and in headache specialists could improve the quality of life of the patients suffering from TACs and HC.

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Accessibility of headache centres for patients suffering from cluster headache: too far from the patients' needs

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Background Due to the extraordinary severity of pain, cluster headache (CH) warrants rapid diagnosis and appropriate treatment. The diagnosis of CH is simple, and rapid and effective treatments exist (injective sumatriptan and oxygen). In spite of this, clinical data have documented that CH is largely under-diagnosed and under-treated and it is common opinion that CH should be managed in a specialist setting. A fast access to headache services for CH patients is required to avoid delays to proper care.

Objective To investigate the accessibility of the headache centres listed on the official websites of the two existing Italian societies involved in the study of headaches (SISC and ANIRCEF).

Methods Volunteers suffering for CH and serving as active members of Alleanza Cefalalgici Cluster (Al.Ce. Cluster) contacted the Italian headache specialists searching for a fast access for a visit or the possibility to talk with a physician. The primary outcome measure was the fast access to the headache specialist, defined as an access scheduled within 7 days from the contact. The secondary outcome measures were: a) the possibility to talk with the physi-

cians, and b) a service measure of call centre efficiency (number of calls necessary before being answered). The study was conducted in April 2012.
Results One hundred and fifty-one headache centres were contacted in the study period. Fast access to a visit was allowed by 41 centres (31.7%, 33 covered by the National Health System and 15 in private practice; in 16 cases a special referral of the GP certifying the urgency was requested). Only 9 centres (5.9%) gave the patients the possibility to talk with a physician. Sixty centres (39.7%) did not answer the phone (at least 3 calls per day at different times for 5 days).
Discussion The accessibility of headache centres for CH patients is inadequate and far from the patients' needs because of an irrational organization and an inefficient use of the technical and human resources. An inacceptable disparity emerges between different geographical areas.

The relationship between social support, and couple's relationship in chronic headache

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Introduction Health psychology investigates the role of the family and social support as a key factor for mediating stress in situations of chronic illness. As regards to chronic headache, there are few studies that correlate this condition with the perception of social support in patients. In fact, patients with chronic headache use little social support as a *coping strategy,* despite this, it is considered an important strategy in the management of disease. It has been reported [1] that poor social support perceived by patients with chronic headache is related to a perception of high stress levels; the patients with chronic headaches, also, could have more difficulties in maintaining social relationships [2].
Objectives The first aim of the study was to investigate the perception of social and family support, the quality of life and the level of dependency on drugs in medication-overuse headache patients (MOH). The secondary objective was to investigate the couple's relationship in understanding how the disease could affect its dynamics; and to identify the possible support that the partner could offer the patient and how the patient perceived this support. Lastly, to understand the modality to help the patient use family and social support as a coping strategy for the management of disease or for the reduction of stress related to headache.
Methods We administered a battery of questionnaires to 50 MOH patients afferent to the Headache Centre of Drug Abuse at the AOU Policlinico of Modena and to 30 control patients. The battery of tests included: SCL-90, SF-36 scale self-assessment of anxiety and depression (SAS) of Zung WWK and the perceived social support's scale. Subsequently, we interviewed 15 couples in which one partner suffered from chronic headache.
Results Presently we have these results: Self Assessment Anxiety: 44.02 ± 9.5 (Student's *t*-test $p < .001$); Self Assessment Depression: 46.39 ± 10.16 (Student's *t*-test $p < .001$). In the psychopathological dimensions of SCL-90 the values for MOH patients were higher compared with normal values in regards to somatization 1.41 ± 0.85 (Student's *t*-test $p < .001$), and sleep disorders 1.73 ± 1.25 (T-Student's test $p < .001$).
Conclusions The preliminary data of the interviews suggest that family support is more important than social support for MOH patients.
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Outcome of medication-overuse headache: a three-year follow-up study according to the "CARE" protocol

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Introduction Medication-overuse headache (MOH) has become one of the major challenges in headache management. The main aim of the present study was to evaluate the factors associated with a negative outcome in a three-year follow-up of a population of subjects diagnosed with MOH.
Materials and methods All consecutive patients with MOH entering, for the first time, the centre's in-patient detoxification programme were analyzed in a prospective, non-randomized way. They were enrolled as outpatients and gave their verbal informed consent to undergo the protocol (in-patient detoxification and three follow-up visits in the first year, then six-monthly clinical controls). The diagnosis of MOH was made according to the revised ICHD-II criteria [1]. All the participants were assessed using an ad hoc patient's record form. Variables analyzed as possible predictors were: gender, age, socio-demographic characteristics, alcohol/coffee/smoking habits, positive family history for drug abuse and/or headache, past medical history, primary headache type, type, duration and quantification of drug overuse and duration of chronic headache. Categorical variables were analyzed with the Chi-square test. For quantitative variables, statistical differences were analyzed with ANOVA. Odds Ratios (ORs) were calculated for dichotomous outcomes as well.
Results One hundred and fifty patients completed the 3-year follow-up (79.3% females, age 46.40 ± 11.31): 13 patients never stopped overuse (Group A), 38 patients stopped drug overuse, but relapsed at least once (Group B) and 99 patients never relapsed (Group C). Patients in Group A differed from B and C groups because they were more frequently single (OR 0.134; $p = 0.007$) and unemployed (OR = 3.273; $p = 0.04$), they took a higher number of acute drugs ($p < 0.001$) and used coffee less frequently (OR 3.273; $p = 0.044$).
Discussion and conclusions The outcome of disease in this group of MOH patients was influenced negatively by the severity of overuse (and possibly of the disease) and by specific socio-economic conditions (e.g. single, unemployed). Other factors that emerged as possible modifiers of outcome were voluntary habits.
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Personality factors in medication-overuse headache: a three-year follow-up study according to the "CARE" Protocol

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Introduction If the association between psychiatric illness and headache is widely recognized, the role of personality factors is less extensively studied. The negative prognostic value of psychiatric disorders in medication-overuse

headache (MOH) [1] has been previously outlined, however, to the best of our knowledge, the role of personality factors as potential predictors of MOH evolution has never been studied. The main aim of this study was therefore to study the role of personality dimensions in the prognosis of MOH.

Materials and methods Among a total of 243 patients, 150 completed the follow-up at three years (79.3% females, age 46.40 ± 11.31). The personality profile was assessed with the Minnesota Multiphasic Personality Inventory (MMPI-2). We explored the occurrence (or not) of at least one episode of drug overuse taking into account the overall 3-year period of follow-up. In relation to this, our population was subdivided into 3 groups: Group A: formed by patients who never stopped overusing drugs after the initial detoxification treatment (n = 13); Group B: formed by patients who stopped drug overuse following detoxification, but then relapsed at least once (n = 38); Group C: formed by patients who stopped drug overuse following detoxification and never relapsed (n = 99).

Results As regards personality profile at MMPI-2, subjects in Group A had higher scores at the Lie scale ($p = 0.004$) as compared to both the other groups (B and C), and at the following scales as compared to patients who stopped abuse and never relapsed (Group C): Frequency ($p = 0.020$), Hypocondriasis ($p = 0.007$), Depression ($p = 0.003$), Paranoia ($p = 0.025$), Fears ($p = 0.003$), Obsessiveness ($p = 0.026$), Bizarre Mentation ($p = 0.046$), Social Discomfort ($p = 0.004$), Negative Treatment Indicators ($p = 0.040$), Repression ($p = 0.007$), Overcontrolled Hostility ($p = 0.040$), Addiction Admission Scale ($p = 0.021$), Social Responsibility ($p = 0.039$) and Marital Distress Scale ($p = 0.028$).

Discussion and conclusions Personality factors are important not only because they characterise patients with MOH, but also probably for their predicting outcome value. In this study we provide support for the existence of a small sub-group of MOH patients (Group A) with addiction-related personality and behavioural problems that are likely to play a major role in influencing and nurturing drug abuse and chronic headache. These findings support the existence of patients with complicated MOH, and point to the need of a thorough clinical-psychological evaluation and an adequate, tailored management.

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Case reports

Headache attributed to cavernous sinus meningioma mimicking TAC-like headache

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Introduction Several cases of secondary headaches with clinical features mimicking primary forms, in particular trigeminal autonomic cephalalgias (TACs), have already been reported. Atypical clinical elements that can be helpful in an early identification of a secondary type are in most cases an abnormal neurological examination and an older age at onset of the attacks [1, 2]. Although TAC-like secondary headaches have been described for each of the three primary headache subtypes, an evolution of the clinical features from one TAC-like form to another has never been described thus far.

Case report A 74-year-old man referred to our Headache Centre, complaining of a very severe pain on the left periorbital region which started one month earlier, lasting 45-60 min, associated with conjunctival injection and tearing, occurring 3-4 times per day. Neurological examination and brain MRI were normal. Having posed a provisional diagnosis of late-onset cluster headache (CH), a preventive therapy combining oral prednisone and verapamil was commenced. Two months later the patient stated the prescribed therapy to be completely ineffective, moreover he reported a significant change of the headache features. As a matter of fact the pain, still located on the left side, had become continuous, moderate and dull, but with exacerbations of severe intensity lasting usually 1 hour, associated with ptosis, conjunctival injection and tearing and occurring 5-6 times per day. These new features seemed to be more consistent with the diagnosis of hemicrania continua and as a consequence the patient was promptly reevaluated. On this occasion the neurological examination revealed a left 3rd cranial nerve palsy; the brain MRI with gadolinium detected the presence of a meningioma in the left cavernous sinus.

Conclusions The evolution of the headache features, suggestive of cluster headache and hemicrania continua, respectively, in a patient with a lesion in the cavernous sinus may indicate a possible role of this structure in the pathophysiology of these two different forms of primary headaches.

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Benefits of palmitoylethanolamide on migraine: a case report

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Case report A 30-year-old woman, suffering from migraine without aura, employee, single, non-smoker, social drinker and regular sleep/wake routine. Comorbidity: ovarian endometriosis surgically treated.

The patient reported headaches since the age of 14 at menarche and with episodic attacks (1-2 per month). Two years ago the patient started an estroprogestinic (etinilestradiolo plus drospirenone) therapy and the headache worsened: the intensity of pain and frequency of attacks increased (about 8 per month) and also the analgesic consumption (about 10 SAID tablets per month). The pain was throbbing, moderate to severe intensity and unilateral in frontal, temporal and orbital regions and it was associated with autonomic symptoms (photophobia, phonophobia, nausea and sometimes vomit).

We suggested changing the type of estroprogestinic drug and prophylactic therapy with amytriptiline (16 mg/day). There were no benefits after three months of the suggested therapy: headache was unchanged and the patient gained weight (5 kg). In the meanwhile, the gynecologist prescribed a drug to better control pelvic pain: palmitoylethanolamide (PEA), 3 tablets/day for three months. After three months, the patient returned for a planned control visit and reported great improvement in headache frequency (4-5 attacks per month) and reduction in analgesic drug consumption and pelvic pain.

PEA is an endogenous fatty acid amide analogue of the endocannabinoid anandamide, it is synthesised during inflammation and tissue damage and has been shown to have a number of beneficial effects and to be useful in the control of neurogenic and neuropathic pain. The exact pathophysiogenetic mechanism of migraine and chronic pelvic pain are still unknown, but the role of mast cells is very important in both diseases [1].

Although its pharmacological efficacy is well known, the mechanism of action of this family of compounds is still unclear. It has been hypothesized that PEA could bind CB2 receptors on mast cells and sensory neurons, according to the ALIA mechanism of PEA (ALIA: Autacoid Local Injury Antagonism) and putative activation of cannabinoids and vanilloid TRPV1 receptors via "entourage" effects.

Focusing on migraine, the dural mast cells play an important role, in particular in case of perimenstrual migraine: estrogen receptors in mast cells modulate histamine release that excites nociceptive terminals. Hormones could affect pain processing at all levels, including peripheral and central mechanism and the mast cells degranulation could be involved in endometriosis pain in the same way [2].

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Agomelatine in cluster headache: a case report

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Introduction Agomelatine is a novel melatoninergic drug (MT1-MT2 receptor agonist with 5-HT2C antagonistic properties), able to modulate circadian rhythms and to perform antidepressant effects in some animal models of depression.

Case report M.C. is a 52-year-old female patient, suffering from episodic cluster headache (ICHD-II) for 18 years with periods of cluster occurring every two years with the change of season, lasting from two to three months. In the last episode, beginning in August 2011, the patient showed an average of 5-10 crises a day, half of them during sleep. All the routine exams (neuroimaging, chemical blood and clinical tests) were normal. As preventive therapy the patient initially took corticosteroids (prednisone 50 mg/die) and then verapamil (240 mg/die) and valproate (800 mg/die) without any positive effects on the crises (4-8 attacks a day). From April 2011, the dose of 25 mg/die of agomelatine was added to the current therapy to treat concurrent depressive condition. After about 7 days, the number of crises was significantly reduced (1 or 2 a day) until the complete disappearance within 1 month. At the same time, the mood was considerably better (HDR-S: from 28 to 15).

At two-month follow-up the patient reported complete resolution of the episode: the patient suspended the therapy with verapamil and valproate, while still taking agomelatine.

Discussion In the past, a positive response to clusters was always obtained with routine drugs (corticosteroids, verapamil, valproate, oxygen). The episodes never lasted more than three months unlike the last crisis that exceeded 8 months with higher daily frequency, even though all were equally responsive to sumatriptan sc. The addition of a melatoninergic antidepressant showed remarkable clinical effects with the disappearance of attacks.

Conclusions The hypothesis of a possible therapeutic role of agomelatine in cluster headache seems to be suggestive, particularly considering the specific pharmacodynamic mechanism of this drug. Further controlled clinical studies in a larger patient sample are needed to clarify its real efficiency in cluster headache.

A case of lateral medullary syndrome associated with presumptive vertebral artery dissection initiating as a migraine attack

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Introduction Cerebral artery dissection is a rare cause of ischemic stroke. With advances in magnetic resonance imaging (MRI), dissections of intracranial arteries are increasingly being recognised [1]. We report a case of severe occipital headache mimicking a migraine attack, followed by a neurological complication with the clinical features of a Wallenberg syndrome attributed to a presumptive vertebral dissection.

Case Report A 58-year-old man was referred to the Emergency Department for sudden onset of occipital headache and vomiting. A few hours after admission he experienced dizziness, swallowing disturbances, hoarseness, and numbness on the right side of his face. Patient denied neck or head injury, and his medical history was notable only for hypertension and diabetes. Neurological examination showed right Horner syndrome, right palatal paralysis, deviation of the uvula to the left side, impaired touch sensation on the right side of the face and left arm, truncal ataxia with right dysmetria.

A brain CT scan showed no obvious abnormalities. MRI revealed a focal T2 hyper-intensity in the right-lateral medulla, which was consistent with a diagnosis of infarction and a focal ischemic lesion in the right cerebellar hemisphere. A CT angiography detected an occlusion of the lumen in the V4 segment of the right vertebral artery. Magnetic resonance angiography revealed the presence of an intra-luminal flap in the low basilar artery. Heparin was avoided because of the increased risk of sub-arachnoid haemorrhage, and the patient was treated with oral aspirin.

Discussion Our patient with posterior circulation involvement showed radiological signs of basilar artery dissection with medullary and focal cerebellar ischemic strokes. We suspected an intracranial vertebral artery dissection with local (medullar) thrombosis and distal (cerebellum) embolism, and partial extension in the initial tract of the basilar artery.

Clinical onset was a typical pulsating headache with vomiting and nausea. In the ICHD-II classification headache or neck pain secondary to cervico-cerebral arterial dissection are classified. Therefore, an accurate evaluation is mandatory in some cases of headache with abrupt onset in order to search for symptoms or local signs of cerebral stroke [2].

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A very special case

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Introduction Behçet's disease is recognized as a disease that causes inflammatory perivasculitis, i.e., an inflammation of the tissue around a blood or lymph vessel, in practically any tissue of the body. Its symptoms include canker sores or ulcers in the mouth and on genitals, and eye inflammation [1]. In addition, patients experience severe headache and papulopustular skin lesions. The disease was first described in 1937 by a Turkish dermatologist, Dr. Hulusi Behçet. Behcet's disease is most prevalent in the Middle East and the Far East regions and is rare in America [2].

The clinical manifestations of Neuro-Behcet disease are: a) meningoencephalomyelitis, which is the most common framework, and b) cerebral angiitis with venous sinus thrombosis and intracranial hypertension.

Case report Female patient, 29 years of age, first born of twins, of a preterm birth (oligohydramnios).

Family history:

- *Maternal line*: Positive for migraine without aura (MO) and unspecified headache, depression and bipolar disorder.

- *Paternal line*: Ischaemic stroke, acute myocardial infarction at a young age.
- *Personal history*: At 8 years of age the patient showed recurrent oral ulcers and acute pain in the right wrist, spreading to all joints about 30 minutes after its onset. At 18 years of age she experienced a similar episode with pain starting from the right wrist. At 19 years of age, after consulting an internist-immunologist, she began taking idroxiclorochine sulfate, colchicine, rofecoxib.

When she was 20 she had four episodes of hemorrhagic cystitis (iatrogenic?) and two episodes of episcleritis. At the same age she began to suffer from migraine with aura (MA). The attacks of throbbing pain occurred upon awakening and were accompanied with nausea, vomit, increased urination, insomnia, sweating, lacrimation, rhinorrhea, photophobia, sonophobia, osmophobia, yawning, ear buzzing and hissing, and subjective vertigo. The pain increased when climbing stairs.

The painful phase was preceded by a scintillating scotoma in the external visual field, sometimes also by transient amaurosis, dysarthria, paresthesia of right upper limb. Headache partially improved with atenolol.

At 27 years of age: first episode of diplopia, fatigue, loss of balance, mild dysphagia, dyspnea: specific tests excluded myasthenia gravis. Evoked motor potentials showed impaired central motor conduction which was more evident on the right side.

Brain MR with contrast revealed the presence of some areas of altered signal, hyperintense to the images in TR sequences, in the peritrigonal white matter from both sides.

At 28 years of age, after admission to a Neurologic Clinic and undergoing eye examination and lumbar puncture she was diagnosed with Behcet's disease with neurological and systemic involvement. Test for HLA-B51 antigen was negative.

Discussion and conclusions This case shows the association of MA and Behcet's disease. It is not clear whether headache could be secondary to angiitis (IHS 6.4.3), to neuro-Bechet or be a primary headache comorbid with it. Given the lack of data in the literature, this kind of association requires further investigation.

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Fusiform aneurysm of a persistent trigeminal artery mimicking a status migrainosus

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Background Persistence of trigeminal artery is a rare vascular condition. The primitive trigeminal artery is the most common of persistent carotid-basilar anastomoses with an angiographic incidence of 0.1–0.6%. Headache is reported as a possible symptom and approximately 14% of patients with a persistent trigeminal artery also have an intracranial aneurysm.

Case Report We report the case of a 37-year-old man. Familial history for headache was positive. When he was thirteen, he had a head and neck trauma caused by a car accident, followed by coma for two days. He was affected by migraine without aura since he was twenty-five. The attacks always showed the same features: pain was localized on the neck, with a frequence of 1-2 episodes per month; it was responsive to treatment with NSAIDs. He presented to our hospital complaining of a severe different headache for site and duration: it was a throbbing pain with a right frontal - temporal and retroorbital location and was associated with phonophobia, photophobia, nausea, vomit and tinnitus in the right ear. Pain and its associated symptoms had suddenly started at 4.00 a.m. 4 days before. Headache was continuous, severe, highly disabling and non responsive to triptans, NSAIDs, and opioids. Neurological exam showed a horizontal bilateral nystagmus. Computer tomography was negative. At first it seemed to be a status migrainosus, however the presence of nystagmus, pain localization (different from patient's usual headache), severity, duration, and drug resistance induced us to investigate further. Audiometric test showed a sensorineural hearing loss in the right ear of low-medium intensity. He could not undergo magnetic resonance angiography because of the presence of a metal prostheses; diagnosis of fusiform aneurysm of a persistent trigeminal artery was established by CT angiography. Aneurysms of the persistent trigeminal artery are rare and endovascular treatment of these aneurysms has not been previously attempted. The patient opted for drug treatment. He was treated with pregabalin titled to 150 mg with persisting benefit.

Conclusions Our purpose was to carefully underline the importance of analysing headache features, in particular when there are changes of pain characteristics compared to the past. In these cases a MRI is recommended. Aneurysm of a persistent trigeminal artery is not dangerous, however approximately 14% of patients with a persistent trigeminal artery also have another intracranial aneurysm. So atypical pain could be a warning sign for an uncommon and more dangerous disease.

Migraine without and with aura, migralepsy, epilepsy: comorbidity or a continuum? A complex case report

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Background Migraine (M) and epilepsy (E) are diseases with comorbidity. Migralepsy (ML) is a rare phenomenon and olfactory aura (OA) is a rare kind of aura not considered in the International Classification of Headache Disorders 2nd edition (1); furthermore there are no reports of ML secondary to migrainous OA.

Case report We describe a complex case of a 39-year-old right-handed medical doctor with a history of migraine without aura (MO) since childhood. From the age of 33, he developed a new kind of severe pain attacks, localized in the fronto-temporal region and then spreading to the omolateral hemicranium on one side or to the other, preceded by olfactory hallucinations, sometimes resembling a gas smell, with a gradual onset (1-2 minutes), lasting 2 to 8 minutes always followed within a few minutes by a M attack. The onset of OA was described as an intermittent perception that within minutes began continuous and the intensity initially vague became more intense. After about ten attacks like this, he presented an episode of olfactory hallucination followed by a migraine attack, after thirty minutes he presented an absence with fixed eyes and masticatory movements lasting about 2 minutes; thereafter, a secondarily generalized tonic-clonic seizure occurred. Laboratory and imaging investigations in the Emergency Department were all negative. Electroencephalogram (EEG) and Holter EEG showed isolated figures of sharp waves in the right temporal region. General and neurologic examinations were normal, and local pathologic diseases have been excluded. After a second episode, three months later, he started a treatment with valproic acid (VPA). During drug titration, he presented another episode of absence but without secondary generalized tonic-clonic seizure. VPA 1500 mg/day caused some adverse events and it was replaced with topiramate 200 mg/day. The follow-up after two years was negative for reappearance of the seizures and of M with OA attacks and showed a good control of MO attacks.

Conclusions In our case epilepsy apparently gradually evolved from MO, through M with OA and ML triggered by OA. The clinical findings support this hypothesis; instrumental data are only for exclusion (interictal EEG, not

significative and brain neuroimaging, normal), ictal recording of the event was not available. Further controlled studies on larger series of migrainous patients could confirm this observation in order to better classify OA and to improve the knowledge of the relationship between M, ML and E.

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Atrial septal defect closure and de novo migraine: exclusive ticlopidine efficacy

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Introduction A number of reports have described the *de novo* onset, or higher frequency and/or intensity, of migraine attacks after percutaneous closure of an atrial septal defects (ASD) [1]. Antiplatelet drugs, such as clopidogrel, used to prevent post-ASD closure thromboembolic events, have been associated in several case reports with migraine improvement [2]. We report the case of a woman who, after ASD closure, experienced *de novo* severe migraine with aura; whereas use of acetylsalycilic acid (ASA) or clopidogrel had no effect, ticlopidine use was associated with migraine improvement.

Case Report A 34-year-old woman with an ostium secundum ASD documented by a transesophageal echocardiography was seen in our Headache Centre in December 2010. When she was 28 years old, the closure of the ASD with the Amplatzer septal occluder was successfully performed. A double antiplatelet treatment with ASA 100 mg and clopidogrel 75 mg was started immediately after the operation. On day 3 after the surgical procedure, the patient experienced a neurological symptomatology with visual disturbances and headache, diagnosed as migraine with aura. After this first attack, the patient had similar episodes that occurred a minimum of 5 times per month until November 2009, when she was advised to discontinue ASA and clopidogrel, and start ticlopidine 250 mg. After beginning ticlopidine treatment, no further episodes of either visual disturbances or headache were experienced by the patient. In the following years, the patient temporarily suspended ticlopidine treatment for two times, showing two positive dechallenges and two positive rechallenges, with an identical latency (4-5 days) between treatment withdrawal and re-start and migraine appearance and disappearance, respectively.

Discussion When treated with ASA and clopidogrel, the patient did not refer any pain relief. For ASA, this may be due to the difference between the analgesic and antiplatelet doses (325 mg and 100 mg, respectively). In the case of clopidogrel, we performed a pharmacogenetic analysis and found only the heterozygosis for ABCB1 gene, for which no conclusive evidence exists on the relationship between the mutation and the variability in the absorption of clopidogrel. The pharmacokinetics of ticlopidine fit well with the timing of headache recurrence; in fact, ticlopidine achieves steady state plasma concentrations just within 5 days.

Conclusions Although the mechanism of thienopyridines as preventive drugs for migraine after ASD closure is unknown, if not contraindicated, a ticlopidine trial could be performed in those patients who, like the present one, do not show any benefit from clopidogrel in association with ASA after ASD closure.

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Headache associated with personality disorder determined by spontaneous intracranial hypotension and reversed by lumbar epidural blood patch

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Background Spontaneous intracranial hypotension (SIH) is characterized by a low cerebro spinal fluid pressure, orthostatic or rarely non postural headache, and distinct abnormalities on magnetic resonance imaging (MRI) [1]. Psychiatric symptoms rarely occur, and include bipolar disorder, psychosis, and even fronto-temporal dementia.

Objective To describe a case with headache and a personality disorder induced by SIH, successfully treated with blood epidural blood patch (EBP).

Results In October 2009, a 55-year-old woman started complaining about non postural, gravative, moderately severe frontal headache associated with generalized weakness, drowsiness, and slowing of mental activity. The patient's husband reported that, during the previous weeks, her behaviour had changed. Her libido was reduced, she had begun smoking many more cigarettes than before, and she had become more superficial at work and at home, failing to do chores as efficiently as before. Three months later, she was admitted to a hospital close to her native town for severe, gravative fronto-temporal headache and confusion. The patient's husband reported that her attention and concentration were progressively decreasing and that she had begun repetitive because of memory difficulties. On brain MRI, pituitary enlargement, brain sagging, and diffuse pachimeningeal enhancement emerged, suggesting the diagnosis of SIH. In June 2011, the patient was admitted to our department to be treated with EBP. Soon after admission, the patient appeared wary, suspicious, and hypocritical about her health. However, from the day after the treatment, all symptoms exhibited previously disappeared, and the patient seemed smiling, talkative, collaborative. In short, she was back to normality. Her reversal to normalcy was confirmed at an eleven-month follow-up visit.

Conclusions This case had the following implications: a) SIH can present as a personality disorder, which is likely to be determined by compression of fronto-basal structures on basal skull bone, caused by caudal brain sagging; b) EBP [2] can reverse headache and the personality disorder induced by SIH.

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Trigeminal neuralgia evolved into SUNCT (or SUNCT-like?) 15 years after Gasserian ganglion radiofrequency thermocoagulation

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Introduction Trigeminal neuralgia (TN) and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) are different clinical entities and are classified in different sections of the International Classification of Headache Disorders (ICHD-II). These two disorders seem to be quite different and well characterized; however, in some case series a coexistence of these two entities was noted, and a switch from one form to the other was reported [1].

Case report We report the case of an 87-year-old male, affected by diabetes mellitus, atrial fibrillation, hypertension, using a cardiac pacemaker. At the age of 71 he began to suffer from TN involving the second right branch, and consequently he was treated with carbamazepine (CBZ 600 mg/day), initially with benefit. After some months he complained of a recurrence of pain, therefore the CBZ dose was increased up to 1200 mg/day without any improvement. Due to the inefficacy of the first-line medication, he was treated with Gasserian ganglion radiofrequency thermocoagulation (RFT), which resulted in the disappearance of TN and subsequent discontinuation of pharmacological treatment 3 months later. One year after, the pain recurred and the patient underwent a further RFT. After the second intervention the patient remained pain-free until the age of 87, when he came to our attention complaining of an orbito-temporal, right-sided, electric shock-like pain, abrupt in onset and cessation, occurring 20-30 times/day, lasting 20-30 seconds, triggered by talking, chewing and mouth opening, without refractory period between attacks, associated with ipsilateral conjunctival injection and tearing. Neurological examination showed a small area of hypoaesthesia in the second right branch trigeminal region, as a consequence of the previous surgical interventions. Physical examination and laboratory investigations were negative; brain MRI could not be performed, due to the presence of a pacemaker. The patient was again treated with CBZ, the dose was titrated up to 1000 mg/day, in association for the first week with oral prednisone 50 mg/day; after two days the patient became pain-free. At 6-month follow-up evaluation the pain-free status was confirmed, and therefore the patient is still being treated with CBZ, with good tolerability.

Discussion and conclusions The new-onset headache, which started 15 years after the successful neurosurgical treatment of TN, fulfils the diagnostic criteria for SUNCT. Treatment of SUNCT is challenging and up to now is supported by little evidence [2]; conversely, the first-line medication for TN is CBZ. Our patient had a quick remission of attacks with CBZ associated with prednisone. To our knowledge this is the first report of TN evolving into SUNCT after Gasserian ganglion RFT, or possibly into a SUNCT-like syndrome [3], given the good results obtained with CBZ.

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A rare case of eosinophilic granuloma of the skull in an adult

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Introduction Eosinophilic granuloma (EG) is a rare benign tumor-like condition which is characterized by a clonal proliferation of Langerhans-type histiocytes in the bone or lung. It is the benign form of three clinical variants of Langerhans cell Histiocytosis (LCH) [1]. The incidence of EG is estimated at 0.05–0.5 per 100,000 and 90% of EG occurs under the age of 15. Flat bones are involved in 70% of the cases and long bones in 30%. Bone lesions are most often asymptomatic. The laboratory tests rarely document leukocytosis and eosinophilia. The causes and pathogenesis of EG are unknown. In spite of extensive genetic studies or virologic analyses, an apparent genetic error or infectious agents have not been found [2].

Case report We report the case of a healthy 61-year-old man, who presented to our clinic with bilateral and frontal high intensity throbbing pain, exacerbated by physical exertion and associated with photophobia and phonophobia but not with nausea and vomiting. Sometimes the pain started from the neck. The symptoms were not attenuated by the administration of analgesics, previously effective. At palpation, a nodule with soft consistency was appreciated in the right parietal region. The neurological examination was normal. The patient reported a previous head injury in the right parietal bone of the skull after an accidental fall down the stairs in childhood. A CT scan showed the presence of an osteolytic lesion localized in the same site, with radiopaque sequestration with "button" aspect, attributable to intact bone in the centre of a circular area of destruction. The radiological features were typical of eosinophilic granuloma. An increase in the amplitude of the subarachnoid space below and a severe sinusopatia were also described. A brain MR with contrast medium confirmed this report. Laboratory tests documented the presence of leukocytosis with increase in neutrophils and monocytes. A bone scan showed no areas of increased uptake, except for the skull lesion. A neurosurgical evaluation did not indicate a need for surgery. A prophylactic treatment with magnesium, tryptophan and serotonin resulted in a reduction of the number and intensity of the crises. The patient currently performs periodic CT scans documenting the dimensional stability of the lesion.

Conclusions According to ICHD-II diagnostic criteria, the reported headache symptoms are suggestive for migraine. The granuloma finding thus seems to be incidental. To our knowledge, this is the first case of migraine associated with an eosinophilic granuloma.

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Does suicide cause suicide headache?

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Background Cluster headache [CH] is also known as suicide headache. Indeed, suicidal ideation is reported to occur among 55% of the CH population, although only 2% does commit suicide [1]. The role of the grief for the suicide of a beloved person as a potential trigger of a CH attack has never been reported.

Case Report A 58-year-old woman with silent unremarkable medical history and healthy habits (she did not smoke nor drink alcohol) came to our observation on June 20th. Since the end of April 2012, she had suffered attacks of "an excruciating pain, impossible to resist to", localized in the fronto-orbital and nasal regions on the right side, which lasted two hours and recurred every day around 11.00 am. She reported that the attacks were accompanied by omolateral ptosis and restlessness. This cluster had come to an end just a few days before. Neurological examination was normal. Cerebral MR without gadolinium showed signs of chronic sinusitis in the maxillary, ethmoid and sphenoid sinuses. An ORL specialist ruled out any causal relation. Sinusitis was treated with corticosteroids and antibiotics for 10 days, during which the patient was asymptomatic; headache reappeared the day after treatment discontinuation. Deepening her clinical history, we found that she had suffered a similar episode in December 2011. This cluster, which lasted just a week, had started four day after the notice of the suicide of a close friend; whereas, the second cluster began three days after she knew that the young son of another close friend had committed suicide.

Discussion and conclusions According to ICHD-II criteria, our patient suffers from episodic CH. Her habits are normal; in particular, she does not

smoke nor drink wine or spirits, conditions reported to be often present in people with CH. In the literature, we did not find data on a potential role of emotional factors, more specifically linked to the death of a beloved person, in triggering CH attacks. In our case both attacks seem strictly related temporally with such an intense grief.
The apparent causal relationship between the emotional impact of these tragic events and CH episodes warrants further investigation on the possibility that an extraordinarily stressing experience, causing a shattered psychological status, could act as a CH trigger.
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A "suspect" migraine

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A 29-year-old male come to our attention because of the sudden onset of a fronto-orbital and nuchal-occipital unilateral headache, preceded by a visual transient unilateral disturbance. The pain was pulsating, intermittent and oppressive, accompanied by nausea, vomiting, and photophobia. It looked like a migraine attack, although the patient had never suffered from and did not have a family history for headache. He took analgesics and antiemetics for three days with no improvement. On the fourth day of headache he went to the Emergency Room. The patient was in good physical condition: the neurological examination was negative, blood pressure, blood count and biochemistry were normal, there was no fever or neck rigidity. An ECG documented sinus bradycardia (about 45 bpm). A CT scan was therefore performed, in accordance with ICHD-II criteria [1], which showed a roundish lesion with a diametre of about 11 mm in the sella turcica and no signs of intracranial hypertension or bleeding. Apparently there was no relationship between headache and pituitary adenoma. The patient was treated with tramadol, antiemetics and anxiolytics improving significantly the pain until headache disappeared completely. The tests were completed with a MRI which detected a craniopharyngioma of about 26 mm, a computed campimetry that showed a lower left-sided hemianopsia of the right eye and a measurement of pituitary hormones. The hormone levels were in the standard range including repeatedly performed prolactin levels. The initial hypothesis that the lesion was an adenoma was therefore confuted and in consideration of the high grade of compression of the optic chiasm surgery became necessary. The patient was sent to the neurosurgeon for the excision of the tumor and the histological examination.
Discussion Can we describe a headache as being a "sentinel"? In this case, probably yes. Our patient had never suffered from headache before, and although young, he was worthy of a clear diagnosis and was right to go to the Emergency Room. In fact, what at first might seem a trivial attack of migraine with aura was a symptom of a serious disease. The beginning of the headache was not described as a "thunderclap" pain, the pain was intermittent, pulsating and progressively improving, all features diverging from the characteristics of headaches secondary to intracranial tumors according to ICHD-II criteria. Surely, however, the pain was related to the intracranial lesion. It is not the first case of an onset or a change in the characteristics of headache in combination with another disease not necessarily involving the brain [2]; thus in our opinion it is appropriate to describe this headache "paraneoplastic" or rather "sentinel".
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Blurred vision and progressively worsening of headache: an unusual presentation of Vogt-Koyanagi-Harada syndrome

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Introduction Vogt-Koyanagi-Harada syndrome (VKHS) is a rare multisystemic disease also known as uveomeningoencephalitic syndrome, characterized by chronic bilateral panuveitis associated with a varying constellation of neurological, auditory and cutaneous manifestations. Although patients may present a range of ophthalmic features such as acute anterior uveitis, vitritis, serous retinal detachment, papillitis, depigmented "sunset glow" fundus [1], bilateral papilledema has never been described at the onset of VKHS.
Case report A previously healthy 45-year-old Chinese man presented to our Neurological Department with a two-week history of blurred vision in both eyes and progressively worsening headache. An ophthalmologic examination on admission revealed a bilateral papillary edema, without other neurological signs. Brain CT scan was negative and a lumbar puncture showed severe lymphocytic pleocytosis with elevated protein levels.
Optical Coherence Tomography showed severe retinal detachments and fundal fluorescein angiography of both eyes demonstrated multiple areas of pinpoint hyperfluorescence. During hospitalization the patient also showed decreased hearing, tinnitus and low-grade fever.
According to revised diagnostic criteria for Vogt-Koyanagi-Harada syndrome published by the International Committee on Nomenclature in 2001 [2], a diagnosis of incomplete Vogt-Koyanagi-Harada syndrome was made based on the lack of specific dermatological features. The patient was treated with methylprednisolone (1 g/day i.v. for 5 days) followed by oral prednisolone (25 mg, tapered off over two weeks) with improvement of headache. For the persistence of blurred vision, cyclophosphamide 50 mg/die and cyclosporine 150 mg/die, were somministrated with a slight improvement of ophthalmological symptoms.
Conclusions This case highlights the importance of performing a complete ophthalmologic examination, OCT and fluorescein angiography, in patients presenting progressively worsening headache and bilateral papilledema to reveal as soon as possible a VKHS, especially in people from China, where the disease is more common. Early detection of this disease is important to treat people affected by VKHS with immunosuppressive therapy which provides the best chance of clinical improvement in patients with this rare disorder.
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Idiopathic intracranial hypertension without papilledema: a case report

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Case report A 36-year-old male patient (F.L.) came to our observation because of the onset, five months earlier, of a unilateral localized headache, right tem-

poro-orbital, severe intensity, continuous-subcontinuous frequency with paroxysmal crises mostly during nighttime. The painful symptomatology was associated with focusing difficulties which lead to the onset of diplopia.
During a previous referral, the patient underwent instrumental exams (cranial CT with contrast, brain MR with contrast, both negative), he followed a steroid therapy (80 mg/day, gradually tapered down) for suspected optical neuritis which resolved the symptomatology. When the steroid therapy was suspended the symptoms reappeared, therefore he began topiramate (75 mg/day) and zolmitriptan with a diagnosis of chronic migraine.
When the patient came to our observation, he suffered from retro-bulbar pain, stabbing type, with irradiation to the cheekbone, mastication difficulties with masseter muscle fatigue, gaze diplopia with right laterality. The continuous pain, referred as untolerable during the paroxysmal episodes, was not associated to neurovegetative phenomenon. The patient denied the presence of lacrimation and/or conjunctival injection and rhinorrhea.
A detailed case history outlined in 2006 an episode of unilateral migraine which lasted about a month, poorly respondent to FANS, with spontaneous resolution. The patient was also hospitalization because of an epileptic crisis; at that time, he underwent an EEG and brain MR with contrast, both resulted negative.
We decided to perform blood tests (including autoimmunity and phlogosis indexes), brain MR with contrast, arterial and venous angio MR, fundus, and field of vision esaminations.
Objective exam did not show any neurological signs, except for the presence of gaze diplopia with right laterality.
In the differential diagnosis we took into account: vasculitis, temporal arthritis, possible thrombosis with venous obstruction, ophthalmic arterial thrombosis, and cerebral masses.
All the above mentioned exams were normal, therefore we diagnosed idiopathic intracranial hypertension (IIH).
The diagnosis was confirmed by the initial and sudden response, until complete resolution of the clinical picture, to the diuretic therapy (acetazolamide, 250 mg up to 750 mg/day) with continuous monitoring of the electrolytic picture, renal functions and blood gas analysis. After three months, the therapy was suspended in view of a complete resolution of the symptomatology.
IIH is a diagnosis of exclusion based on the Modified Dandy criteria, and on the updated diagnostic criteria proposed by Friedman and Jacobson later [1]. We decided not to perform a lumbar puncture, the "gold standard" for the diagnosis because results of the neurologic examination were negative, except for the presence of diplopia, the results of the field of vision were in the norme, and the prompt response to pharmacological therapy. IIH without papilledema is a rare pathology (about 5%) [2], and usually affects people who are not overweight and have a minor cerebrospinal fluid pressure. The risk that it may lead to blindness is much lower compared to patients with papilledema.

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Comorbidities

Migraine and hypothyroidism: a new comorbidity?

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Introduction The International Classification of Headache Disorders (ICHD) – 2nd edition included as a "new entry" in the secondary headache group the so-called "headache attributed to hypothyroidism" [1]. The diagnostic criteria require the headache to resolve within two months after effective treatment of hypothyroidism (HT). However, this condition seems to be quite rare in clinical practice, whereas it is more common to see migraine patients also affected by HT.
Materials and methods We retrospectively evaluated the clinical records of 3,727 patients diagnosed with primary headaches referred to our Headache Centre from 2005 to 2011. We studied the prevalence of HT in the different groups of headache sufferers.
Results The population consisted of 2,232 patients with migraine without aura (MO), 485 with tension-type headache (TTH), 367 with MO + TTH, 228 with migraine with aura (MA), 203 with MO + MA, 143 with cluster headache, and 69 with other primary headaches. Overall, 98 cases (95 females and 3 males) of full-blown HT requiring hormone therapy were observed. Ninety of these cases (2 males) were migraineurs and 8 suffered from TTH (1 male). Therefore, the prevalence of HT was 3.0% in migraine and 1.6% in TTH. The mean age of headache sufferers with HT was 48.4 ± 14.2 years.
Discussion HT was found in a notable proportion of migraineurs, while its prevalence was significantly lower in patients with TTH. Interestingly, HT occurred after migraine onset in 87 patients (96.7%), whereas it preceded migraine in 2 MO subjects and in 3 TTH patients. For the latter subjects headache attributed to HT was ruled out, due to the headache persistence after levothyroxine treatment. In a population-based study the prevalence of HT resulted to be 0.84% [2]. In our clinic-based survey the prevalence of HT in migraineurs was 3.0%. For 52.0% of patients the headache showed a significant worsening after the onset of HT and hormonal replacement therapy. It is challenging to speculate whether the worsening could be attributable to the hormonal disorder, to levothyroxine treatment or both.
Conclusions We found a high prevalence of HT in migraine, significantly higher than in the general population, even if these data cannot be directly comparable, due to different study methodology. HT should be considered as one of the varieties of migraine comorbidities, even if possible pathophysiological relationships remain unclear. In case of worsening of a pre-existing migraine, thyroid function should be investigated to rule out a possible HT.

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Survey about headaches in patients with obstructive sleep night apneas

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Objective To evaluate the prevalence of headache in patients suffering from obstructive sleep night apneas syndrome to subsequently put into place a series of preventive measures also in view of preventing complications.
Materials and methods We enrolled 254 subjects, 173 men and 81 women, mean age 56.8 + 15.0 years, suffering from obstructive sleep night apneas syndrome. The subjects were recruited in a period of 2 years at the Department of Pneumology of the Teramo Hospital. Apneas were graded as mild (AHI between 5-10), moderate (AHI between 11-20), severe (AHI

greater than 20). Headaches were classified according to the ICHD-II criteria. Twenty patients (8.1%) referred a history of primary headache: 3 were affected by migraine (1.2%) and 17 (6.9%) by headache. One hundred and eighty (70.9%) had headache upon awakening, with a greater frequency of breathing pauses during sleep, insomnia of central type and episodes of sweating. All patients underwent an interview with a standardised questionnaire on sleep features, on related conditions, on the type of headache, and on risk factors for headache.

Results The severity of obstructive sleep night apneas is related to the frequency of morning headache (frequency greater than in patients with insomnia), suggesting the relevant role of the hypercapnia consequential vasomotor phenomena.

Discussion The study group had a high prevalence of morning headache confirming results of previous studies concerning both its high frequency and severity in patients with sleep disorders. The strength of our study is the large sample size assessed, the detailed information collected on sleep disorders and other risk factors for headache.

Conclusions Our study suggests the need for patients with morning headache to undergo careful screening for sleep disturbances related to breathing disorders, for a correct diagnostic and therapeutic approach.

Prevalence of rheumatoid arthritis in migraine: possible action of stress and anxiety on neuroendocrine trim

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Rheumatoid arthritis (RA) is a chronic disease characterized by joint swelling, joint tenderness and destruction of synovial joints. The causes of RA are still unknown but autoimmune mechanisms are included in the etiopathogenesis. A susceptibility gene has been confirmed on Human Leukocyte Antigen (HLA), that mirrored outcomes stressing a genetic substrate for migraine (M) within the HLA region. Several data demonstrated the role of stress in progression of RA. Similarly, the precipitating role of stress in primary pain has been known since 1949. Thus, stress and anxiety might link M and RA on the ground of the neuroendocrine system.

Objective The aim of the study was to: a) evaluate the possible comorbidity of M and RA by considering prevalence of RA, in subjects suffering from M, in headache exempts, observed in a stratified sampling; and b) evaluate the possible RA promoting role of stress/anxiety in M sufferers and in exempts.

RA eligibility: Rheumatoid Arthritis Classification Criteria 2010 with particular reference to the following items 1) at least 1 joint where currently active clinical sinovitis is detectable, and 2) the criterion must be applied only when sinovitis cannot be better explained by another diagnosis. Migraine eligibility: Diagnosis of M without aura in agreement with the IHS criteria. For measuring stress: Life Stress Events and Scale Values where score of 300 = risk of illness, score 150-299 = moderate risk of illness, score 150 = slight risk of illness. For measuring anxiety: Zung test (cut off = 40). The psychometric tests were used in M and headache exempts. Subjects: The study population consisted of 2,160 patients and included M Group (n = 636, mean age 41.1 SD ± 5.2 years) and Headache exempts Group (n = 1160, mean age 41.3 SD ± 9.8 years). Recruitment period was November 2010 - December 2011.

Results and conclusions Prevalence in M was 0.5% for males and 1.7% for females, prevalence in headache exempts was 0.1% for males and 0.4% for females. Thus, RA is more frequent in M sufferers ($p > 0.0004$ and $p < 0.0001$ ANOVA, Cohen's kappa 0,8 - M versus general population and exempts, respectively). Scores in stress were similar in M and exempts, while anxiety was present in 50% in M sufferers versus 11% in exempts ($p > 0.0001$ ANOVA, Cohens' kappa 0,8). Thus, RA seems more frequent in M and anxiety might impact neuroendocrine trim linking RA to M.

Migraine and comorbid disorders: a pharmacoepidemiological study using a pharmacy claims database

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Introduction Many comorbidities were described in migraine patients from population-based studies, mostly with questionnaires based on self-reported diagnosis [1]. The aim of our study was to determine whether there was a positive relationship between the prescription of triptans, marker medications for migraine, and other specific drugs used in other diseases, as an index of comorbid diseases in migraine. This is a part of a large programme of integration between the general practitioner (GP), the headache centre and the pharmaceutical department, with the aim of: 1) registering headache diagnosis with ICHD-II criteria included in the software used by the GP, 2) using migraine screenings (ID migraine), and 3) optimizing the drug prescription for headaches.

Materials and methods The pharmacy claims database covering the total population of a Local Health Authority (about 240,000), filed between January 2009 to December 2011, was analyzed using Anatomical Therapeutic Chemical (ATC) codes. Variables were compared using the chi-square test.

Results A total of 1,108 subjects, that is, 0.7% of the population aged 15-65 years (155,829 residents) received triptan prescriptions in 2011. Pharmacy claims of drug markers for depression, psychosis, epilepsy, asthma and chronic obstructive pulmonary diseases (COPD), allergies, diabetes, hypertension, thyroid diseases, were analysed in triptan users and in the population aged 15-65 years.

The percentage of triptan users receiving drug markers in comparison to the control population were respectively: 22.8/6.8 antidepressants, 0.9/1.4 antipsychotics, 8.2/2.5 anticonvulsants, 12.9/7.9 antiasthma/COPD, 9.7/5.6 antihistamines, 1.3/2.8 antidiabetics, 22.8/11.9 antihypertensives, 4.6/3.7 thyroid hormones, 0.1/0.2 antithyroids. These findings were also found for the years 2009 and 2010. Therefore, a statistically significant higher percentage of triptan users also received a prescription for antidepressants, anticonvulsants, anti-histamines, anti-asthma/COPD, antihypertensives, in comparison to the general population. These differences, with the exception of anti-asthma/COPD and antihypertensives, were also found considering the entire population.

Among antihypertensives, only beta-blockers were prescribed more frequently in triptan users.

Conclusions Considering triptans as marker drugs for migraine, our study showed that migraine patients received more drug prescriptions for depression, epilepsy, allergy and respiratory diseases, but not for diabetes, hypertension (except beta-blockers), thyroid disease, and psychosis than the general population. We are considering whether some of these differences may be due to preventive drugs used for migraine or if they are related to sex therapy. These results partially agree with those of a large medical and pharmacy claims database [2]. The analysis of pharmacy claims for drug markers of pathologies may be a useful way to assess comorbidities in a large migraine population.

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Psychiatric comorbidities and factors related to the discontinuation of preventive migraine treatment: results from a naturalistic longitudinal study

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Introduction Few studies have researched systematic adherence to preventive migraine treatment. The aim of this study was to investigate which psychiatric comorbidities and others factors are independently responsible for discontinuation of preventive therapies prescribed to migraine outpatients.
Patients and methods The sample included 120 subjects, 94 F (78.3%) and 26 M (21.7%), aged between 16 and 65 years (mean 38.4), fulfilling ICHD-II criteria for episodic migraine 74.1% (n = 89), and chronic migraine 25.9% (n = 31), attending three Headache Centres in the Province of Salerno.
Mood and anxiety comorbidities were diagnosed using the Mini International NeuroPsychiatric Interview, a structured interview for the diagnosis of DSM-IV TR anxiety and mood disorders. All migraineurs enrolled received accurate education and a new preventive therapy at Baseline (Mo), based on the best clinical judgment: antidepressants (only tricyclics), anticonvulsivants, beta-blockers, Ca-channel blockers and "others". From baseline (Mo), follow-up was conducted at 1st, 3rd, 6th month. At the first follow-up (M1) preventive therapies were adjusted or changed. Dropouts were defined as those patients that missed one or more follow-up and failed to reschedule and complete the missed visit. Statistical analysis of data was carried out using independent sample *t*-test and χ^2 test comparing study completers (n = 66) and dropouts (n = 54).
Results The percentage of patients who did not complete the study (Dropouts) corresponded to 45% (n = 54). The majority of them, 76% (n = 41), abandoned treatment within the first three months from beginning of therapy.
Dropouts versus completers were patients with: more than one DSM IV Axis I disorder ($p < 0.1$); panic/agoraphobia disorder ($p < .03$); chronic depression ($p < .03$); chronic migraine ($p < .05$); less education ($p < .05$); younger ($p < .02$); assuming tricyclics ($p < .03$).
Discussion Many factors seem to play a role in determining the discontinuation of migraine preventive treatments: some chronic conditions - depression and migraine - more than their severity, as well as low education levels, young age and better tolerability of some drugs despite their efficiency.
Conclusions A systematic definition of factors independently determining non adherence to preventive migraine treatment represents a fundamental step to ensuring a favourable therapeutic outcome. It could allow: 1) to predict discontinuation of pharmacotherapy among migraine patients with psychiatric comorbitities; and 2) to prevent such discontinuation through an intervention including education and a possibile action on "modifiable" factors, enhancing adherence to treatment.

Thyroid dysfunction in episodic and chronic migraine: a preliminary study

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Introduction The role of thyroid dysfunction in migraine is still unclear. Disorders of thyroid function have been claimed to exacerbate migraine. In the large population-based study Head-HUNT, hypothyroidism seems to be related to low prevalence of migraine; conversely, other authors stated that hypothyroidism can induce transformation from episodic migraine (EM) to chronic migraine (CM) [1, 2].
Objective Aim of our study was to evaluate thyroid function in a sample of chronic and episodic migraineurs followed at the Headache Centre of the University of Turin (Italy).
Materials and methods We analyzed thyroid functions in 38 patients: 11 with EM and 27 affected by CM, defined as more than 15 headache-days/month. Familial history for migraine and thyroid dysfunction was collected and patients were questioned on previous prophylaxis for headache and for prophylactic antimigraine drugs. Blood sample was drawn to evaluate concentrations of: Thyroid Stimulating Hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), thyroid peroxidase antibodies (TPOAb), thyroid receptors antibodies (TRAb) and thyroglobulin antibodies (TGAb). To analyze our data a one-tail Chi-square test and a two-tail Student's T-distribution test were used.
Results Mean age was 46.7 years in the EM group and 49.6 years in the CM group. Mean duration of disease was 22.5 and 26.8 years, respectively ($p > 0.5$). Familial history of migraine and thyroid disease was common in the two groups ($p > 0.5$).
Small anomalies in thyroid profiles were detected in a large percentage of patients in both groups, 36.7% of EM and 51.9% of CM. Values of TSH, fT3 and TGAb were the more frequently altered, TGAb being the only one that showed a statistically significant difference between EM (mean of 216.3 UI/mL) and CM (mean of 59.8 UI/mL) ($p > 0.005$).
Discussion Thyroid dysfunction is extremely common in both populations of patients affected by EM and CM; it goes often undetected and, thus, untreated. In our small series we did not identify a clear difference of incidence of anomalies of the thyroid profile in the two groups, apart from a small predominance in the EM group showing TGAb positivity, nor a trend toward hypo- or hyperthyroidism in one or both arms.
Conclusions According to our results, there is no significant difference of thyroid function between EM and CM patients. New studies with larger sample of patients are needed to investigate thyroid function involvement in migraine.
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Association between migraine and restless legs syndrome

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Background An association between primary headaches and sleep disorders has long been recognized. In particular, migraine is known to be comorbid with a number of neurological and psychiatric disorders, and recently it has also been correlated with several sleep disturbances. As a matter of fact, according to recent studies, a significant association between restless legs syndrome (RLS) and migraine has been reported [1, 2]. RLS is a common but still frequently undiagnosed sensorimotor disorder, with a notable impact on sleep quality.
Objective Aim of the study was to further examine the association between RLS and migraine and to explore the clinical correlates of comorbid RLS.
Materials and methods One hundred and thirty-six migraine patients, 102 females (75%, mean age 52.8 yrs ± SD 11.7) and 34 males (25%, mean age 65.3 yrs ± SD 12.8), referring to the outpatients clinic of the Headache Centre of the University of Turin, were enrolled in the study. Migraine diagnosis was made according to ICDH-II criteria (2004). Clinical characteristics of migraine, MIDAS questionnaire, subjective evaluation of headache intensity,

number of days with migraine in the last 3 months, as well as anxiety and depression; daylife habits were also evaluated. Sleep habits and characteristics were collected from each patient, using Pittsburgh Sleep Quality Index (PSQI), Berlin Questionnaire, Epworth Sleepiness Scale (ESS), and Restless Legs Syndrome Scale (RLSS). Statistical analysis of data was performed using SPSS 18.

Results The prevalence of RLS in migraine patients in the study group resulted significantly higher (34.5%), in comparison with the prevalence of disease in the general population. A statistically significant association was found between RLS and migraine severity. The association between RLS and attack frequency was significant ($p = 0.032$), as well as that with BDI results ($p < 0.001$). We also found that the association between RLS and SE, PSQI, RLSRS showed a significant correlation ($p < 0.001$).

Discussion and conclusions Our data further support the association between migraine and RLS, adding weight to the theory of migraine and RLS as comorbid conditions, and suggests a strict relationship between migraine severity and the development of RLS. Finally, a higher frequency of sleep disturbances was found in RLS migraineurs. Additional studies are warranted in order to investigate the neurobiological basis of this phenomenon.

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Primary headaches and disorders alvus: possible comorbidity

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Introduction The nature of functional gastrointestinal disorders are characterized by extra-intestinal symptoms (gynecological, urinary, psychological, dermatological, neurological). As part of the functional nature of gastrointestinal disorders (constipation) the presence of headache affects over 30% of patients, with a prevalence in females and with a peak of 63% in the age group between 16 and 40 years.

Materials and methods All patients referred to an outpatient clinic of the Headache Centre of the University of Pavia in the last 6 months of 2010 were included in our study. The diagnosis of migraine according to ICHD-II criteria or other conditions, age, sex and alvus disorders were analyzed.

Results Of the 286 patients undergoing outpatient visit, 206 had a diagnosis of primary and 4 secondary headache. Of the 206 patients with primary headache (96 migraine without aura, 18 migraine with aura, 45 tension-type headache, 11 episodic or chronic cluster headache, 36 mixed-type headache with 8 patients with analgesic abuse. One hundred and forty-one were women and 56 men (mean age 31.7 + 9.8). Statistical analysis performed by crossing the various subgroups was significant crossover between the patients suffering from constipation and migraine without aura ($p < 0.04$).

Discussion The analysis of the results obtained with this observational method emphasised that the change of physiological rhythms (alvus alterations: constipation) may influence or be influenced by mechanisms that come into play with the onset of migraine.

Conclusions Thus, it would be desirable to study the changes in the physiological rhythms and particularly in those alvus (constipation) as a function of the pathophysiology of migraine. The modulation of gastric visceral sensitivity (constipation), taking into account the role of serotonin on gastric tone and phasic activity, could represent a new target for therapies aimed at improving the severity of headache at least in some subgroups of patients.

Shift work and primary headaches: a population study of the association of workers in the chemical industry

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Introduction Today it is known that exposure to certain occupational risk factors have a causal relationship with the onset of headache. However, in the workplace, the exposure to non-causal factors of the disease which prepare and facilitate the emergence of a new attack in patients already suffering from primary headaches is more important.

Materials and methods Health surveillance and medical history questionnaires targeted 95 workers, 91 males and 4 females. Fifty workers (52.6%) worked in night shifts while 45 workers (47.4%) worked in the round of daily work. The shift system was kind of anterograde and always performed on three shifts.

Results The form of primary headache with a higher prevalence, in both groups, is represented by migraine without aura (51.5% of all headache workers), followed by episodic tension headache (42.5%) and migraine with aura (6%). From the study of only the male working population, the research data showed a statistically significant association between the prevalence of primary headache and outreach night shift work. Although numerically appreciable, the difference in prevalence of primary headache in the two groups of workers did not reach statistical significance considering the four female employees. However, because there were females in one group of workers in the day shift and in the light of literature data documenting a significantly higher prevalence of migraine in females than males, the exclusion of the four female subjects from our study appears justified in view of the need to ensure maximum homogeneity of the two populations under study.

Conclusions Considering only male workers, the prevalence of primary headache was 42% in shift workers and 22% among others. The study shows a significant association between the conduct of work in night shift and the onset of headache. Scientific literature has documented the negative effect that night work has on the subject as shown on various organs and systems of the human organism, and its ability to configure itself as an important etiological factor in undermining the state of mental and physical well being of the worker. A possible negative effect of work at night as headache trigger seizures in people with acute primary headache has already been suggested in previous research. To date, however, there are few studies that have shown an association between shift work and an increased risk of headache. The results of our work strengthens the hypothesis that the two events may be associated.

Neurophysiology/Neurochemistry/Magnetic Resonance Imaging

Migraine in the elderly: a neurobiochemical profile

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There is a clearly decreasing prevalence of migraine (M) with older age. Our aim was to identify possible biochemical differences distinguishing old M sufferers when compared to control subjects or young/adult M sufferers showing an overlapping M severity and frequency (4-6 attacks/month, A2). The 3 groups under observation were matched in regards to moderate regular exer-

cise – cycling on a leg ergometer at 80% ventilator threshold 5 days/week, at least during the following 3 months after the study started. Old M sufferers included in the study reported an age-related improvement of 25% when compared to 10 years prior as demonstrated by pain diaries of the last 10 years. We measured CGRP levels and nitric oxide (NO) synthase activity in the aforementioned 3 groups.

Methods Exclusion criteria were hypertension, dementia (DMS-IV), diabetes, anxiety, and depression (cut off = 40 Zung test, Wang test). Blood and saliva samples were obtained in the 3 Groups: A) M sufferers (n = 10, 6 males, 4 females age: 66 years at the time of first evaluation), B) control subjects (n = 10, 6 males, 4 females, age: 66 years at the time of first evaluation), and C) young/adult (6 males, 4 females) affected by M (age 30-42 years). Samples were obtained once from Group C, whereas they were obtained yearly, for a 6-year period in older M sufferers (Group A) and controls (Group B). We measured salivary CGRP-LI and plasmatic L-citrulline, equimolar co-product in the synthesis of NO in samples obtained from the 3 Groups at the given times.

Results and conclusions Salivary CGRP-LI levels were similar in M sufferers, either old or young. In fact, it showed scant, non significant variations: 35.9 ± 12.1SD pmol/l in young migraineurs vs. 35.6 ± 11.2SD pmol/l in old sufferers. As expected NO level had decreased in elderly subjects (ANOVA $p < 0.0001$ versus young subjects). The decrease was dramatic in old M sufferers versus young migraineurs and controls: 10.2 ± 3.5SD nmol/ml L-citrulline vs. 34.35 + 7.6SD nmol /ml and 19.4 ± 2.8SD nmol/ml, respectively ($p < 0.0001$ ANOVA). Moreover, with increase in age, L-citrulline levels slowly and less markedly decreased in exempts from 19.4 ± 2.8SD nmol/ml toward 15.1 ± 3.1SD nmol/ml. The finding of a decrease NOs activity in old migraineurs compared to young M sufferers ($p < 0.0001$) and controls ($p < 0.0001$) does not support a pivotal headache-promoting role of NO in M of the elderly. Based on these observations, it could be relevant to measure modulators/transmitters in different age groups for migraine.

Changes in glutamatergic neurotransmission within the migraine cycle

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Background Although some neurophysiological studies have shown cortical excitability changes during different phases of the migraine cycle, the pathophysiological mechanisms underlying attack recurrence remain unknown. Here we evaluated the response of the migraine motor-cortex to brief trains of 5-Hz repetitive transcranial magnetic stimulation (rTMS) in order to study, indirectly, presynaptic mechanisms of glutamatergic neurotransmission across the different phases of the migraine cycle.

Methods Forty migraine with aura (MA) and 40 migraine without aura (MO) patients underwent suprathreshold (130% of the resting motor threshold) brief trains of 5-Hz-rTMS to the motor-cortex, recording motor evoked potentials (MEPs) at each train stimulus. Patients were studied whatever the phase of the migraine cycle: interictal (n = 51), preictal (n = 9), ictal (n = 10) or postictal (n = 10).

Results As we previously showed, in the interictal phase MEPs decreased significantly in size during 5-Hz trains. A significantly greater inhibitory response was recorded during the ictal and postictal phases. Conversely, in the preictal phase, we observed a facilitatory response to the trains similar to that of normal subjects. No significant differences were recorded between MA and MO patients.

Conclusions Our results support the hypothesis that in migraine a transient increase in intracortical glutamatergic activity could trigger the migraine attack. Inhibitory homeostatic mechanisms of glutamate release could be involved in the resolution of the migraine attack and in preventing further attacks.

TRPV1, CGRP and SP in scalp arteries from patients suffering with chronic migraine

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Introduction The neuropeptides calcitonin gene-related peptide (CGRP) and substance P (SP) and the vanilloid receptor TRPV1 appear to be differently involved in migraine pain. A role of scalp arteries in migraine is suggested by several data [1]. Recent experiences indicate a beneficial effect of the ligature of scalp arteries in chronic migraine (CM) [2]. The possibility to examine surgical specimens of human scalp arteries from CM patients and control subjects prompted this study.

Materials and methods Treatment-resistant patients with CM were submitted for surgery of one or more scalp arteries by one of us (E.S.). Short segments of 9 arteries were examined. Similar segments of 4 superficial temporal arteries were collected by R.B. during surgery for intracranial pathologies and used as controls. All patients gave informed consent. Specimens were examined by immunohistochemistry for TRPV1, CGRP, SP and, as comparison, for the pan-neuronal structural nerve marker protein gene product 9.5 (PGP9.5), which marks all nerves. Immunoreactive nerve fibres in vessel cross sections were quantified by computerised image analysis by an observer unaware of sample origin. Density of innervation was evaluated in three sections per specimen as the ratio of the total length in mm of the immunostained fibre segments detectable in each section to the section area.

Results Immunoreactive material to TRPV1, CGRP, SP and PGP9.5 was detected in adventitial nerve fibres. Density of stained nerve fibres differed for each marker and varied among specimens. The average of the innervation within CM and control specimens showed statistically significant differences between the two groups for TRPV1 ($p = .009$), CGRP ($p = .001$) and SP ($p = .037$), and not for PGP9.5 ($p = .31$) (t-test). Analysis of the ratio of TRPV1-, CGRP- and SP-positive fibres to PGP9.5-positive ones for each artery gave a statistically significant higher amount of TRPV1-positive fibres in CM compared to control samples ($p < .02$, U-test), while the peptide-positive fibres, though more abundant in CM tissue, did not significantly differ between the two groups.

Discussion Our data show that in the wall of scalp arteries of subjects affected by CM there is an increased presence of nervous fibres containing the vanilloid receptor TRPV1 and, in a lower measure, the peptides CGRP and SP. This supports the viewpoint of a role of scalp arteries and the involvement of TRPV1 and possibly CGRP and SP in CM.

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Effects of URB937 on an animal model of migraine pain

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Experimental studies have suggested the existence of several interactions between the endocannabinoid system and pain mediation in migraine. Recently it has been demonstrated that URB937, a potent fatty-acid amide hydrolase (FAAH) inhibitor that does not penetrate the blood-brain barrier - and therefore increases the levels of anandamide only in the peripheral tissues - causes analgesia in animal models of pain. In this study we evaluated whether the peripheral modulation of the endocannabinoid system, by means of URB937, may alter nociceptive responses in an animal model specific for migraine based on nitroglycerin-induced hyperalgesia. Animals received systemic nitroglycerin and URB937 before being evaluated at the Tail flick test or at the Formalin test. URB937 induced analgesia at both tests. Furthermore, it did inhibit NTG-induced hyperalgesia at the Formalin test, with only a minimal influence on NTG-induced hyperalgesia at the Tail flick test. These findings suggest that increased availability of anandamide at the peripheral (probably meningeal) level is potentially effective in the management of migraine pain and provide a potential therapeutic probe (URB937) for testing this hypothesis.

Influence of primary motor area and left dorsolateral prefrontal cortex transcranial direct current stimulation on laser evoked potentials in migraine patients and normal subjects

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Introduction Non-invasive brain stimulation techniques induce an electrical stimulation of the brain in an attempt to reduce chronic pain by directly altering brain activity. In this case-control study we compared the effects of transcranial direct current stimulation (tDCS) of the left primary motor cortex (M1) and left dorsolateral prefrontal cortex (DLPFC) both on subjective pain and on evoked responses induced by laser stimulation (LEPs).
Methods The study was conducted in a cohort of twenty-six migraine patients without aura during the inter-critical phase, and ten age- and sex-matched non-migraine healthy controls. Among migraine patients, we stimulated the left DLPFC area in 15 cases and the M1 area in 11 cases. Evoked laser potentials were recorded in basal, sham and during tDCS, by stimulating the controlateral hand and supraorbital zone. For tDCS a constant current of 2mA intensity was applied for 20 minutes. For sham stimulation, the electrodes were placed in the same positions as for real stimulation, but the stimulator was turned off after 30 s and thereafter received no stimulation for 10 minutes. The one-way ANOVA was used to analyze the data where the LEP latency, amplitude, N2–P2 amplitude, and the laser pain rating were variables, the session (baseline, tDCS and sham) within subject factor. To compare the variables across the three different sessions, a post hoc multiple comparison Bonferroni test was applied to single groups.
Results We found a significant reduction of N2-P2 amplitude among cases who received tDCS of the left DLPFC, while the stimulation of M1 gave no significant change in any LEPs parameters. We found a reduced sham effect in migraine patients.
Discussion Only few studies with small sample size examined the effects of tDCS on chronic pain and gave conflicting results [1, 2]. tDCS seems to inhibit laser evoked responces in migraine patients and controls by stimulating the DLPFC. This modulation involves only the N2-P2 vertex complex. Effects of M1 stimulation appears mild and contradictory.
Conclusions Our results confirm a previous study demonstrating that tDCS over the DLPFC significantly improved laser pain perception and various symptoms related to chronic pain syndromes. Further studies are needed to clarify the possible role of tDCS in the management of migraine.
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A study on arterial and endothelial functions in migraineurs

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Background Migraine with aura (MA) represents a risk factor for cardiovascular disease and stroke while migraine without aura (MO) does not represent a definite risk factor. Some studies showed an impairment of systemic arterial and endothelial functions in migraineurs with respect to non migraineurs. This arterial study was aimed to investigate arterial and endothelial functions in subjects suffering from MA and MO during the interictal period.
Methods Consecutive subjects with migraine referring to our Regional Headache Centre and diagnosed, according to the ICHD-II criteria, were included and classified as suffering from MA and MO. A control group including subjects admitted to our Hospital for traumatic injuries was also enrolled. Flow mediated dilation, photoplethysmography, and arterial tonometry were performed according to International recommendations. The assessed parameters included estimated systolic (AoSP) and diastolic (AoDP) aortic pressures, Augmentation Index (AIx), Stiffness Index (SI), and Flow Mediated Dilation (FMD). Informed consent was obtained from all subjects involved. The study was performed according to the Declaration of Helsinki. Comparisons were performed by Student's *t*-test, ANOVA, or χ^2 test when appropriate. Spearman's test was used to assess correlations among variables.
Results So far, we have included 91 subjects (mean age ± SD 35.5 ± 10.0 years; 22% men), 78 migraineurs (37 with MA) and 13 control subjects. Mean age ± SD was similar in subjects suffering from MA, MO, and controls (35.4 ± 9.5 vs. 36.8 ± 10.1 vs. 31.8 ± 10.5 years; $p = 0.29$). Among included subjects, arterial hypertension was present in 12% of the cases, hypercholesterolemia in 11%, and cigarette smoking in 24%. The distribution of all those factors was similar in MO sufferers, MA sufferers, and control subjects. In MA sufferers, MO sufferers, and control subjects mean values of AoSP (114.1 ± 15.5 mmHg vs. 110.1 ± 10.9 mmHg vs. 103.6 ± 12.5; $p = 0.06$), AoDP (81.1 ± 10.8 mmHg vs. 79.8 ± 8.6 mmHg vs. 74.4 ± 9.8 mmHg; $p = 0.12$), AIx (21.5 ± 13.4% vs. 18.1 ± 14.1% vs. 11.9 ± 13.6%; $p = 0.113$), SI (7.62 ± 1.78 m/s vs. 7.80 ± 2.19 m/s vs. 7.72 ± 1.45 m/s; $p = 0.917$), and FMD (8.02 ± 2.91% vs. 7.69 ± 2.52% vs. 7.51 ± 1.83%; $p = 0.893$) were similar. There was no correlation between any of the parameters assessing arterial and endothelial function, arterial hypertension, and cigarette smoking.
Conclusions According to our preliminary data, there is no difference in arterial and endothelial functions among sufferers of MA, MO, and control subjects.

Allodynia in different forms of migraine

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Background Activation of meningeal perivascular pain fibres is one of the fundamental pathogenic steps of migraine attacks. Persistent pain tends to increase the responsiveness of central nociceptive neurons to intracranial and extracranial afferent. Pre-clinical studies have shown that the underlying mechanism is sensitization of primary nociceptors and central trigeminovascular neurons and that patients have a lower pain threshold for mechanical stimulation compared to controls. Cutaneous allodynia is defined as the perception of pain or discomfort generated by a non-noxious stimulus to normal skin.
Objectives To assess the prevalence of acute allodynia in patients with different clinical variants of migraine.
Methods We collected data from 186 patients consecutively evaluated for headache day service from September 2010 to December 2011 at the Headache Centre of the Pugliese-Ciaccio Hospital of Catanzaro. One hundred and four of these patients had only migraine without aura (MO), 33 had migraine with aura (MA), and 49 had chronic migraine (CM) with and without drug overuse. Diagnosis was made according to ICHD-II criteria. Presence of allodynia was investigated by a semi-structured interview (DN4, NRD, VAS), through the identification of annoying or painful sensation at touch during acute migraine attacks.
Results Of the 104 MO patients, 41.2% complained of acute allodynia, 21 out of 33 MA patients (64%) and 34 out of 49 CM patients (67%). A higher prevalence of acute allodynia in both MA and CM patients with respect to MO patients was observed (MA vs. MO p 0.002; CM vs. MO $p = 0.004$).
Conclusions Our results confirm the association between allodynia and migraine. Acute allodynia was significantly higher in MA and CM patients compared with the MO group. Our results indicate the need to separately study the different migraine forms and to analyse the possible mechanisms.

Heart rate variability in sleep-related migraine

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Introduction Migraine has a close relationship with sleep and circadian rhythms. The activity of the autonomic nervous system (ANS) is characterized by circadian and ultradian oscillations, which are deeply linked with wake and sleep stages. The aim of our study was to investigate the reciprocal interactions among sleep, ANS and occurrence of migraine attacks.
Methods We studied 8 consecutive migraineurs (two men and six women, mean age 41.9 ± 13.9 years), with high frequency of attacks (> 5 per month), sleep-related (> 50% of the attacks occurred during sleep). Patients were evaluated during a headache-free period. Patient underwent polysomnography (PSG) and HRV analysis, and results were compared with a large sample of normal subjects. All subjects underwent a full-night laboratory video-PSG. For the HRV analysis, in time and frequency domains, periods of 5 minutes were selected, from quiet wakefulness (W), stage 2 (N2) and 3 (N3) of N-REM, and REM sleep (R).
Results PSG and HRV data obtained in patients were compared with data recorded in 55 healthy subjects (23 men and 32 women, mean age 44.2 ± 13.0 years) randomly selected from the database of our Sleep Laboratory. We found a statistically significant reduction of LF/HF ratio during N2 and N3 sleep stages in migraineurs compared with controls. Conversely, during REM sleep, the HF/LF ratio showed a trend to increase in patients, which however did not reach statistical significance.
Conclusions The ANS activity in migraineurs showed a higher level of fluctuation compared with normal subjects, a lower parasympathetic activation during N-REM and a higher parasympathetic activation during REM sleep. These findings demonstrate instability, during sleep, of the sympathetic/parasympathetic balance in migraineurs. Moreover, the sharp reverse of the sympatho-vagal balance during REM, more rapid than in normal subjects, is probably correlated to increased occurrence of migraine attacks during REM sleep.

Umbellularia Californica, the 'headache tree', via umbellulone and TRPA1 activates the trigeminovascular system

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Introduction We report the case of a 69-year-old gardener affected at a young adult age by cluster headache (CH), who, 10 years from his last cluster episode, developed shorter-lasting cluster-like headache attacks after and at any time he exposed himself to Umbellularia californica, commonly known as **'**headache tree**'** [1]. It is likely that in our patient susceptibility to exogenous triggers remains active, while endogenous mechanisms causing CH were no longer present. The identification of U. californica constituents responsible for triggering CH-like attacks in our patient may improve the understanding of the CH mechanism. We focused on the possible interaction between U. Californica constituents (i.e., umbellulone) and transient receptor potential (TRP) channels. We hypothesized that umbellulone activates the trigeminovascular system and finally causes CH via its action on TRP ankyrin 1 (TRPA1), TRP vanilloid 1 (TRPV1) or TRP menthol 8 (TRPM8) channels, expressed on peptidergic nociceptors.
Materials and methods We performed *in vitro* (calcium imaging on transfected and native cells), *ex vivo* [calcitonin gene-related peptide (CGRP) release from trigeminal neurons, pharmacokinetics assay] and *in vivo* (eye wiping in mice, dural blood flowmetry in rats) experiments.
Results Umbellulone, from mM to sub-mM concentrations, selectively stimulated TRPA1-expressing HEK293 cells and rat trigeminal ganglion neurons, but not untransfected cells or neurons in the presence of the selective TRPA1-antagonist, HC-030031. Umbellulone evoked a calcium-dependent release of CGRP from trigeminal nerve terminals in the dura mater. In wild-type mice, umbellulone elicited excitation of trigeminal neurons and released CGRP from sensory nerve terminals. These two responses were absent in TRPA1 deficient mice. Umbellulone caused nocioceptive behaviour after stimulation of trigeminal nerve terminals in wild-type, but not in TRPA1 deficient mice. Intranasal or intravenous umbellulone increased rat meningeal blood flow in a dose-dependent manner; a response selectively inhibited by systemic administration of TRPA1 or CGRP antagonists.
Discussion Data indicate that umbellulone activates, through a TRPA1-dependent mechanism, the trigeminovascular system, thereby causing CGRP release and nocioceptive responses. Pharmacokinetics of umbellulone suggests that TRPA1 stimulation, which eventually results in meningeal vasodilatation, may be produced via different pathways, depending on the dose: directly by umbellulone, which diffuses from the nasal mucosa to perivascular nerve terminals in meningeal vessels, or by stimulation of trigeminal endings within the nasal mucosa and activation of reflex pathways.
Conclusions We demonstrated that umbellulone is a selective TRPA1 agonist. TRPA1 gating and the consequent trigeminovascular activation represents a plausible mechanism of U. californica induced-headache [2].
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Multimodal evoked potentials in chronic migraine

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Background Chronic migraine (CM) is a disabling health disorder. The exact pathophysiological mechanisms are not completely elucidated, but a pivotal role was attributed to central sensitization. Migraine, when it is still episodic, is characterized by a deficient habituation to any kind of sensorial stimulation between attacks, and by an ictal evoked potential (EPs) normalization. Less is known about how central sensitization alters this electrocortical profile in CM.
Methods Sixteen episodic and 15 chronic migraine patients randomly underwent median-nerve somatosensory evoked potentials (SSEPs) (right stimulation, 500 sweeps, 4.4 repetition rate, 1.2 motor threshold) and visual evoked potentials (VEPs) (right eye stimulation, 600 sweeps, 3.1 repetition rate, 15 min of arc check) during the same recording session. Patient groups were compared to a group of 22 healthy volunteers of comparable age and gender distribution. Habituation was calculated as the slope of the linear regression between block 1 to 3 for SSEPs or between block 1 to 6 for VEPs.
Results In episodic migraineurs, interictal SSEP and VEP amplitudes tended to be reduced in block 1, but thereafter failed to habituate. Chronic migraine SSEP and VEP amplitudes increased in block 1, then habituated normally.
Conclusions Our results show abnormalities in chronic migraine that are also reported during attacks in episodic migraineurs, namely response habituation, which contrasts to the lack of stimulus habituation detected between attacks. This suggests that from an electrophysiological point of view, CM looks like a never ending migraine attack.

Deciphering task of N-acetyl-aspartate in migraine

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Proton magnetic spectroscopy studies have demonstrated the decrease of N-acetyl-aspartate (NAA) in several neurological disorders, such as ASL, multiple sclerosis, cluster headache and migraine with aura (MA). The evaluation of serum levels of NAA may be a huge advantage in the clinical practice for the monitoring of the status of disease.
Migraine is a common neurological disorder producing significant personal and societal burden. In the evaluated study, N-acetyl-aspartate, a biomarker of neuronal integrity, was found decreased in serum patients suffering from migraine with aura. These interesting results could suggest a dual clinical readout. Since MA patients show an increased risk for stroke, the evaluation of serum levels of NAA is crucial in the control of the conventional risk factors. On the top of that, the therapeutic metabolite monitoring of NAA may be helpful for the assessment of the chronicization process.
Clearly, it will be necessary to evaluate a large number of patients to make peripheral levels of NAA a useful tool for the evaluation of progression of the disease. Thus future studies will also need to include the evaluation of NAA serum levels to assess both the instant status of a single MA patient and its possible evolution towards the appearance of silent and/or evident cardiocerebral complications.

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White matter hyperintensities are associated with age and self-reported depression in a sample of patients with chronic headache

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Background Patients with white matter hyperintensities (WMH) may be at higher risk for affective disorders and chronic headache may play a significant role in mood disorders. The present study aimed to assess whether sociodemographic features and self-reported depression were associated with WMHs in subjects with chronic headache.
Methods Participants were 85 outpatients (16 men and 69 women) of 18 years of age or higher with a diagnosis of chronic headache. All the patients performed a brain magnetic resonance imaging (MRI) and were administered the Behavioural Inhibition System and Behavioural Activation System (BIS/BAS) Scales, and the Centre for Epidemiologic Studies Depression Scale (CES-D).
Results More than 40% of patients had periventricular WMHs (PWMHs) and almost 98% had deep WMHs (DWMHs). Patients with PWMHs differed from those without periventricular lesions for depression severity ($t_{77.76} = 2.30$; $p < 0.05$). Patients with PWMHs had lower CES-D scores (13.79 ± 7.51 vs. 18.19 ± 9.68) than patients without PWMHs. Patients with more severe DWMHs were older (53.89 ± 13.26 vs. 47.40 ± 11.91) and had lower scores on the dimension Drive (9.97 ± 2.86 vs. 11.14 ± 2.52) than patients with mild lesions or without lesions. After bivariate analyses, patients with PWMHs were 1.06 less likely to have higher CES-D scores ($p < 0.05$) than patients without PWMHs. Patients with more severe DWMHs differ from other patients as they were 1.04 times more likely to be older ($p < 0.05$).
Conclusions Differences in brain lesions are associated with differences in depression severity as measured by the CES-D and age, indicating that old subjects with chronic headache and MRI abnormalities may be at higher risk of self-reported depression.

NGF and NO levels following short-term ketamine treatment in chronic migraine sufferers

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Introduction Research in man *in vivo* indicated that chronic ketamine, a non competitive NMDA receptor antagonist capable of interfering with the action of excitatory amino acids (EAAs), can increase serum levels of neurotrophic factor as brain-derived neurotrophic factor, whereas nerve growth factor (NGF) levels resulted unaffected by chronic ketamine use [1]. It has also been proved that ketamine can inhibit nitric oxide (NO) production in mouse macrophage-like cells of via inhibition of tumor necrosis actor-alpha [2].
Objective The aim of the study was to verify the potential effects on NGF and NO of a short-lasting treatment with ketamine in chronic migraine patients with overuse of acute abortive medications. A possible decrease of pain and changes of NO but not of NGF levels were expected.
Methods Enrolled subjects included males 40-45 years old suffering from chronic migraine (CM) (ICHD-II criteria). Patients underwent a short-lasting (5 days) ketamine treatment (75 mcg/Kg/i.m./four times a day). NGF and NO as plasma L-citrulline, equimolar co-product in NO synthesis were measured immediately prior and one day after following ketamine treat-

ment. Changes in pain intensity were evaluated on a 0-10 visual analogue scale (VAS) applied during run-in (1 month), treatment and follow-up period (20 days). Acute abortive medication use was also recorded daily on a pain diary.

Results NGF levels were higher ($p < 0.0001$ ANOVA) following ketamine administration (131.9 ± 5.1 SD pg/ml versus 100.2 ± 1.5 SD pg/ml). A significant decrease of L-citrulline was also evident ($p < 0.0001$ ANOVA) indeed the levels decreased from 35.3 ± 11.1 SD nmol/l, baseline value, to 15.7 ± 14,1 SD nmol/l, following ketamine treatment. Noteworthy, in all the ketamine treated subjects headache showed a significant decrease ($p > 0.0001$ decrease = 85.5% versus baseline). A corrisponding decrease of acute abortive medications also occurred ($p < 0.0001$ ANOVA post-treatment and follow-up values versus baseline).

Conclusions The significant and unexpected increase in serum levels of NGF might not be due directly to ketamine since it may relate to transmitter changes linked to a significant decrease in the intake of acute abortive medications as shown by our group. Also the inhibited production of NO may be independent of a direct effect of ketamine on NMDA receptor sites since it might be mediated via other pathways, as seen in animal.

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MRI findings in migraine with and without aura and tension-type headache. A retrospective study on 121 patients

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Introduction There is much evidence in the literature that brain white matter hyperintensities are more prevalent in migraine patients than in the general population, particularly in the case of migraine with aura [1], longer disease duration and higher attack frequency. Very few studies have investigated the association between white matter lesions and other primary headaches (e.g., tension-type headache) [2], with conflicting results. Based on the above, our study was aimed at investigating the relationship between white matter lesions and migraine (with and without aura) or tension-type headache. We also examined whether a correlation exists between the lesions and location, intensity and frequency of headache symptoms.

Methods Medical records of 2,046 patients examined at our Headache Centre in the period January 2010-December 2011 were analyzed. Inclusion criteria were: both sexes, a diagnosis of primary headache according to IHCD-II criteria for migraine without aura, migraine with aura, tension-type headache, availability of a brain resonance imaging (MRI) not older than 5 years. Patients with mixed, cluster, secondary headaches or neuralgia were excluded. One hundred and twenty-one patients (99 F, 22 M; mean age 34.93 ± 14.59 yrs) were selected and subdivided into three groups: 74 with migraine without aura, 23 with migraine with aura and 24 with tension-type headache. For all patients: site of pain, number of crises per month and their mean intensity (numeric scale from one to ten) were noted at the time of the first visit. We compared the three groups of patients relative to the MRI parameters (positive vs. negative lesions, chi-square test). Within each group, we compared the frequency and intensity of crises of MRI positive (MR+) and MRI negative (MR-) subgroups (Student's *t*-test for unpaired samples).

Results MRI was positive in: 21 out of 74 patients in the migraine without aura group; 1 out of 23 patients in the migraine with aura group and 11 out of 24 patients in the tension-type headache group. There was a statistically significant difference between the: migraine without and with aura groups ($p < 0.03$), migraine with aura and tension-type headache groups ($p < 0.002$), while there was no statistically significant difference between the migraine without aura and tension-type headache groups. In both the migraine without aura and tension-type groups, the number – but not the intensity – of crises was significantly higher in the MR+ than MR- subgroups ($0.04 < p < 0.05$) (mean n^ of crises for migraine without aura: 12.5 MR+ vs. 7.4 MR-; for tension-type headache: 25.0 MR+ vs. 14.1 MR-).

Conclusions The results of our study show a similar prevalence of brain white matter hyperintensities in migraine without aura and tension-type headache and a higher prevalence in both with respect to migraine with aura. The latter result is in contrast to findings reported in the literature demonstrating the maximal expression of these lesions in migraine with aura. Our results also suggest a major link between the frequency of crises and MRI positivity, irrespective of the diagnosis of primary headache.

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Headache treatment

Symptomatic or prophylactic treatment of weekend migraine: an open label, non-randomized, comparison study of frovatriptan vs. naproxen or no therapy

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Background Migraine is often triggered by a period of stress and overwork followed by relaxation. This particular form of migraine, called weekend migraine, has been poorly investigated over the years. Moreover, evidence of drug efficacy for this type of migraine is lacking. We compared the efficacy of frovatriptan (F), naproxen (N) or no therapy, for the acute or prophylactic treatment of weekend migraineurs.

Methods Twenty-eight subjects (18 females, mean age ± SD 36 ± 12 years) suffering from weekend migraine without aura were followed-up for 6 consecutive weekends. During the first 2 weekends no treatment was administered. On the third and fourth weekend patients were given one 2.5 mg dose of F on Saturday and one on Sunday morning, regardless of the occurrence of migraine. On the fifth and sixth weekend patients were given a 500 mg dose of N. All patients were allowed to take a rescue medication, consisting of any analgesic drug at least 6 hours after morning awakening. Efficacy was evaluated through a migraine diary, where patients had to report the severity of migraine, on a scale ranging between 0 (no migraine) and 10 (severe migraine), and the use of rescue medication.

Results Score of migraine severity was significantly lower with F [4.8 (95% confidence interval: 3.8 / 5.9)] than with N [5.7 (5.1 / 6.4) $p < 0.05$ vs. F] or no therapy [6.6 (6.2 / 7.0) $p < 0.01$ vs. F]. The difference in favour of F was more striking in patients not taking rescue medication [1.9 (1.5 / 2.3) vs. N 3.6 (3.0 / 4.2) $p < 0.001$ and vs. no therapy 5.1 (4.4 / 5.8) $p < 0.001$] and for the second day of treatment (Sunday). The proportion of patients taking a rescue medication was significantly ($p < 0.05$) lower under F (12.5%) than under N (31.3%) or no therapy (56.3%): in particular the chance of taking rescue medication was 18% less with F than with N ($p < 0.01$).

Conclusions This relatively small, open-labeled, non-randomized pilot study provides the first evidence of the efficacy of a last generation triptan either as symptomatic or prophylactic treatment of weekend migraine.

Efficacy of frovatriptan versus almotriptan for acute treatment of menstrual migraine: analysis of a double-blind, randomized, crossover, multicentre Italian, comparative study

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Objective To compare the efficacy and safety of frovatriptan and almotriptan in women with menstrually related migraine (ICHD-II criteria) enrolled in a multicentre, randomized, double-blind, crossover study.
Methods Patients received frovatriptan 2.5 mg or almotriptan 12.5 mg in a randomized sequence: after treating 3 episodes of migraine in less than 3 months with the first triptan, the patient switched to the other triptan.
Results Sixty-seven of the 96 female patients of the intention-to-treat population of the main study had regular menstrual cycles and were thus included in this subgroup analysis. Seventy-seven migraine attacks classified as related to menses were treated with frovatriptan and 78 with almotriptan. Rate of pain relief at 2 and 4 hours was 36% and 53% for frovatriptan and 41% and 50% for almotriptan (p = NS between treatments). Rate of pain free at 2 and 4 hours was 19% and 47% with frovatriptan and 29% and 54% for almotriptan (p = NS). At 24-hrs, 62% of frovatriptan, and 67% of almotriptan-treated patients had pain relief, while 60% vs. 67% were pain free (p = NS). Recurrence at 24 hours was significantly ($p < 0.05$) lower with frovatriptan (8% vs. 21% almotriptan). This was the case also at 48 hours (9% vs. 24%, $p < 0.05$).
Conclusions Frovatriptan was as effective as almotriptan in the immediate treatment of menstrually related migraine attacks. However, it showed a more favorable sustained effect, as shown by a lower rate of migraine recurrence.

An open label, retrospective study assessing efficacy and tolerability of the combination paracetamol-caffeine in the symptomatic treatment of migraine without aura attacks

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Introduction The combination of paracetamol-caffeine has been proven to be effective and well tolerated in the treatment of different pain conditions, including tension-type headache. However, data concerning its use in migraine symptomatic treatment are still missing. An open label, retrospective study was carried out in order to assess the efficacy and safety profile of the combination of paracetamol 1000 mg and caffeine 130 mg in the symptomatic treatment of migraine without aura attacks.
Materials and methods One hundred and seventy-five patients, fulfilling ICHD-II criteria (2004) for the diagnosis of migraine without aura, were enrolled at the Headache Centre of the University of Pisa; patients were instructed to take paracetamol-caffeine in combination at the beginning of a migraine attack (early treatment) and to carefully fill in a headache diary. The primary endpoint examined in the study was *Pain Relief* (pain reduction of at least 2 points in a 4 points pain severity scale at 2-h after treatment assumption), whereas, *Pain Free* (absence of pain at 2-h post-dose) and *Sustained Pain Free* (free of pain at 2-h post-treatment, maintained for at least 24 hours) represented the secondary endpoints. Furthermore, the ability of the combination paracetamol-caffeine to control neurovegetative symptoms associated with migraine attacks (i.e., photophobia, phonophobia, nausea and vomiting) was evaluated. Tolerability was assessed recording adverse events in the 4-h post-dose treatment.
Results In the total sample of 175 migraineurs, the primary endpoint *Pain relief* was achieved in 134 patients (76.6%) whereas absence of pain in the 2-h post-treatment (*Pain Free*) was obtained in 111 patients (63.4%); the criteria for the parameter *Sustained Pain Freedom* were fulfilled by 99 patients (56.6%). A remission of neurovegetative symptoms was reported in 130 patients (74.3%). After taking the paracetamol-caffeine combination, only one patient presented mild and transient orthostatic hypotension as side effects.
Discussion The results of the present study, even if preliminary, showed a good profile of efficacy and safety of the paracetamol-caffeine combination in the early symptomatic treatment of migraine attacks, both on pain control and remission of neurovegetative symptoms, with important implications in clinical practice, especially in patients that cannot take, due to contraindications and/or side effects, triptans or non steroid anti-inflammatory drugs. Further randomized, double-blinded and placebo-controlled studies are necessary in order to better verify the efficacy-safety profile of the combination of paracetamol 1000 mg and caffeine 130 mg in migraine symptomatic treatment.

Transcranial magnetic stimulation in the treatment of medication-overuse headache: preliminary results

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Background Repetitive TMS (rTMS) may have a role as migraine prophylaxis.
Purpose To investigate the efficacy of high-frequency rTMS over left dorsolateral prefrontal cortex (DLPFC) in the treatment of medication-overuse headache (MOH).
Methods A randomized, controlled, double-blind trial on patients suffering from medication-overuse headache (MOH) consecutively presenting in a six-month period to the Headache Centre of Trieste was performed. Patients were randomized into the rTMS or the sham-TMS group. Treatment consisted of 10 consecutive TMS sessions delivered on left DLPFC, each session being 10 trains of 2-s duration, separated by 30-s pauses, 20 Hz frequency, 100% motor threshold intensity. Demographic and clinical information, headache days (HD), hours of headache (HH), and symptomatic drugs (SD) in the 3 months before (t1), and in the first (t2) and second month (t3) after stimulation were analysed using SPSS 14.0.
Results We enrolled 8 patients (7 F, 1 M; mean age 44 ± 11), four patients undewent rTMS and four sham-TMS. All patients were migraineurs without aura as initial primary headache. We found no significant difference, in both rTMS and sham-TMS groups, between the 3 months before and the 2 months after stimulation (rTMS: HD = 22 ± 6 t1 vs. 22 ± 11 t2 vs. 19 ± 14 t3, HH = 223 ± 205 t1 vs. 219 ± 198 t2 vs. 205 ± 196 t3, SD = 22 ± 10 t1 vs. 18 ± 7 t2 vs. 16 ± 8 t3; sham-TMS: HD = 22 ± 5 t1 vs. 12 ± 6 t2 vs. 13 ± 8 t3, HH = 180 ± 117 t1 vs. 99 ± 73 t2 vs. 97 ± 28 t3, SD = 22 ± 10 t1 vs. 16 ± 3 t2 vs. 17 ± 4 t3).

Conclusions Our preliminary data suggest that high-frequency rTMS over left DLPFC is not useful in treating MOH; however, the small sample does not allow to draw reliable conclusions.

Occipital nerve stimulation: lights and shadows

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Background Medically intractable chronic migraine is a disabling illness that occurs on 15 or more days per month for more than 3 months. Occipital nerve stimulation (ONS) has been employed off-label for medical refractory head pain. The mechanism of action is poorly understood but it seems that the balance within the impaired central pain system could be restored through slow neuromodulatory process in the pain neuromatrix [1, 2] .
Case report A 70-year-old, right-handed woman presented in early 2007 with a 3-year history of daily headaches. For 30 years prior to the onset of daily headaches, she had episodic headaches which satisfied the ICHD-II criteria for migraine without aura. In 2004 the frequency and duration of the headaches began to increase gradually, such that since mid 2006 she has had daily, constant headaches. She described a bilateral headache, which was worse on the left than on the right side. It was centred in the occipital region with radiation to the vertex, temple, retro-orbital and orbital region. It was severe in intensity (Verbal Rating Scale, VRS 10) and had a throbbing and tightening quality. It was associated with nausea, vomiting, photophobia, phonophobia, worsening with movements and stressing life events. During the years she had tried all kinds of prophylactic therapies but with unsuccessful results and a concomitant overuse of symptomatic acute headache treatments (triptans and NSAIDs). In September 2010, temporary bilateral suboccipital stimulators were sited. They were highly effective, markedly reducing the severity (VRS 2/10) and the frequency of pain (> 50%). Thus, in December 2010 permanent bilateral suboccipital stimulators were implanted. The patient was pain-free for 1 year, then the stimulators stopped working. At the visit the neurosurgeon concluded that the high amperage needed to obtain an analgesic stimulation led to an early exhaustion of the pacemaker's neurostimulators. The only solution would be a new surgical procedure with implantation of a new type of stimulator. The patient decided not to undergo additional surgery because she considered it too stressful. The migraine began to be daily with a concomitant overuse of medications. Presently, the daily head pain is treated with 3 NSAIDs and 2 triptan tablets daily.
Conclusions Neurostimulation can be a very promising approach in the management of medically intractable headache disorders but, further studies are needed to improve the surgical and stimulation techniques, the handling of the devices and to minimize the adverse effects. Another fundamental aspect would be the choice of the patient both from the clinical phenotype and the psychological profile.
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Treatment of tension-type headache with bite plane and botulinum toxin type A

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Introduction Tension-type headache (TTH) is the most frequent headache (90%). TTH is characterized by a bilateral, pressing tightening pain associated with masticatory muscle hypertonicity. Pain is often described like an acute sensation of head's compression. The pain is not pulsating, mild to moderate, but sometimes it can also be intense. The headaches are often associated with stress, anxiety and depression.
Materials and methods Fifty patients, 30 females and 20 males, (18-50 years old; affected by TTH) were selected. All patients were affected by dental malocclusion correlated with masticatory muscle dysfunction. All patients received a bite plane and were instructed to apply it on the upper dental arch during the night and as long as possible during the day for the first week. After the first week the bite plane was used only during the night.
Ten patients (eight females and two males) were treated with injections of botulinum toxin type A into the masseter muscles.
Results Forty patients had a complete remission of headche within three to ten days. Ten patients that could not wear the bite plane during the day had fewer benefits and were treated with injections of botulinum toxin type A into the masseter muscles. After ten to fifteen days they also had complete remission of headache while using the bite.
Discussion TTH originates from dental malocclusion associated with stress, anxiety and depression. Examination, supported by electromyography, should highlight a dysfunction of masseter, anterior temporal, sternocleidomastoid and anterior digastric muscles.
Conclusions Bite plane is the first line therapy for TTH since it prevents masseter muscles hypertonicity during the night. Patients that cannot wear bite plane can be treated with injections of botulinum toxin type A into the masseter muscles.

Migraine topiramate treatment and potential effects on the cognitive sphere: a critical review

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The aim of our study was to analyse the rationale of prophylactic use of topiramate (TPM) in the treatment of migraine [1, 2], based on the evidence reported in the literature and on the findings of our previous research. In this study we asserted that it was possible to select patients who could benefit from prophylactic therapy with TPM without significant side effects, based on the presence or absence of a reduced verbal fluency, clinically detectable and verifiable by FMRI with BOLD effect. In this study changes in brain activity were observed during a phonemic task in patients with language disturbances after receiving TPM [3]. With this approach the forehead's evocative strategies could be precisely measured, which may explain the executive domain, which is the most frequently affected in migraine patients. This aspect has rarely been described in the literature.
As is well known the executive functions are the most susceptible to the reduction of the glutamatergic transmission, which is compromised by the TPM administration.
Based on the above and on the proven efficacy of TPM in improving the frequency and intensity of the migraine crises, we suggest identifying those patients who could benefit from the treatment without cognitive side effects from those who could have cognitive adverse effects with the use of a battery of brief tests, easy to administer, like the test for verbal fluency.
Many studies published between 2009-2012 were reviewed, which highlighted the modest percentage of side effects on the cognitive sphere, the reversibility of these symptoms after the treatment was suspended, and the lack of a clear diagnostic, clinical and instrumental protocol to identify them.

In conclusion, although the TPM therapy does not produce significant effects on the cognitive functions, patients should be carefully selected after having collected detailed clinical history, validated tests, and continuosly monitored during the treatment.

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Occipital nerve stimulation role in the treatment of intractable chronic primary and secondary headache

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Introduction Chronic daily headache (CDH) is a serious global health problem affecting 3-5% of the population. It may be a secondary form, resulting from an underlying disease, or established by appropriate investigations according to a temporal criterion, or primary form, which does not derive from a functional disorder of the neuronal pathway responsible for the pain. A significant minority of these patients are resistant to conventional medical treatments (medically intractable headache), with serious negative implications on the quality of life. It is this background that fits the neuromodulation, peripheral or central, which has emerged as a very promising terapeutical approach.
Objectives To explain occipital nerve stimulation (ONS) indications and results in the treatment of headaches.
Materials and methods We analyzed retrospectively six consecutive clinical cases of chronic intractable headache treated with ONS in the period between June 2010 and May 2012. Age range was between 30 and 65 years, 5 patients were affected by primary chronic intractable headache and one with headaches secondary to occipital-cervical arthrodesis.
Results All patients showed an improvement of the clinical features and therefore the quality of life; we have not seen complications related to the procedure, to date, and in the short- and long-term.
Conclusions In accordance with the literature and our experience, ONS represents, in selected cases, an effective and relatively low risk therapeutic strategy. Its sphere of action is extended not only to primary headaches but also to secondary headaches, particularly, in the neurosurgical field, dealing with headaches resulting from trauma or post-cranial cervical surgery.

Lacosamide as a potential prophylactic treatment of migraine

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Introduction The relationship between migraine (M) and epilepsy (E) is complex and covers different aspects: epidemiological, pathophysiological and therapeutical. The prevalence of M in patients with E is remarkable and ranges from 8.4 to 20%. The Italian Guidelines for the treatment of headaches (IGL) indicate four antiepileptic drugs (AEDs) for the prophylaxis of M: valproate, topiramate, gabapentin and lamotrigine [1].
Case report We report the case of a 55-year-old female, obese, suffering since the age of 6 from epilepsy with generalized, tonic-clonic seizures and, since the age of 20, from M without aura. Over the years she changed different AEDs, becoming seizure-free after taking for the last 15 years clonazepam 15 mg/day and phenobarbital 100 mg/day in association. She came to our attention for a worsening of M, with increased frequency of attacks (4-5 days/week) for the last 6 months. The results of physical and neurological examinations, and laboratory investigations, which included a complete blood count, coagulation studies, basic metabolic and thyroid function tests, electrocardiogram and brain magnetic resonance imaging (MRI) with inversion recovery and gadolinium, were negative. The EEG revealed slightly abnormal left fronto-temporal theta activity, with sporadic sharp waves and photosensitivity. We changed her therapy adding topiramate, which was discontinued, a month later, when the dose was 100 mg/day, due to the occurrence of sleepiness, tremor and itching, though with no improvement of her M. A new treatment with lacosamide was commenced, with one month titration, up to the final dose of 200 mg/day; M attacks were recorded on a diary card After one month of therapy, the frequency of attacks decreased; at a 10-month follow-up, the mean attack frequency was 5.1 (± 2) per month. The association of lacosamide with clonazepam and phenobarbital for E treatment did not provoke significant side effects. She continued to successfully treat M attacks using a combination of indomethacin, prochlorperazine, and caffeine (Difmetrè® tablets), taking a significantly lower number of tablets (from 4/week to about 1/week).
Discussion and conclusions Among the four AEDs recommended by IGL for migraine prophylactic treatment, three share a sodium channel blocking activity (valproate, topiramate, lamotrigine). Lacosamide is a newly registered antiepileptic drug with a dual mechanism of action: it selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibits repetitive neuronal firing. Lacosamide was tried in the prophylaxis of chronic daily headache with good results in an open-label study [2] including 22 patients, but currently no reports on its possible role as preventive treatment of episodic M are available. Our observation needs further randomized, double-blind studies focused on the potential efficacy of lacosamide in the prophylaxis of M.

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Pulsed radiofrequency in the treatment of headache: neuro-stimulation, neuro-modulation or micro neuro injury?

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Introduction The use of radiofrequency in the framework of craniofacial neuralgias finds its principal application in occipital neuralgia (13.8 ICHD-II Classification).
When mentioning radiofrequency in medicine, reference is made to the energy used in a series of procedures for creating heat and necrosis of the target tissue. Radiofrequency techniques are transcutaneous procedures aimed at making neuro injuries at the somatosensorial system level (both central and peripheral).
Pulsed radiofrequency (PRF) is a method of distribution of radiofrequency that limits the temperature of the tip of the electrode to 40-42° C throughout the entire procedure.

Neurobiological studies have proven that the exposure to PRFs causes at dorsal root entry zone (DREZ): induction of c-fos, induction of cytokines, increase in CGRP, and increase in activating transcription factor 3 (ATF3). What are the real consequences of the activation of these genes and proteins are not yet clear, even though they are comprised in the action of PRF [1].
Low frequency stimulations of 0.5-3 Hz induce long-term depression (LTD) in the synaptic transmission. Low frequency pre-synaptic spikes activate post-synaptic Ca++ NMDA channels inducing a light depolarization such as to reduce the synaptic efficiency [2, 3].
Pulsed radiofrequency with its 2 Hz pulsation would be comprised in this type of stimulation.
Methods From 2006 to present, the following headache patients were treated with PRF (2-3 applications): 159 with suprascapular nerve injury (127 F, 22 M; age range 43-73 years); 61 affected by chronic tension-type headache with pericranical tenderness (2.3.1); 98 by cervicogenic headache (11.2.1); 72 patients (61 F, 11 M; age range 43-79 years) greater occipital nerve intervention; 24 with chronic migraine (1.5.1), and 46 occipital neuralgia (3.8). The results were evaluated at 3 and 6 months follow-up.
The evaluation was done using the number rating score (NRS), which measures the intensity of pain, and the Italian Questionnaire on Pain (QUID), which evaluates the painful experience considering its sensory, affective, evaluative and mixed components.
Results Patients in both treatments reported improvement of pain. For the suprascapular nerve intervention there was also a statistically significant decrease in all parameters examined (NRS 5.6 +/- .7; -3.4 +/- .3; -3.2 +/-.2 $p <$ .05) (Quid 25.6 +/- 2.4; -13.7 +/- .7; -13.8 +/- .4 $p <$ .05).
Conclusions PRF may be considered for the treatment of many forms of refractory headache because of the ease of performing the procedure and the limited number of applications, and the absence of side effects.
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Electromagnetic therapy in cephalalgia: a new approach with neurosensorial access facilitation (Magnetosound)

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Introduction The Authors describe a new electromagnetic therapy device, Wireless Magnetosound, an integrated appealing therapeutic procedure with several indications in human pathology.
Traditional magnetotherapy (PEMF) has been developed and approved by FDA in the joint-bone area where it has been proven effective in fracture healing and bone regeneration and calcification.
Its use was also successfully developed in rheumatology and pain clinics, enclosing vascular and microvascular flow impairment, and chronic painful ischemia.
In this study we approached and clinically tried in a simple open trial the use of multifrequency electromagnetic therapy (1-5000 Hz) in idiopathic cephalalgia with a new wireless device developed in our lab, potentially suitable to enhance the electromagnetic absorption and rebound effect into the brain. The wireless technology, developed by F&B International, is very helpful because it allows the patients free motility during the treatment.
The device's basic mechanism of action is a facilitated electromagnetic energy input delivery through acoustic fibres that are properly stimulated by rhythmic music that is perceived through earphones and in real time modifies the electromagnetic energy wave frequency accordingly to sensorial fluctuation. In this music–modulated electromagnetic energy delivery our challenge is to recruit a greater number of neuronal cells in the brain to enhance the cephalalgia suppressing effect.
Materials and methods Twenty patients affected by long standing and chronic headache were enrolled in the study. All the patients were using drugs to relieve the pain symptoms and were almost addicted to FANS oral therapy (paracetamol 1 gr, caffeine 130 mg) (10 cases), beta blockers (3 cases), calcium antagonists (2 cases), tricyclic antidepressants (1 case) and triptans (4 cases).
Each session lasted 30 minutes and was repeated 3 times a week for 2 weeks; the patients were asked to describe on a Scott Huskisson scale drawing their before-after pain intensity perception and also the day after drug oral intake variation was recorded.
Results The patients were followed-up 2 weeks after the end of the treatment to observe the effect of the Magnetosound in time. No inconvient effects were observed due to "Magnetosound" use.
The improvement of headache symptoms, as measured with pain perception scores before the procedure versus immediately after the procedure, was between 30-80% (mean 75%) and the drug consumption the day after dropped to 30% of the daily use. A moderate hypnagogic effect was recorded at the end of the administration.
Conclusions Wireless Magnetosound can be safely and effectively used as a supplemental electromagnetic home device for treatment of headache. A potential sleep induction effect might be helpful since the wireless technology allows the patient to move freely in bed (supine, prone and lateral positions) during night rest.

Osteopathic manipulative treatment and chronic tension-type headache: research outcome

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Introduction Baird [1] and Smitherman [2] published their first studies about the osteopathic treatment in subjects suffering from headache using the data recorded in the headache diary and comparing it with those subjects who performed mobility exercises.
Objective The purpose of this study was to verify the effectiveness of osteopathic manipulative treatment (OMT) in those patients suffering from chronic tension-type headache as a support treatment working along side with pharmacological treatments.
Materials and methods Thirty-three patients were found and fourteen of them, suffering from chronic tension-type headache, of both sexes and between 28 to 64 years of age, were enrolled.
The HIT-6 scale was analysed as primary outcome and the prevalence of somatic dysfunctions (SD), found during the osteopathic analysis, was analysed.
The study provided five osteopathic treatment sessions; the first three sessions within one week of each other, the last two sessions within fifteen days of each other. During the first session (T0) and the last one (T1), and within one month after the last treatment (T2), the patients filled in the HIT-6 questionnaire.
Results The fourteen patients enrolled completed the study. Analysing the prevalence of somatic dysfunctions (SD), the osteoarticular system presented a higher SD value (48%) compared to craniosacral (15%), fascial (23%) and visceral (14%) systems.
The visceral osteopathic analysis showed 41% of SD in the large intestine,

28% for SD compression in the craniosacral system, while the highest score of SD resulted in the fascial system in the neck region (29%). In the osteoarticular system, 34% of SD were found in the cervical area; 60% of these were on C1 vertebra. The analysis of the prevalence of all the detected SD showed a prevalence of 10% of the first cervical vertebra SD (C1 + + left rotation).
The main outcome (HIT-6 questionnaire), analysed by comparing measurements of T0 and T1, and then of T2 to T0, in order to evaluate the change in the first follow-up after the end of the treatment, and in the second follow-up after one month, showed in the first case a significant reduction of the HIT-6 scores between T0 (M 66, SD 5.07, 95% ± 2.65) and T1 (M 59.64, SD 7.89, 95% ± 4, 13). The reduction of ($p = 0.002$) in HIT-6 scores at T2 (M 55.93, SD 10.72, 95% ± 5.61) vs. T0 (M 66, SD 5.07, 95% ± 2.65) was also statistically significant ($p = 0.001$).
Conclusions The prevalence of SD on C1 indicates that this vertebra could be involved in the mechanical triggering of chronic tension-type headache. We hypothesised that the vertebra rotation dysfunction could alter the vertebral artery because of an extreme traction of the posterior atlanto-occipital membrane, and that the tension of suboccipital superior and inferior oblique muscles could affect suboccipital nerves and of the third occipital nerve. A further possible hypothesis is that C1 dysfunction, by altering the rectus capitis lateralis muscle tone, could lead to an involvement of the posterior meningeal artery in the jugular foramen.
The promising results obtained in this study as shown by HIT-6 variations suggest the potential efficacy of OMT for the treatment of chronic tension-type headache.
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The use of migraine attack drugs on current clinical practice. An analysis based on a series of 1000 patients

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Introduction In 2002 the Italian Society for the Study of Headaches (SISC) introduced a second version of guidelines (GL) aimed to determine the most appropriate choice of drugs for the therapy of migraine. The impact of attack GL in general practice had been assessed in 1999, when drug use was evaluated respectively before (1989-92, n 200) and after (1995-98, n 206) the introduction of 1993 GL [1]. During a previous national SISC Congress, we presented preliminary data about this topic on a limited population (200 patients) [2]. We now present results obtained from a large series of patient, in view of the just published 2011 version. We aimed to establish the impact in migraine patients of the 2002 SISC GL.
Materials and methods We assessed the experience with attack drugs, before coming to our observation, by a consecutive series of patients suffering from migraine without aura (ICHD-II criteria, 2004), seen in the period 2009-2011, making a comparison with those taken in the periods '89-'92 and '95-'98.
Results The experienced drugs are, in decreasing order: NSAIDs 78% (vs. 80% in '89-'92, 87% in '95-'98), acetaminophen 10.5% (vs. 3% and 9.2%), triptans 29.8% (vs. sumatriptan, the only triptan available in '95-'98, 17%), combinations 25.8% (vs. 79.5% and 51%), ergotamine 1% (vs. 37% and 9%), antiemetics < 1% (vs. 2% in '89-'92). Among NSAIDs, the most commonly used are propionic acids 62% (vs. 37.5% and 68%), and nimesulide 30.6% (vs. 15.6% in '95-'98); among triptans, rizatriptan (44.3%), and almotriptan (28.2%); among combination drugs, indomethacin + prochlorperazine + caffeine 52.7% (vs. 27% and 19%), acetaminophen + codeine 17% (vs. 5% in '95-'98), butalbital + prophyphenazone + caffeine 7% (vs. 27% and 23%).
FANS lost effect over time in 58.5% of patients, combination drugs in 37.2%, triptans in 10%. The oral way of administration is used by 86.2% of patients (vs. 86.5% in '89-'92, 88% in '95-'98); rectal by 8.8% (vs. 23% in '89-'92, 36% in '95-'98); intramuscolar by 1.4%, subcutaneous by 1%, nasal by < 1% (vs. 3%, 2% and 1% respectively in '95-'98).
Conclusions Our study showed some positive changes in the use of attack drugs, in keeping with the current SISC GL recommendations: such as a net reduction of combination drugs, and a drastic diminution of barbiturate-containing combination and of ergotamine. The use of first line attack drug, triptans, has doubled, but FANS still appear very largely prescribed. Furthermore, we noticed a low use of antiemetics and a decreased use of the already limited parenteral ways of administration, partly justified by the concomitant increase in the use of oral triptans, possessing intrinsic antiemetic action.
Our results underline the fact that the common use of migraine attack drugs in current clinical practice differs in many aspects from the 2002 SISC GL. A more adequate diffusion of the just published 2011 GL should be planned in order to effectively impact current practice.
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Paracetamol versus paracetamol plus caffeine in migraine treatment during pregnancy: an open label study

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Introduction Migraine affects about 25% of women during childbearing years (age 18 - 49 years). Even if migraine usually improves during pregnancy, particularly in the third trimestre, rarely it may even worsen, particularly in the first trimestre [1].
Unfortunately, few clinical trials regarding pharmacologic strategies have evaluated drug safety and efficiency on migraine during pregnancy. A symptomatic pharmacological approach is particularly needed during pregnancy, since some crises amy occur in pregnant women, mainly in the first trimestre. Here we report a case series of migraine attacks occurring during pregnancy and treated with paracetamol (1 gr per os), suggested to be a safe drug during the first, second and third trimestre of pregnancy [2], with (PC+) or without (PC-) caffeine (130 mg) combination.
Methods Pregnant patients received prescription to treat alternatively each migraine attacks with PC- or PC+ for a total of 6 attacks (3 treated with PC- and 3 with PC+) with the aim to choice the preferred one. They were also required to send via mail the headache diary after each migraine attack pharmacologically treated. Fisher's exact test was performed to find differences between treatment outcome. A binary logistic regression analysis was performed to find any predictors of treatment efficacy (age, headache frequency, strong nausea, pregnancy trimestre, latency of drug assumption from the onset of headache, presence of caffeine).
Results Eighty-five pregnant patients were enrolled, and a total number of 363 pharmacologically treated crises were observed. Among 189 crises treated with PC-, in 87 cases treatment was effective and in 102 it was not. Among 174 crises treated with PC+, in 108 cases treatment was effective and in 66 it

was not. No major side effects were reported by patients. The Fisher's exact test two-tailed P value was 0.0023. At binary logistic regression analysis only latency of drug consumption from the onset of headache (as negative) and presence of caffeine (as positive), emerged as predictors of efficacy.

Discussion Symptomatic migraine treatment during pregnancy is a clinical challenge for physicians, but not enough effort is being spent by the Scientific Community to resolve the conundrum. In fact, very few data are available about safety and efficacy of different drugs. Paracetamol and caffeine are considered safe options during pregnancy and drugs of combination containing both are widely available across the country. Our observational study unveiled a higher efficacy of PC+ in absence of any side effects, thus we conclude that in pregnancy this combination could be recommended.

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Vitamin D for the prophylaxis of headache

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Vitamin D plays a fundamental role in calcium homeostasis and bone metabolism. Recent research showed that the nervous system is also a target of Vitamin D and enlightened its role both in physiologic and in pathologic processes. Its possible role in the prophylaxis of headache has been suggested mainly by clinical experience.

Thys-Jacobs in 1994 [1] described four female patients suffering from persistent migraine that improved following Vitamin D administration. These patients had insufficient or deficient levels of Vitamin D. Their symptoms improved with daily supplement of 1200 or 1600 IU of Vitamin D combined with 1200 mg of calcium in two cases, and with the weekly administration of 50000 IU of Vitamin D together with a daily dose of 1000 or 2000 mg of calcium in the other two cases. The author suggests that changes in the levels of these two molecules may cause vasomotory instability and vasospasm clinically expressed by migraine, thus the supplementation may determine membrane stabilization and improvement of the symptoms. Another study, conducted among 54 migraine patients, showed a prevalence of 40.7% of deficient levels of Vitamin D. Prakash and Shah described 8 patients with chronic tension-type headache and Vitamin D deficiency: these patients improved with the daily supplementation of 1000 or 1500 IU of the vitamin and 1000 mg of calcium. The authors suggested a possible interaction between Vitamin D deficiency, chronic tension-type headache and chronic muscular-skeletal pain. Furthermore patients suffering from these conditions frequently have a comorbidity with depressive disorder which, in turn, is linked with low levels of Vitamin D. The same authors, in a recent study [2] reviewed the literature to delineate a relation of prevalence of headaches with latitude. They noted a significant relation between the prevalence of both tension-type headache and migraine with the latitude. There was a tendency for headache prevalence to increase with increasing latitude. Also serum Vitamin D level shows a strong correlation with the latitude. Furthermore available data indicate increased frequency of headache attacks in autumn-winter and less attacks in the summer. This profile of headache matches with the seasonal variations of serum Vitamin D levels.

In our study, we identified a higher prevalence of Vitamin D deficiency in hospitalised patients with neurologic disorders with respect to patients with osteoarticular disorders (62.5 vs. 50.7%, $p < 0.001$).

Several mechanisms have been suggested in order to explain the possible correlations between Vitamin D deficiency and headache: an anti-inflammatory action mediated by a reduction of matrix metalloproteinases, C reactive protein, TNF-α, and other pro-inflammatory mediators; direct analgesics effects; nitric oxide reduction; improvement of magnesium absorption. However the pathogenic link between headache and Vitamin D deficiency is still unclear. Vitamin D level in all patients with chronic headache, above all, in the presence of other symptoms like asthenia, muscular-skeletal pain, and depression should be investigated.

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New therapeutic approach to idiopathic stabbing headache

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Introduction Idiopathic stabbing headache was first described in 1964. Since then it has been defined as: "icepick-like pains", "sharp short-lived head pains", and "jabs and jolts syndrome". The ICHD-II 2004 used the term "idiopathic stabbing headaches," classified under chapter 4 "other primary headaches". The pathophysiology is still not understood; its main features consist of brief, short-lived attacks of headache with multiple recurrences throughout the day, that mainly last between 5 and 30 seconds [1].

Materials and methods A 47-year-old woman was evaluated in 2011 for stabbing right temporal headache that appeared several times a day for 2 months. The patient was also suffering from anxiety disorder with panic attacks, which was the reason why she was treated with benzodiazepines for suspected somatization disorder. Symptoms resolved after a few days of therapy and did not recur even after discontinuation of therapy. In 2012 a 58-year-old woman was diagnosed according to the ICHD-II criteria. She presented for the first time recurrent left temporal daily headaches lasting a few seconds, without associated symptoms. The patient did not suffer from any other type of primary headache. Neurological examination and MRI with intracranial vascular study were entirely normal. Infrared images were performed to study the autonomic nervous system involvement resulting in no sympathetic activation in both first and second trigeminal branch.

Results Indomethacin 50 mg twice per day was introduced for 5 days with a partial improvement. Afterwards bromazepam, slowly increased from 0.5 mg to 3 mg three times per day, was prescribed with recovery of symptoms in a few days.

Discussion Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. The actions of benzodiazepine are due to the potentiation of the neural inhibition that is mediated by GABA on type A GABA receptor system that is also the primary pharmacological target for many drugs. GABA and its receptor are involved in nociceptive signals and its facilitation can mediate the analgesic effect of bromazepam and other benzodiazepines.

Conclusions Only case reports are present in the literature and they show a therapeutic response to melatonin, indomethacin, celecoxib, nifedipine and gabapentin. No therapies have been evaluated in controlled trials. Gamma-aminobutyric acid receptor type A modulation with agonists and allosteric modulators evokes analgesia and anti-nociception and thus it can be taken into consideration as a therapeutic target for primary stabbing headache. A larger cohort of patients is necessary to confirm this hypotesis.

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Factors influencing response to physical therapy in chronic migraine with or without medication overuse

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Background Chronic migraine (CM), without or with medication-overuse (MOH), is a disabling health problem that affects 2-5% of the general population and causes considerable long-term morbidity and disability. Patients with higher levels of disability induced by their chronic headache are more likely to need a multidisciplinary treatment, which may include physical therapy.
Methods Thirty-seven chronic daily headache patients (9 CM and 28 MOH) were admitted to day hospital (DH) treatment. MOH patients received simple advice to acute drugs discontinuation as a withdrawal strategy before they were admitted to DH. Both patient groups underwent 5 daily sessions over 4 weeks each lasting 1 hour of superficial massage, manual traction, strengthening of neck and shoulders, dynamic neck extension, flexion and rotation and magnetotherapy. Both analysis of variance and logistic regression were performed.
Results After 4 weeks of physical therapy mean days with headache significantly decreased in both groups. When the chronic headache patients were pooled together, seven out of 37 patients did not respond to the treatment since they still experienced more than 15 monthly days of headache. In multiple regression analysis, only the presence of a history of a psychiatric symptomatology was an independent predictor of response to physical activity during DH. We did not find any significant predictors of relapse of medication overuse.
Conclusions A combination of advice and physical therapy helps patients to came out of the chronification phase. This is particularly true in those patients who experienced psychiatric comorbidity and thus the greater morbidity and disability.

Onabotulinumtoxin-A (Botox®) for chronic refractory migraine: two years experience in a headache centre

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Materials and methods Thirteen patients (3 males and 10 females) affected by chronic refractory migraine were treated with Botox® in our Headache Centre. According to the PREEMPT clinical programme we injected 5U of Botox® in 31 fixed-sites of head and neck muscles every 12 weeks [1, 2].
Results Six patients (45%) had a reduction of the headache frequency (-50%) and intensity: 3 of them completed the cycle of five injections, 2 patients underwent 2 injections and one underwent 3 injections.
In 7 patients (55%) headache was unchanged: one patient dropped out after 4 treatments, 3 patients after 3 injections, 2 patients after 3 treatments and one after 1 injection.
Treatment was well tolerated: only one patient complained of neck and shoulder pains but its intensity was decreasing at every injection. No patient had motor side effects.
Conclusions Our experience with Botox® treatment for chronic migraine shows that this approach is effective, safe and well tolerated.
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The use of migraine preventative drugs on current clinical practice. An analysis based on a series of 400 patients

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Introduction In 2002 the Italian Society for the Study of Headaches (SISC) introduced a second version of guidelines (GL) aimed to determine the most appropriate choice of drugs for the therapy of migraine. The impact of preventative GL in the general practice had been assessed in 1999, when drug use was evaluated respectively before (1989-92, n 351) and after (1995-98, n 204) the introduction of 1993 GL [1]. During the previous national SISC Congress, we presented preliminary data about this topic on a limited population (104 patients) [2]. We now present results obtained from a large series of patient, in view of the just published 2011 version. Our aim was to establish the impact in migraine patients using the 2002 SISC GL.
Materials and methods We assessed the experience with preventative drugs of a consecutive series of patients suffering from migraine without aura (ICHD-II criteria, 2004), seen in the period 2009-2011, before coming to our observation, and compared them with those taken in the periods '89-'92 and '95-'98.
Results Our data showed that among 400 patients, 142 (35.5%) have experienced preventative therapy (vs. 38% in '89-'92 and 41% in '95-'98). They suffered high (> 5/month), intermediate (3-5), low (< 3) attack frequency, 68.3%, 21.8%, 9.9%, respectively (vs. 17%, 54%, 29% in '89-'92 and 30%, 36%, 34% in '95-'98). In the remaining 258 patients (64.5%) without preventative therapy, attack frequency was high in 37.6% (vs. 11 and 21%), intermediate in 31.8% (vs. 46% and 32%), and low in 30.6% (vs. 43% and 47%).
Therefore, according to the 2002 SISC GL, in the 2010-2011 group of patients taking preventative drugs, this treatment is not indicated in 15.1% (vs. 29% in '89-'92 and 34% in '95-'98); whereas in the group not taking preventative drugs more than 50% of patients should receive a prophylactic therapy (58.3% vs. 56.8% and 53.8%).
The most prescribed drugs were amitriptyline in 47.8% (vs. 27% in '95-'98 and 6% in '89-'92), flunarizine in 38.7% (vs. 48% and 54%); propranolol in 16.9% (vs. 18% and 7%); pizotifen in 9.2% (vs. 18%, and 27%); and topiramate 14.1% (included only in 2002 GL).
Conclusions Our results underline the fact that the common use of migraine preventative drugs in current clinical practice differs in many aspects from the 2002 SISC GL. Very relevant is the fact that the number of patients who, despite having the indication for preventative treatment are not receiving it, is very high (58.3%) and remains substantially unchanged during the years. A more adequate diffusion of the just published 2011 GL should be planned in order to effectively impact current practice. Furthermore, the promotion of the use of a headache diary could improve the therapeutic choice when a preventative strategy is being considered.
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A case report on the possible role of warfarin in migraine prophylaxis

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Introduction In the '70s Newmann demonstrated the efficacy of heparin in reducing frequency and severity of migraine attacks; between 1979 and 2000 only case reports and open studies on small populations have been performed, which showed a consistent reduction of frequency and severity of migraine attacks during treatment with vitamin K antagonists. In 2000, from a questionnaire administered to 400 subjects, it emerged that treatment with adenocumarol for non neurological diseases caused an improvement in headache symptoms in 63% of migraine patients, and in 38% of patients with headache without migraine. In 2001 a retrospective study reported that, during adenocumarol treatment, patients experienced a decreased use of drugs for acute headache treatment. Eventually, in 2004, a prospective open study showed a significant headache improvement in patients with cardioembolic risk treated with acenocumarol. Single cases were described in which patients who suffered from diseases requiring anticoagulant therapy reported an improvement of migraine symptoms [1, 2]. The efficacy of warfarin in the disappearance of migraine attacks in these cases seems indisputable, in fact the patients had a complete remission of the attacks, which reappeared in the two instances when ACT was withdrawn.
Case report A.R., a 31-year-old male patient, on January 2012 came to the Modena Headache Outpatients Clinic with his mother (54 years old), who suffered from migraine with aura unresponsive to pharmacological therapy from adolescence. Familial medical history reported that also his father (60 years old), his sister (28 years old), and his brother (18 years old) present migraine with aura. A.R. was the only family member without the disease, although from our interview it emerged that approximately 1 time every month he presented visual aura without migraine following. Asking him more information on his medical history, we find out that, from the age of 16, after surgery for aortic valve substitution, he has been taking warfarin.
Conclusions Many studies in the literature describe experiments with new anticoagulant drugs that could improve the benefit-risk balance by extending anticoagulant therapy beyond the usual limited periods estimated for the actual clinical indications. The use of these new anticoagulants could clarify if the possible efficacy in migraine treatment might be related to an anticoagulation effect "per se" or is bound to a specific mechanism in the coagulation cascade.
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Beta-blocker, a therapeutic "compromise" between neurologist and cardiologist. A case report

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Introduction For some time treatment with beta-blockers has been used in the prophylaxis of migraine, even if, in most cases, it is not the first choice therapy. The use of this type of drug should also be related to the possible cardiologic problems or adapted in the case of concomitant antiarrhythmic treatment.
Materials and methods We report a case of a 32-year-old woman, followed at our Division of Electrophysiology, for a recurrent supraventricular tachycardia (SVT), who underwent a Cardiac Ablation Therapy (CAT) last year, also suffering from migraine without aura with high frequency of attacks, sleep disorder and depressive syndrome. After cardiological procedure, the patient had no recurrence of tachycardia, but for mood disorder and persistent headache, prophylactic therapy with amitriptyline was started [1]. This treatment was efficacious, and reduced the attacks by about 50%. However, about a year after the CAT, the patient had two episodes of supraventricular tachycardia, which warranted a review of the treatment, moreover, tachyarrhythmia is considered a frequent side effect in amitriptyline.
Results Treatment with a beta-blocker (propranolol) was started as a prophylactic therapy for migraine [1] and to prevent the recurrences of arrhythmia, despite the first choice cardiologic therapy was flecainide [2]. In six months of monitoring the patient did not present any further episodes of tachycardia and the frequency of headache attacks was reduced to 2 episodes/month at the most.
Conclusions The evaluation of comorbidity is important in the treatment of migraine, since the therapies available have a multiple and multidisciplinary use. Propanolol is not a first choice treatment for the prophylaxis of STV and migraine, nevertheless, in this case, it showed a good compromise between neurological and cardiological treatment. Further studies are needed to confirm its suitability in patients, in particularly if mood disorders coexist with indication of a specific therapy.
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Treatment of perimenstrual migraine with triptans: an update

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Pure menstrual migraine (PMM) and menstrually related migraine (MRM) are difficult challenges in migraine management. Triptans are a class of highly selective serotonin receptor agonists, which interfere with the pathogenesis of migraine and are effective in relieving the associated neurovegetative symptoms. In recent years triptans have been extensively proposed for the treatment of severe, disabling, and recurrent perimenstrual migraine attacks.
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CGRP receptor antagonists: an expanding drug class for acute migraine?

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Introduction Migraine afflicts approximately 11% of the population worldwide producing substantial disability, resulting in loss of productivity both at home and at the workplace. Calcitonin gene-related peptide (CGRP) is closely involved in the cascade of molecular events leading to migraine painful crisis.
Areas covered Acute treatment of migraine is actually based on the use of triptans, class drug which presents a clear limitation due to its cardiovascular

side effects. Gepants, a CGRP antagonist class, might offer a new nonvasoconstrictive approach in the acute treatment of migraine. Four chemically unrelated CGRP receptor (CGRP-R) antagonists (olcegepant, telcagepant, MK-3207 and BI 44370 TA) have displayed efficacy in the treatment of migraine.
Expert opinion When compared with triptans, gepants class showed a similar efficacy, moreover corresponding to the best published results for oral triptans. CGRP antagonists are in different phases of their development, and the treatment of migraine could be based on the use of gepants, as class of acute medications. However, CGRP-R antagonists clinical trials seem to be discouraging for their forthcoming use in clinical practice. New CGRP-R antagonists, such as BMS-927711 and BI 44370 TA, are in the pipeline and their developments will outline the future of this drug class.
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Pharmacokinetic evaluation of zolmitriptan for the treatment of migraines

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Introduction Migraine is a multifactorial neurovascular disorder characterized by recurrent episodes of disabling pain attacks, accompanied with gastrointestinal, neurological systems dysfunction. The pharmacologic treatment of migraine is classically divided in the management of the acute attack and preventive strategies. Acute treatments consist of triptan, ergot, opioid, antiemetic and NSAID classes of drugs.
Areas covered This review discusses pharmacodynamic and pharmacokinetic of zolmitriptan. The data were obtained by searching the following keywords in MEDLINE: zolmitriptan, pharmacokinetics, pharmacodynamics, triptans, migraine, menstrual related migraine, cluster headache, relatively to the period 1989-2012.
Expert opinion Zolmitriptan has been considered an effective treatment in the acute phase of migraine, menstrual related migraine and cluster headache attacks. Pharmacokinetic parameters may vary as a consequence of gender differences, inter and intra-subjects variability and delivery system. Zolmitriptan was developed with the aim of obtaining a lipophilic compound in order to be more rapidly absorbed and centrally active. Pharmacologically, pharmacokinetic parameters are responsible for its wide efficacy and the limited adverse effect profile.
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Developmental age

Prevalence of celiac disease in children and adolescents with primary headache

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Introduction Although celiac disease (CD) was primarily thought to be a gluten enteropathy, it is now considered to be a multisystem disorder, with most patients being asymtomatic or presenting with only extraintestinal manifestations. Among these manifestations various neurological syndromes, including headache, have been found to be associated with celiac disease [1].
Objective The aim of this study was to assess the prevalence of celiac disease, using specific serological investigations, in a large group of pediatric patients with primary headache.
The practical implication was to assess the usefulness of a serological screening for diagnosis of celiac disease in patients with headache.
Materials and methods A total of 221 patients (age range 2-17 years) with migraine (with and without aura) and tension-type headache, according to the International Headache Society criteria, were enrolled in the study.
All patients answered a questionnaire investigating the prevalence of symptoms or signs indicative of celiac disease. Serum tissue transglutamminase IgA (tTGA) antibodies, deaminated antigliadin (AGA) IgA, IgG antibodies and IgA concentrations were measured in all patients. The control values of serum tissue transglutamminase (tTGA) and anti endomisium (EMA) antibodies were obtained from the literature (i.e., 3,188 Italian children without history of headache or other medical diseases) [2].
Results The positivity of AGA IgG antibodies was very frequent in headache patients (52%). Only three patients from the study group (1.36% of the total sample: 2 patients with migraine without aura and 1 patient with tension-type headache) were positive to tTGA antibodies. The comparison of this prevalence with that from the control population showed no significant difference (1.36 vs. 1.5%, $p > 0.95$). Moreover, no differences were found comparing migraine and tension-type headache patients.
Discussion The results of this study showed that the prevalence of tTGA antibodies positivity (i.e., a reliable indicator for the presence of celiac disease) was not higher in patients with headache compared with the control group. Moreover, no differences were found comparing migraine and tension-type headache patients.
Conclusions Although there may be a link between headache and celiac disease and despite the high and not yet elucidated prevalence of AGA IgG positivity, the routine serological screening for celiac disease in headache patients does not appear justified at present.
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Pychological features and migraine equivalents: is there a relationship?

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Introduction Migraine equivalents (ME) [recurrent abdominal pain (RAP), cyclic vomiting, lower limb pain (LLP), periodic torticollis, motion sickness and benign paroxysmal vertigo] are common clinical conditions in children suffering from headache. In a recent study, we found a high prevalence of such symptoms (68.7%) in patients referred to our Headache Centre. The most common migraine equivalents were RAP (52.3%) and LLP (47.6%).

Very few studies have compared the psychological features in migraine children with (ME) and without migraine equivalents (MWE).
Objectives Our aims were: 1) to compare the psychological features between ME and MWE children, and 2) to study the psychological profile depending on the number of the migraine equivalents.
Materials and methods One hundred and thirty-nine patients with primary headaches were considered. Their age ranged from 8 to 17 years (mean age 11.3 years; s.d. 2.2; F: 67; M: 72).
Patients were divided into ME and MWE groups. Moreover, patients with migraine equivalents were divided into three subgroups according to the number of symptoms (only one migraine equivalent; two migraine equivalents and three or more equivalents). The psychological profile was assessed by means of the "Scale Psichiatriche di Autosomministrazione per Fanciulli e Adolescenti" self-report questionnaire. We administered the SAFA-Anxiety (Generalized, Social, Separation, School subscales) and the SAFA-Somatization (Somatic symptoms and Hypochondria subscales) scales.
Results Migraine equivalents were present in 88 patients (63.3%). No differences were observed between the MWE and ME groups in SAFA-A (Total score: $p = 0.13$) and SAFA-S (Total score: $p = 0.78$). We found significant differences between the three ME subgroups in SAFA-A subscales (Total score: $p = 0.002$), SAFA-Somatic symptoms ($p = 0.000$) and SAFA-S Total score ($p = 0.04$).
SAFA-A subscales mean scores were significantly higher in children suffering from three or more ME symptoms than patients suffering from only a single migraine equivalent (SAFA-A Total score: $p = 0.004$).
Conclusions Our findings suggest that there are no differences in the psychological profile between ME and MWE children. However, in the ME group children who suffered from three or more equivalents had greater emotional difficulties than those with one or two equivalents.

Migraine with autonomic features or cluster headache? A case in pediatric age

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Introduction Headache is a common disease in children. In spite of ICHD-II criteria, differential diagnosis of primary headaches in children is challenging due to some peculiar features of headache at that age. We describe a case in a very young child who presented with headache resembling characteristics of both migraine without aura (MO) and cluster headache (CH).
Case report A 5-year-old boy referred to our Headache Centre suffering from headache for the past 20 days. Headache characteristics were: frontal pain, throbbing in quality, and excruciating pain intensity. Duration of attacks was initially referred to last several hours, headache occurred daily, during daytime and nighttime and it awakened the child. Attacks recurred many times in a day. During the headache attacks, the child presented photophobia and phonophobia; pain was worsened by physical activity; furthermore, the patient showed ptosis, lacrimation, conjuntival injection of the right eye. Personal medical history was negative. He suffered from recurrent abdominal pain attacks, periodic lower limb pain and motion sickness. Familial history was positive for MO (mother). General and neurological examination, including fundus oculi, were normal. MRI scan resulted normal. Headache attacks were monitored by clinical diary for the subsequent 10 days: the attacks continued to occur daily, lasted 1-2 hours and recurred at least two times in a day. Paracetamol was not completely effective. The patient also presented a conjunctival injection in both eyes during interictal period. Thus, the patient started treatment with topiramate 1 mg/kg/day, and continued to record headache attacks in a diary. After one week of treatment, he no longer referred any attacks. Topiramate was well tolerated and no side effects were recorded.
Discussion In children, the characteristics of headache often do not fulfill ICHD-II criteria and overlapping between different forms is possible. Cluster headache is a rare form and very few cases under 10 years of age have been described. Our patient presented headache attacks with migraine features, regarding pain quality, duration, as well as accompanying symptoms, such as photo- and phonophobia. However, autonomic activation (lacrimation, conjunctival injection and ptosis) is not frequent during migraine attacks and it is rarely reported in migraine children. On the contrary, these features are thought to be specific of TACs. Furthermore, the clustering of attacks, more than one in a day, the occurrence of attacks during sleep, the incomplete response to paracetamol, support the diagnosis of cluster headache in our patient. Finally, in our child topiramate resulted effective in the prophylaxis of headache. This supports the diagnosis of migraine since topiramate effectiveness in CH is still debated, especially in children where steroids are commonly used to interrupt the cluster period.

Migraine and syncope: report of two cases with distinct aetiology

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Introduction Some patients with migraine may present syncope immediately before or after the onset of pain [1]. We report two cases of patients with migraine and syncope.
Case 1: Y.E., a 12-year-old boy with a history of episodic migraine without aura since the age of 9; his mother also suffered from migraine. He was referred to our Centre because of 4 episodes of migraine in one month, each time presenting severe pain followed a few minutes later by short-lasting syncope with spontaneous resolution. Complete ophthalmologic evaluation with fundus oculi, cardiologic evaluation with ECG and echocardiogram and EEG were all normal. Brain MRI showed a cyst of the septum pellucidum producing mild compression of the lateral ventricles, without neurosurgical implication. During the 6-month follow-up, he presented weekly episodes of migraine, but only in one case syncope was also reported.
Case 2: L.V., a boy with infrequent headache since the age of 3 and whose mother was affected by migraine with aura. A history of migraine preceded by ocular impairment, left hand weakness and dysphasia was reported by the age of 13. Brain and angiographic MRI proved negative. At 14, while he was cycling, he experienced sudden loss of consciousness and fell to the ground; severe headache was reported when he awoke. Brain computed tomography (CT), echocardiogram and ECG were negative, while the EEG showed multifocal irritative anomalies and was performed again one week and two months later, also, while sleeping, proving negative. On follow-up, monthly episodes of migraine with aura without syncope were reported. When he was 17, he fell again because of sudden loss of consciousness and presented severe headache when he awoke. Brain CT was normal, while the EEG showed multifocal irritative anomalies. Epilepsy was then diagnosed by a neurologist and oral sodium valproate was started.
Discussion In the first case, vasovagal syncope was diagnosed and only prolonged follow-up will clarify whether syncope is accidentally associated with migraine, if it is a consequence of pain or a manifestation of aura [2]. In the second case, loss of consciousness was read as a feature of epilepsy in a patient with migraine with aura. Possibly the follow-up will let us define epilepsy characteristics, the therapeutic efficacy and variation of clinical features of his migraine with aura.
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Clinical presentation of headache in children younger than age 6

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Objective To investigate clinical characteristics of headache at the onset in a cohort of children aged < 6 years.
Methods Charts of outpatients referring to our Headache Centre were analyzed. Only children with primary headache were included. Clinical characteristics of headache included: characteristics of the referred pain, frequency of headache, and duration of headache. Accompanying symptoms were also investigated, in particular nausea, vomiting, photo- and phonophobia. In the history, occurrence of periodic syndromes of childhood and familiar history of any primary headache were analyzed.
Results Three hundred and sixty-seven patients ranging from 1 to 6 years old (mean age: 4.4 ± 1.22 SD) were eligible for our study (males: 46.67% and females: 53.33%). The site of headache was without lateralization in most of the cases. The frequency of headache at the onset was < 2/month in 30.3% of cases, in 23.5% frequency ranged between 2 and 4 episodes per month, 4 per month in 22.7%, daily in 11.2%, and in cluster attacks (daily for one week) in 12.3%. The duration of the attacks was less then 1 hour in 70.8% of cases. As far as associated symptoms are concerned, we found that nausea was present in 25.8% of cases; vomiting in 26.2%, photophobia in 50.5%, and phonophobia occurred in 48%. Surprisingly, photophobia and phonophobia were both associated only in 36.2% of patients, while nausea and vomiting were associated in 9% of cases. Moreover, considering at least one symptom between nausea or vomiting associated to another between phonophobia and photophobia, we found that patients presenting at least one combination ranged between 12.6% and 17.2%. At least one periodic childhood syndrome was found in the history of more than 50% of children. When we tried to classify patients according to the ICHD-II criteria more than 60% of patients did not fulfill criteria for migraine or tension-type headache, thus the diagnosis remained undefined.
Conclusions Primary headaches are very frequent in the children population under age 6. However, applying criteria for primary headaches in children, it is not possible to classify most of these patients. In the present study we showed that the major determinants are the duration of attack (< 60 minutes) and the presence of accompanying symptoms, in particular photophobia and phonophobia. Finally, many other features need to be considered in this special population.

Psychological disorders in childhood and adolescent migraine and tension-type headache: a meta-analysis

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Introdution The role of psychological factors in headache patients have been investigated quite thoroughly in the last century, stressing their importance in influencing child and adolescent headache. A recent systematic review on this topic [1] questioned the existence of psychological difficulties in migraine children, concluding that children with migraine in a clinical setting "do not exhibit more psychological dysfunctioning and (to a lesser extent) do not exhibit more psychiatric comorbidity compared with healthy controls". Moreover, we do not know exactly how different types of headache are influenced by different kinds of psychopathology. To address this topic, we evaluated whether young migraine patients do or do not show significant levels of psychopathology compared with healthy controls and tension-type headache (TTH) patients.
Materials and methods Ten studies were selected on the basis of rigorous criteria and a common psycho-diagnostic tool (Child Behaviour Checklist). The studies were compared in order to study Internalizing (mainly anxiety and depression) and Externalizing (mainly behavioural problems) disorders in different headache sub-types (and versus healthy controls). Data were analyzed using Comprehensive Meta-Analysis Software version 2. As a measure of effect size, the Hedges' g was adopted. Specifically, we conducted three meta-analyses on the selected databases comparing: migraine patients vs. controls, non-migraine patients vs. controls and migraine vs. TTH. The Externalizing/Internalizing scale scores were entered in the models as categorical moderator factors.
Results Migraine patients showed more psychopathology than healthy controls ($p < .001$) with a more marked effect in the Internalizing than in the Externalizing scale. TTH patients also had more psychopathology than controls ($p = 0.002$), although the difference was more marked in the area of internalizing disorders ($p = 0.009$) rather than the Externalizing scale ($p = 0.051$). Finally, no differences emerged between migraine and TTH.
Discussion and conclusions Psychopathology affects migraine children, but TTH as well. Biological, pathophysiological and clinical links have to be drawn. Preventing chronic evolution and treating affected children and adolescents is imperative and, in this context, the CBCL may be a very good Instrument for the psychological evaluation.
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Relationship between childhood physical maltreatment and migraine: a case report

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Introduction Primary headaches are multifactorial syndromes whose therapy involves different branches of medicine, also including psychological, social and economic aspects, thus making therapeutic approach by one specific discipline impossible. The role of psychological factors in the pathogenesis, course and treatment of primary headache is a major topic both for researchers and clinicians. The increasing attention of the scientific community towards psychiatric comorbidity in patients with migraine, has produced a significant amount of publications in all major journals. Several studies showed that abuse could be the cause of the onset of migraine, as well as, the indicator of a worse prognosis [1, 2]. The aim of this study was to present a case of migraine which became non-responsive to pharmacological treatment after sexual abuse.
Clinical Case A 10-year-old girl came to our Neuropsychiatric Clinic in Modena suffering from migraine, with onset 3 years before, which had significantly worsened in the last 2 years, considering frequency, duration and pharmacologic response. General and neurological examinations, laboratory tests, EEG and brain MRI were all normal. After these tests, a diagnosis of migraine with aura was formulated according to the ICHD-II criteria. During the second visit we performed a philological examination and administered Achenbach (CBCL/6-18 – Child Behaviour Check List; YSR/11-18 – Youth Self Report), CDI and STAI tests, that led us to a diagnosis of major depres-

sive disorder. Unfortunately, the patient's headache did not improve with pharmacological treatment, and continued to occur with long-lasting and frequent attacks. In the course of our third visit, during a second psychological examination, the patient admitted having been sexually abuse by her stepfather for the last 2 years. After this confession and the consequent judicial measures undertaken against the crime perpetrator, the girl began to refer an important improvement of the headache frequency and gravity.

Conclusions The prevalence of physical and sexual abuse during the developmental age was estimated to be between 13% and 27% and these patients may suffer from chronic pain, headaches and depression. There are still many unresolved questions concerning the nature of interaction between psychological variables and headache. There is nevertheless a global agreement on a crucial point: the attention of the clinician to the psychosocial and emotional distress associated with migraine, and vice versa, especially in the chronic forms should be considered a structural part of the evaluation process.

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Ophthalmoplegic migraine beginning early as painless ophthalmoplegia

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Introduction Ophthalmoplegic migraine is a relatively rare disorder with different pathophysiology, which is classified as a "cranial neuralgia" (ICDH-II: 13.17). Most cases occur in people having a history, and often familiar occurrence, of migraine without aura. Contrast enhancement of the IIIrd cranial nerve at MRI has been frequently found, suggesting a transitory demyelinating neuropathy. However, other etiologies are reported, like a probable compression by an artery [1] and tumors of the nerve [2].

We describe the case of a child with very early onset and frequent recurrences.

Case report M.P., male, now 8 years old, has a mother suffering from migraine without aura.

At 2 years of age he had a sudden right palpebral ptosis and diplopia, without headache, which resolved after 3 months. Similar episodes occurred when 4 y.o. and 6 y.o., always without headache, the last episode treated with deltacortene 10 mg/day and headache resolved in 6 weeks.

In April, in May and in December 2011 other 3 episodes occurred, which were preceded by right frontal headache, nausea, vomit, photo-, phono- and osmophobia, palpebral ptosis for 1 or 2 days, and diplopia which appeared only after the cessation of headache. Ophthalmoplegia was due to insufficiency of the IIIrd cranial nerve. These episodes were treated with deltacortene 30 mg/day which was given immediately at the onset of ophthalmoplegia and the motor deficit resolved in a few days.

A few months before the episode of April 2011, the child began to complain of accesses of right orbito-frontal headache with nausea, vomit, phono-, photo-, and osmophobia, lasting hours, without oculomotor paresis, with frequency of 1-4/month. The accesses continued without improvement with propranolol, while flunarizine reduced the intensity but not the frequency.

MRI performed during the first episode (when 2 y.o.) showed contrast enhancement with focal thickening of the right IIIrd cranial nerve at the mesencephalic emergency. The same finding was found in all the following episodes. An angio-MRI did not show morphological and hemodynamic abnormalities, nor neurovascular conflicts. MRI was performed also after the resolution of the ophthalmoplegia, and showed no more contrast enhancement, but persistence of the focal thickening, also at a distance of 5 months after the episode (that of May 2011).

Discussion The peculiarity of the reported case, besides the early onset, is the absence of headache during the first 3 ophthalmoplegic episodes, leading to diagnostic difficulties. Moreover, it showed a persistent thickening of the IIIrd cranial nerve also after several months from the resolution of ophthalmoplegia.

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A case of unilateral persistent orbital pain associated with ipsilateral facial nerve palsy without ophtalmoplegia

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Case report We report the case of a 9-year-old child, who referred to the Pediatric Emergency Department for unilateral persistent right orbital pain accompanied by conjunctival injection and photophobia. The symptoms began one month before the presentation with spontaneous mild remission. The intensity of pain was so severe that the child could not open his right eye because of an eyelid spasm. The child also presented mouth deviation on the left side and a marked tenderness when the trigeminal trigger points were compressed by the examiner. No signs compatible with ophthalmoplegia were referred. The child was hospitalized and subjected to several investigations including ophthalmologic observation, ocular ultrasonography, visual evoked potentials and Doppler ultrasound of neck vessels, which resulted all normal. The brain MRI and of the orbital regions showed the presence of an altered signal area on the right side between the channel of the greater superficial petrosal nerve and the posterior border of Gasserian ganglion. This finding was interpreted as inflammatory material.

A screening for infectious disease was performed. An elevated title of VZV antibodies was found (Ig G levels: 1593 mIU/mL (n.v. < 135), IgM levels: < 0.5 mIU/mL). CMV serology resulted negative while the search for CMV DNA in salivary sample was paradoxically positive (2848 copies/ml, n.v. < 800).

No therapy with corticosteroids was undertaken. At a further observation after one month the child still referred facial pain along the territory of innervation of the trigeminal nerve, but no more orbital pain. The laboratory test confirmed an increased VZV antibodies title (IgG 1829), but not salivary CMV DNA presence. A control MRI showed no difference from the previous one.

Discussion Unilateral persistent orbital pain is a clinical entity unusual in children. Neurological etiologies are probable. Cluster headache is probable, even if rare in children. Secondary etiologies include Tolosa-Hunt syndrome, pseudotumor orbitae and several conditions involving the nervous structures of the orbital apex and neighbouring areas. In the case reported some symptoms are suggestive of Tolosa-Hunt syndrome. But the lack of ophthalmoplegia is an exclusion criteria for this diagnosis (ICHD-II criteria, 2004) and furthermore the side of neuroradiological abnormalities is not the classical one. The facial spasm and the side of pain reflect an exaggerated trigeminal-facial reflex.

Conclusions A clinical, laboratory and neuroradiological picture suggests the involvement of trigeminal and facial nerves compatible with a viral ganglioneuritis.

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The "periodic syndrome" in children: nosology and predictive significance

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The "periodic syndrome" (PS), including different clinical conditions characterized by recurrent stereotyped and reversible symptoms, has been described for the first time in 1933 by Wyllie and Schlesinger with the term "periodic disorders of childhood".

Cyclic vomiting (CV) was the first PS described by Heberden about two centuries ago (1806); it is characterized by recurrent, stereotypical and self-limiting episodes of severe nausea and vomiting associated with pallor and lethargy with periods of well-being.

Abdominal migraine (AM) was described by Buchanan in 1921 as "attacks of abdominal pain without headache" and the term "abdominal migraine" was used by Brams in 1922.

Benign paroxysmal vertigo (BPV), originally described by Basser (1964), consists of paroxysmal dizziness in neurologically healthy subject, without premonitory signs and with a spontaneous resolution.

Benign paroxysmal torticollis (BPT), a rare dyskinesia reported by Snyder (1969), is characterised by recurrent and stereotyped attacks of inclination and rotation of the head with both a spontaneous resolution and a good prognosis.

All these entities, grouped under the common name of PS, are considered to be predisposing factors for migraine (M). In 2004 CV, AM and BPV were included in the International Classification of Headache Disorders (ICHD-II) (code 1.5) [1], whereas BPT was listed in the Appendix of the same classification (A1.3.5).

However, in the literature growing pains (GP) and kinetosis (K) have been considered as PS but these two clinical entities have not been included in the ICHD-II [1].

We conducted a multicentre study on 950 Italian children showing that PS were significantly associated with M ($p = 0.03$) only if all of the 6 PS are considered together (VC, AM, BPV, BPT, GP, K). The association with M, however, was not significant if we considered only 3 PS included in ICHD-II criteria (VC, EA, VPB). Evaluating each PS separately, only the GP showed strong correlation with the diagnosis of M ($p < 0.0001$) [2].

In a patient affected by primary headache the presence of one among the 6 PS increased the probability of becoming a migraineur from 65.5% (prior probability) to 70.7% (posterior probability); this probability increased to 73.5% if K was present and to 77.7% in patients with GP. Therefore PS could support the diagnosis of M, particularly at headache onset when all the diagnostic criteria are not fulfilled [2].

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Different balance between excitation and inhibition in the primary somatosensory cortex of migraine children with imploding or exploding pain

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Different pathophysiological mechanisms are supposed to work in migraineurs with either imploding (IP) or exploding (EP) pain [1]. The aim of the study was to record the short-latency scalp somatosensory evoked potentials (SEPs) in migraine children and to investigate whether the inhibitory and excitatory tone of the primary somatosensory (SI) area depend on pain direction. We studied 4 migraineurs with IP (3 girls and 1 boy; mean age 13 ± 2 years) and 5 migraine children with EP (5 girls; mean age 12.3 ± 3.9 years). SEPs to both right and left median nerve stimulation were recorded from 31 scalp electrodes. The parietal P24 amplitude was significantly higher ($p = 0.005$) in EP (3.6 ± 1.8 mV) than in IP patients (1.3 ± 0.9 mV). In order to have a measure of the balance between excitation and inhibition in the SI area, we calculated also a $SI_{e/i}$ index [(N20–P24)/(N20+P24)]. This index was significantly higher ($p = 0.0008$) in IP (0.37 ± 0.34) than in EP (-0.34 ± 0.23) migraineurs, meaning that the N20 amplitude was higher than the P24 amplitude in IP patients, while the opposite occurred in EP children. Since the parietal N20 and P24 SEP amplitudes represent, respectively, the excitatory and inhibitory phase of the somatosensory primary response [2, 3], our results suggest that inhibitory mechanisms are dominant in the SI area of EP children, while in IP patients the excitatory tone is prevailing.

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A child with an acute secondary headache due to X histiocytosis

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Case report The propositus, an 8-year-old male, was born at term (40 weeks of gestation) by an uneventful natural delivery to unrelated, healthy parents without a family history of genetic or neurological diseases. At birth the child's parameters were: weight 2.580 g (3th centile), head circumference 32.5 cm (10th centile), length 48 cm (10th centile). His clinical history was only characterized by the presence of two episodes of febrile seizure respectively at 18 and 23 months. At the age of 8 because of an acute temporo-parietal headache the patient was referred to our Department. Our patient's evaluation included physical and neurologic examinations, which were normal except for a 3 x 3 cm nodulary swelling in the right parietal region of the skull. No fever or neck stiffness were present. Laboratory evaluation demonstrated normal red blood cell, white blood cell, and platelet counts. The results of coagulation function tests, urine analysis, and biochemistry profile analysis were normal. Neuroimaging studies were performed and revealed:

- Skull X-rays: right parietal thecal reduced-intensity bone area rounded of 20 mm in diameter
- Brain MRI: a right parietal osteolytic lesion is appreciable with an oval shape and a diameter of 16 x 22 mm approximately. The lesion is provided with intense enhancement and infiltrates the surrounding soft tissues. The mass marks the underlying cerebral convolutions and is not associated with edemigen phenomena.

The patient was therefore hospitalised for NCH removal surgery. Histological examination showed: a richly infiltrated eosinophils, dense proliferation of

Langerhans cells (CD1a, S-100: +); furthermore the lesion was characterized by necrotic-hemorrhagic phenomena and showed a growth fraction of about 2-3 mitoses XHPF.

Discussion Histiocytosis X, an uncommon disorder characterized by an abnormal proliferation of Langerhans cells, is a spectrum of diseases which should be classified among the wide spectrum of histiocytic disorders, consisting of proliferation of the Mononuclear Phagocyte System [1]. The clinical manifestations reflect the site of histiocytic proliferation and may vary from a solitary bone lesion discovered by chance by X-ray to a disease with a rapidly fatal course affecting almost any organ. However if, as in our case, eosinophilic granuloma of the skull is the most common presentation of the disease, the classic classification into eosinophilic granuloma of bone, Hand-Schüller-Christian disease and Letterer-Siwe disease fail to demonstrate the variable course and the smooth transitions, and do not correlate with the histologic findings and prognosis [1, 2]. Because of the variable course of Histiocytosis X, and for prognostic and therapeutic reasons, an early diagnosis based on clinical and histologic manifestations is desirable [3].

Conclusions In conclusion, our case illustrates once again the clinical heterogeneity of headache as well as the complexity of Histiocytosis X. An histiocytic disorder must be suspected in a child with cranial swelling and acute headache.

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Psychiatric comorbidity and correlations among migraine, attachment, anxiety and depression: a controlled study

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Introduction The association between migraine (M) and psychiatric comorbidity is well known even in children and adolescents. What is really difficult to understand is why this association is so common.

The aim of our study was to analyze the attachment style of children and adolescents with M and to try to understand how it could be correlated to anxiety (A) and or Depression (D) in migraine.

Matherial and methods One hundred patients (47 M, 53 F) (age 8-14, mean age 12.2 years) with migraine with aura (MA) were compared to a control sample of 100 students (49 M, 51 F) from a secondary school of Rome. Instruments used were: 1) Self-Administrated Psychiatric Scales for Children and Adolescents (SAFA) to determine A and D; 2) Security Scale to evaluate the attachment behaviour. Factorial Analysis was performed.

Results In the SAFA Test, the study group showed higher levels for depressive disorder ($p = 0.03$), irritable mood ($p = 0.001$), and insecurity, ($p < 0.00000001$). The Security Scale showed a lower level of scores in all the dimensions (security with the mother, security with the father, general security).

Conclusions The finding of a strong association between attachment, insecurity, depression and anxiety in children and adolescents with migraine suggests a strong influence of the parental model of attachment in the development of psychiatric comorbidity in patients with migraine.

AUTHOR INDEX

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THE ITALIAN SOCIETY FOR THE STUDY OF HEADACHES

ANNOUNCES

THE ENRICO GREPPI AWARD 2013

The Italian Society for the Study of Headaches (SISC) announces the competition of the Enrico Greppi Award 2013. The award will be granted to the best unpublished original paper dealing with clinical, epidemiological, genetic, pathophysiological or therapeutic aspects of headache. The prize amounts to € 10,000 and is open to researchers of all nationalities. The papers must be submitted in accordance with the editorial instructions of *The Journal of Headache and Pain*. The winning article will be published *ex officio* in *The Journal of Headache and Pain* within three months of the Award presentation. The remaining papers are considered as submitted to *The Journal of Headache and Pain* and may be published after undergoing the peer-reviewing process. The Award is endorsed by the European Headache Federation (EHF).

Manuscripts should be sent by e-mail to the President of SISC at sisc@sisc.it not later than 1 May 2013.

Rules for the Enrico Greppi Award

1. The Italian Society for the Study of Headaches sponsors an Award in memory of Enrico Greppi, pioneer and expert in the study of headache.
2. The Award is assigned to an unpublished paper dealing with clinical, epidemiological, genetic, pathophysiological or therapeutic aspects of headache. Competing papers must be written in accordance with the editorial instructions of *The Journal of Headache and Pain*, which can be found at http://www.springer.com/10194. Papers submitted for the Enrico Greppi Award should be sent by e-mail to sisc@sisc.it and not submitted via Editorial Manager.
3. There is no limit of age for participants of the Enrico Greppi Award.
4. All researchers in the headache field may compete for the Award. Members of both SISC and EHF Boards of Directors may compete as well, if they are not serving on the Selection Committee and did not participate in the nomination of the Selection Committee.
5. The Award winner will receive € 10,000, along with a certificate signed by all members of the Selection Committee.
6. The competition will be announced in the EHF official journal, *The Journal of Headache and Pain*, and in other scientific journals. Within three months of the announcement of the Award, *The Journal of Headache and Pain* will publish *ex officio* the winning manuscript, including the list of members of the Selection Committee. The remaining papers are considered submitted to *The Journal of Headache and Pain* and may be published after undergoing the peer-reviewing process.
7. The Selection Committee will be composed of the SISC President as chairman, an EHF representative, the Editor-in-Chief of *The Journal of Headache and Pain*, one member of the SISC Board of Directors and two members chosen from international experts in the headache field. The Committee is nominated by the SISC Board of Directors. Should the SISC President not be able to chair, the oldest member of the Committee will assume his role. The papers will be judged by each Committee member individually on a scale from 0 to 10. Each Committee member is responsible for sending his scores to the President of the Committee. The scores of at least four Committee members are necessary to determine the winner. The winning paper must receive an average score of not less than 6. In the case of a tie, the President's vote will have a double value. Should a tie persist, there will be a random drawing in the presence of a notary. No Award will be assigned if less than four judges send their scores or if no paper receives a score of at least 6. In this case the Award amount will be deposited in the prize funds.
8. The competing manuscripts must be e-mailed to the SISC President at sisc@sisc.it not later than 1 May 2013.

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