

The Journal of Headache and Pain

SUPPLEMENT

**XXVII National Congress of the Italian Society for the Study of Headaches.
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of Headaches**

Perugia – September 26 – 28, 2013



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The Journal of Headache and Pain

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**Edited by:
Giorgio Bono
Paolo Calabresi**

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PREFACE

The National Congress stands as a crucial moment, among the scientific and educational activities of the Italian Society for the Study of Headaches (SISC), intergrating the most important aspects in headache research and clinical and therapeutic advancements. Its objective is to provide the most appropriate recommendations for the management of adult, child or adolescent patients, in different care settings, in accordance with the multidisciplinary nature of SISC.

Particular attention will be placed on the psychobiological bases underlying this heterogeneous group of disorders and on the therapeutic strategies best suited for their treatment. Specific sessions will cover physiological conditions and comorbidities (psychopathological disorders, in particular, depression, sleep, and vascular disorders) that modulate the expression of the disease in patients. Other topics of interest will include the relationship between headaches and neuropathic pain (including clinical, pathophysiological and therapeutic aspects) and the chronic forms, especially those with symptomatic drug overuse, which present management difficulties in clinical practice and require the development of targeted and validated protocols. Pharmacological and non-pharmacological approaches will be addressed with specific reference to the related pathophysiological interventions at different levels: i.e., control of the neurovascular and cardiovascular responses, modulation of the transmission/perception of pain, role of inflammation and immunity mechanisms, and hormonal regulation. Among the most recent therapeutic aspects botulinum toxin, new neurostimulation techniques, antiepileptic drugs and antidepressants, anxiolytics and hypnotic drugs, hormone therapy, and specific symptomatic and anti-inflammatory drugs will be discussed.

The conference is open to: neurologists, neurophysiologists, pharmacologists, internists, psychiatrists, juvenile neuropsychiatrists and paediatricians, anaesthetists, general practitioners and psychologists, and all professionals working within the National Health System operating in the field of headaches.

The National SISC Congress of Perugia 2013 would like to be an innovative learning project that enhances the content and the interaction between specialists of different disciplines, in an environment that is characterized, also structurally, as an example of an effective exchange between the University and the National Health System.

Giorgio Bono
President
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Paolo Calabresi
President
XXVII National SISC Congress

Lectures

“Federigo Sicuteri” Lecture

Migraine: a disorder of brain excitatory-inhibitory balance?

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Migraine is a common disabling brain disorder whose key manifestations are recurrent attacks of unilateral headache and interictal hypersensitivity to sensory stimuli. The molecular and cellular mechanisms of the primary brain dysfunction(s) leading to the onset of a migraine attack and to susceptibility to cortical spreading depression (CSD), the neurophysiological correlate of migraine aura and a likely trigger of the headache mechanisms, remain largely unknown and major open issues in the neurobiology of migraine. Gain-of-function mutations in the neuronal CaV2.1 (P/Q-type) calcium channel and loss-of-function mutations in the glial alpha2 Na/K-ATPase cause a rare subtype of migraine with aura: familial hemiplegic migraine (FHM1 and FHM2, respectively). Knockin (KI) mouse models carrying FHM1 or FHM2 mutations show a lower threshold for CSD induction and a higher velocity of CSD propagation. We have investigated the cortical mechanisms underlying the facilitation of CSD in FHM1 KI mice and the functional consequences of FHM1 mutations on synaptic transmission and short-term synaptic plasticity at the main synapses of the cortical microcircuit involving pyramidal cells, fast spiking interneurons and somatostatin-expressing interneurons. Our findings support the view of migraine as a disorder of brain excitability characterized by deficient regulation of the cortical excitatory-inhibitory balance, and point to episodic disruption of the excitatory-inhibitory balance and neuronal hyperactivity due to excessive recurrent glutamatergic transmission as the basis for vulnerability to CSD ignition in FHM.

Pharmacogenomics of headaches

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Headaches are widely prevalent diseases causing relevant disability and worsening quality of life. Several pharmacological options are available for headache therapy, despite a significant fraction of patients are non-responders and often have serious side effects.

Variability of therapeutic effect and adverse events might be influenced by genetic factors, even though findings have so far been inconclusive. To this regard, pharmacogenomics, studying the role of genetic determinants in modulating the individual response to drug treatment or the onset of adverse drug reactions, represents a promising approach to therapy of headaches.

For this purpose, our group performed a genome-wide gene expression (GWGE) study in patients with cluster headache (CH) and patients with bipolar disorder (BD). Lithium is an effective prophylactic agent used both in CH and BD, which are different diseases sharing cyclicity and episodic

course. Lithium significantly reduces frequency of recurrent attacks of short-lasting excruciating pain in CH patients. This clinical effectiveness is even higher in BD, where one-third of treated patients present remission from recurrence of mood episodes. Thus, it is conceivable that lithium-responsive episodic CH and lithium-responsive BD might also share a fraction of their genetic and biological makeup. Therefore, we compared gene expression levels of 10 BD and 8 CH lithium full responders to investigate pathways commonly regulated by lithium in both diseases.

Moreover, we will perform a sequencing study to investigate functional genetic variants involved in valproic acid response in medication-overuse headache (MOH) patients.

In conclusion, these approaches could contribute to identify predictors of response and new drug targets to improve both effectiveness and safety.

Is migraine a disease?

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The migraine attack is a reversible brain dysfunction characterized by pain autonomic symptoms and passive coping strategies consistent with sickness behaviour. The migraine attack may be interpreted as an example of genetically determined adaptive behavioural response to internal or external stressors that is orchestrated by a threatened brain. In this view, the migraine attack itself may not be categorized as a disease i.e., a deviation from or interruption of the normal structure or function of the brain but it may turn into a disease in an allostatic perspective, when the repeated migraine attacks start maladaptive mechanisms (inefficient turning on or shutting off of the mechanisms underlying the migraine attack) that result in a chronic pain of the brain. In the future we should recognize and treat early all the conditions able to transform a normal response of the brain into a morbid state, i.e., we have to categorize migraine not only as a type of headache attack but also as a symptom of different syndromes.

Functional neuroimaging in headache (migraine?)

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Migraine is a neurologic disorder characterized by disabling attacks of throbbing headache with specific features and associated symptoms. The diagnosis of migraine is based on well-known clinical features as proposed by the International Headache Society criteria but its pathophysiology is not completely understood and is a matter of ongoing research. Functional neuroimaging of patients with migraine, rather than improving diagnostic purposes, has been employed to study the underlying pathophysiology of migraine. Indeed, since the first report on the blood oxygen level dependent (BOLD) contrast which is based on different magnetic characteristics of oxygenated/deoxygenated haemoglobin, many researchers have applied func-

tional magnetic resonance imaging (fMRI) as a surrogate marker of neuronal activity to study pain and migraine related brain functional changes. fMRI studies have addressed crucial migraine-related issues, improving our understanding of the circuitry that may be involved in the generation, maintenance and recurrence of pain symptoms in migraine. Today, thanks to fMRI studies, it is well known that migraine involves abnormal brain functions and that the headache phase of a migraine attack depends on a nociceptive signal flow, originating in pain-sensitive cranial structures, conveyed to central trigeminovascular neurons and that migraine attack could depend on, or be modulated by, dysfunctional brainstem nuclei and other cerebral areas controlling neuronal excitability and pain. Correlation analysis between fMRI findings and clinical data highlighted the impact of enduring migraine pain over brain function and contributing to the idea that long-term and high-frequency headache attacks may cause functional connectivity network reorganization. Moreover, fMRI studies have shed some light on pathophysiological mechanisms underlying migraine associated symptoms. More recently, the study of brain functional connectivity at rest has revealed abnormalities in cognitive and sensory pathways in patients with migraine. The purpose of this review is to present an overview of BOLD-fMRI findings that have led to a better understanding of migraine pathophysiology.

Drug prescription liability

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The prescription of drugs is the most frequent medical action, and medicines are one of the principal causes of adverse events from medical cares. Nevertheless, if a huge judicial casuistry exists regarding malpractice in the phase of diagnosis or surgical treatment, there are very few cases about physicians' liability for drug related morbidity.

The 1998 Italian Law regarding off-label drugs provides legal parameters for a legal off-label prescription, and judges have already affirmed civil and criminal liability for those who violate this Law.

A second peculiar juridical aspect in the prescription of medicines concerns generic drugs: there are many legal implications concerning bioequivalence and liability caused by generic drug prescription, such as: bio-creep, differences in excipients and therapeutic indications, physician's liability vs. pharmacist's liability.

Physicians should be aware of the legal principles in drugs prescription liability, both criminal and civil, and avoid illegal behaviours and consequent lawsuits.

Non-invasive neuromodulation in primary headaches

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Preventive drug treatments have partial efficacy in primary headaches and unpleasant side effects. In the chronic subtypes, they become notoriously inefficient. There is thus room, and even need, for alternative therapies.

Invasive neurostimulation procedures have been explored in patients with refractory headaches, but evidence-based data remains scarce. In cluster headache, ONS has overall an efficacy similar to hypothalamic deep brain stimulation DBS (>60% responders) but the advantage of having no serious side effects. It acts by modulating the descending pain control system and has no effect on the hypothalamic "generator" explaining why attacks recur when stimulation stops. ONS has also modest efficacy in chronic migraine, but more studies are needed. In a recent sham-controlled trial, (blocking) stimulation of the sphenopalatine

ganglion with an implantable stimulator activated on demand by an external remote controller is effective both for acute treatment and prevention of cluster headache attacks: overall 68% of patients responded for either one or both.

Non-invasive neurostimulation methods are of major interest in headaches, as they can be used also in less disabled patients. Transcutaneous SNS was superior to placebo in a recent sham-controlled trial for the prevention of episodic migraine. The 50% responder rate of 38.1% is below that of topiramate (45%), but, contrary to the latter, SNS is quasi devoid of adverse effects. By contrast with peripheral nerve stimulation, repetitive transcranial magnetic (rTMS) and direct current stimulations (tDCS) aim at influencing directly cortical and subcortical structures known to be dysfunctioning in episodic and chronic migraine. It is known from imaging and neurophysiological studies, however, that these dysfunctions vary over the migraine cycle and between the two migraine forms. While this has little relevance for peripheral nerve stimulation, it is of uttermost importance for transcutaneous neuromodulation where the target and the planned change in activity have to be clearly defined. We will illustrate this by comparing the negative results of studies using inhibitory rTMS or tDCS over the visual cortex to prevent episodic migraine and preliminary results we have obtained recently with excitatory stimulation protocols in episodic migraine but inhibitory protocols in chronic migraine. Studies of novel devices targeting transcutaneously the vagus nerve to treat acutely and prophylactically migraine and cluster headache are underway.

To summarize, the future for neuromodulation, in particular non-invasive methods, is bright in the management of primary headaches as long as evidenced-based data support their efficiency and further research allows to understand how they act.

Migraine and women

Different faces of the same migraine in women

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Background The prevalence of migraine in women after puberty, the fact that more than 50% of women report menses as a trigger factor for the attacks, the occurrence of attacks only during menstruation and/or ovulation in a fifth of the cases, the improvement of migraine during pregnancy, the possibility of modifying the course of migraine with hormonal treatment/contraceptives: all of these conditions reveal a relationship between female hormones and migraine [1].

Migraine and menarche In childhood, migraine prevalence ratio female/male is equal to 1, after puberty it reaches a ratio of 2:1 in favor of females for both migraine with aura and without aura.

Menstrual migraine The International Headache Society (IHS) classification contemplates menstrual migraines only in the appendix. The variability of definitions of this subtype of headache influences the prevalence of migraines related to the menstrual cycle. The fall in estrogen levels that precedes the onset of menstruation is the hypothesized pathogenetic mechanism.

Migraine and pregnancy In about 60-70% of migraine without aura patients a significant improvement of migraine during the gestation period is observed. Instead, migraine with aura remains unchanged or may even worsen during pregnancy up to 30% of cases.

Migraines and menopause The prevalence of migraine is reduced with age in both sexes. Female predominance, although less important, still persists after menopause. In contrast, there is a worsening of migraine in about 2/3 of women after surgical menopause.

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Comorbidities in headache

Sleep disorders and primary headache disorders

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Epidemiologic studies offer strong evidence of comorbidity between primary headache and a wide set of sleep disorders including not only insomnia but also sleep related breathing disorders, circadian rhythm disorders, and parasomnias. Lack of sleep as well as oversleeping are well known to be triggering factors for headache attacks. Insomnia is the most common sleep complaint among patients with migraine and tension-type headache, largely contributing to the worsening of their quality of life. Snoring and obstructive sleep apnea (OSA) have shown to be modifiable risk factors for progression from episodic migraine to chronic daily headache. Cluster headache, which is associated with an 8.4-fold increased risk for OSA, can be triggered by sleep and is related to sleep stages suggesting that it may be considered as a chronobiological disorder. Hypnic headache, is characterized by chronic dull head pain recurring only during sleep so it is perhaps the best example of an interrelationship between sleep and headache and can be considered as a chronobiological disorder too. Recent studies have been focused on other specific sleep disorders such as restless legs syndrome and parasomnias, showing a higher frequency of these conditions in headache patients than in controls. Sleep and pain perception share some anatomic structures and neural pathways that, when dysfunctional, may generate a sort of individual vulnerability to both sleep and headache disorders. The comorbidity of headache and sleep disorders supports the recommendation to collect sleep history in headache patients. Subjects suspected to suffer from specific sleep symptoms or disorders should be identified and treated to improve headache management.

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Headache and epilepsy: a controversial comorbidity

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The comorbidity of headache and epilepsy is still controversial. Published reports mostly focus on migraine and epilepsy while the association between epilepsy and other primary headaches still requires investigation. The prevalence of migraine in patients with epilepsy ranges from 14 to 24% and the prevalence of epilepsy among migraine sufferers ranges from 1.1 to 17%. An association with migraine has been reported in specific epileptic syndromes, including benign occipital epilepsy of childhood and epilepsy with centro-temporal spikes. The association between headache and epilepsy has been found to be bidirectional. While headache is a common complication of seizures and epilepsy, migraine with aura may carry a higher risk of unprovoked seizures. Although the above findings suggest a correlation between migraine and epilepsy, several studies found no correlation and questioned the existence of a definite comorbidity. In a recent Italian cross-sectional study comparing patients with migraine and/or tension-type headache from headache centres and patients with focal or generalized epilepsy from epilepsy centres, comorbidity was detected in 1.6% of cases from headache centres and in 30% of cases from epilepsy centres. These percentages overlap those expected in the general population and do not support the comorbidity between headache and epilepsy. In addition, there is virtually no evidence of phenotypic differences between patients with headache and epilepsy and those with headache or epilep-

sy. These contrasting results may be explained by differences in the methodology of the existing reports: variability of study populations, use of differing diagnostic criteria, varying, often suboptimal, study designs and methods. Limitations also include clinical series, inappropriate control groups, and ill-defined diagnostic criteria. For these reasons, there is no conclusive evidence of a real causal relationship between the two disorders.

Headache and systemic dysimmune diseases

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Migraine and other recurrent headache disorders represent a major public health problem and are associated with relevant patient disability. Indeed, this disabling symptom may be expression of several functional and organic pathologic conditions and more than a single etiopathogenetic mechanism often contribute to it. Thus, diagnostic approach to chronic headache represents a major challenge. Headache is frequently reported in patients with systemic vasculitides or connective tissue diseases (CTD)s, often representing the clinical epiphenomenon of an organic central nervous system inflammatory or immune-mediated damage. In this setting, headache, in particular migraine, has been reported to be the most common neurological symptom among patients with Beçhet disease (BS) and may represent the first clinical manifestation in Horton's arteritis. In these diseases, a vascular headache may be triggered by immune-mediated disease activity or may be due to direct central nervous system parenchymal involvement, cerebral venous sinus thrombosis or association with uveal inflammation, as reported in 4% of BS patients.

Chronic headache is common in CTD patients, including antiphospholipid (aPL) syndrome and systemic lupus erythematosus (SLE), and can antedate the diagnosis by many years. However, although migraine prevalence in SLE appears to be nearly twice than in healthy subjects, prospective studies failed to demonstrate a direct association between aPL and migraines in SLE and no association has been demonstrated between migraine and disease activity or damage, immunological variables or cerebral magnetic resonance imaging findings. On the other hand, the prevalence of primary headache in Sjögren's syndrome patients has been demonstrated to be similar to the general population, thus hypothesizing a different pathogenic mechanism underlying central nervous system involvement in the spectrum of CTDs.

Finally, some rare forms of chronic "primary" headache, including stabbing and nummular headache, have been reported to occur more frequently in patients with different autoimmune disorders, suggesting that some forms of headache may be directly immune-mediated and predicting the efficacy of corticosteroids or other immunosuppressants as "disease-modifying" drugs in specific subgroups of headache.

Headache, fibromyalgia and visceral pain: the role of comorbidities

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Introduction Epidemiologic studies show a high degree of comorbidity among headache (H), fibromyalgia (FS) and visceral pain, particularly irritable bowel syndrome (IBS), dysmenorrhea, and pelvic pain from endometriosis. We report on the impact of concurrent visceral pain syndromes and their treatment on pain symptoms from headache and fibromyalgia in comorbid patients.

Materials and methods Headache and fibromyalgia female patients (19–42 years) were examined who presented concurrent: IBS (n. 29), dysmenorrhea (n. 31) or endometriosis (n. 22). They underwent pain threshold measurement to pressure and electrical stimulation of somatic tissues (skin, subcutis and muscle) in both painful (TePs) and nonpainful areas (trapezius, deltoid, quadriceps) in basal conditions and after a 6-month treatment [dietary for IBS (n. 19), hormonal for dysmenorrhea (n. 20), laser for endometriosis (n. 11) or no treatment (n. 10, 11, 11)] of the visceral pain syndromes. Headache and fibromyalgia symptoms (no. of monthly crises/flares, their intensity (VAS scale), symptomatic drug consumption) after visceral pain treatment, or no treatment, were compared with those preceding treatment.

Results After visceral pain therapy there was a significant reduction of number and intensity of monthly headache crises/fibromyalgic flares and the relative symptomatic drug consumption ($0.05 < p < 0.01$) as well as the generalized pain hypersensitivity [significant increase in pain thresholds in all tissues and body sites ($p < 0.02$)]. No improvement was obtained in H and FS comorbid patients not undergoing visceral pain treatment.

Conclusions Visceral pain contributes to the triggering of headache and fibromyalgic symptoms in comorbid patients. Its specific treatment is thus suggested as an indispensable complementary step towards optimal management of these conditions.

From birth to adulthood

Early onset headaches

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Objective ICHD-II criteria are often difficult to apply to very young children. Our study aimed at investigating the clinical characteristics of the primary headaches in a group of children aged <6 years.

Methods Charts of outpatients referring to our Headache Centre were analyzed. Only children with primary headache were included.

Results Three hundred and sixty-seven patients ranging from 1 to 6 years of age (mean age: 4.4 ± 1.22) were eligible for our study (Males: 46.67%, Females: 53.33%). The site of headache was without lateralization in most cases. The frequency of headache at the onset was <2/month in 30.3% of cases, in 23.5% it ranged between 2 and 4 episodes per month, >4 per month in 22.7%, daily in 11.2% and in cluster of attacks (daily for one week) in 12.3%. The duration of attacks was less than 1 hour in 70.8% of cases. Nausea was present in 25.8% of cases, vomiting in 26.2%, photophobia in 50.5%, and phonophobia occurred in 48% of patients. At least one periodic syndrome of childhood was found in the history of more than 50% of children. When we tried to classify patients according to the ICHD-II criteria, most patients did not fulfill criteria for migraine or tension-type headache, thus the diagnosis remained undefined.

Conclusions Although primary headaches are very frequent in children younger than 6 years, the ICHD-II criteria cannot classify most patients. In the present study, we show that the major determinants are the duration of attack (<60 minutes) and the presence of accompanying symptoms, in particular photophobia and phonophobia.

Headaches and cranial autonomic system: a clinical study and review of the literature

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Background and aims Recently cranial autonomic signs (CAS) have been reported in adult migraineurs, but the prevalence of CAS in children affected by primary headaches is unknown. Therefore, the aim of this study was to evaluate the prevalence of CAS during headache attacks in the pediatric headache population and to study the correlation between CAS and the main symptoms of migraine.

Methods A total of 230 children suffering from headache (105 males, 125 females, aged: 4–17 years) were consecutively enrolled in a two-year period. A short questionnaire investigating the presence of CAS was administered to all the children. The following CAS were included in our study: conjunctival injection, tearing, palpebral oedema, nasal congestion, rhinorrhoea, red ear, facial flushing, miosis, ptosis, forehead or facial sweating.

Results In total, 198 children (86%) (94 males, 104 females) were found to be affected by migraine with/without aura, and 32 (14%) by other primary headaches. The observed prevalence of cranial autonomic features (CAS) in headaches was: general population, 116/230 (50.4%); other headache 9/32 (28.1%); migraine 107/198 (54.04%). CAS occurred significantly more frequently in migraine than in the other primary headaches (107/198 versus 9/32 $p = 0.008$). The most common signs were facial flushing, red ear and conjunctival injection. At the univariate analysis CAS were significantly associated to the frequency of attacks ($p < 0.02$), to the aura ($p < 0.05$) and male gender ($p < 0.05$).

Conclusions These findings indicate that CAS are rather common in the course of pediatric migraine attacks and prevalence differs significantly from other headaches. The prevalence of signs associated to local vasodilatation, shows an important activation of parasympathetic control on cranial vascular tone in this subgroup of pediatric migraineurs. The significative association between the presence of CAS and the frequency of attacks suggests that activation of the parasympathetic system has a role in the severity of disease in pediatric migraine, supporting the role of the trigemino-autonomic reflex in migraine.

The school: learning disorders and headache

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Introduction The association between headache and learning disorders (LD) could be associated with an attention and memory deficit, but psychiatric comorbidity of headache children and LD are frequent and thus consistent.

Materials and methods One hundred patients, 51 F and 49 M (mean age 11.32 yrs) with primary headache, were compared with 90 patients, 33 F and 57 M (mean age 10.25 yrs), with LD.

Methods Patients underwent: test AC-MT evaluation skills, calculation and solution of problems to Cornoldi, MT reading tests for elementary and middle school to Cornoldi and the Wechsler Intelligence Scale for Children C-III. The headache diagnosis was made according to the IHS criteria 2004. Statistical analysis: chi-square statistic index and linear regression.

Results The migraine without aura was the prevalent headache, (60% of cases, 67.3% M and 52.9% F), 17 children, including 8 males and 9 females, were found to have a learning disorder; 4% reported a diagnosis of specific learning disorder (SLD), while 3% of the total sample non specific learning disorder (4.1% M and 1.9% F). In this group tension-type headache was prevalent. The somatization pain prevalent in the group with dual diagnosis was abdominal pain (63% M and 44% F). In the group without LD, the EEG abnormalities were present in 20% of the sample, but in the group with LD abnormalities were found in 59%. On the basis of linear regression analysis the independent variable headache frequency is correlated with the presence of LD.

Conclusions LD are prevalent in the headache group compared to the general population (17% vs. 3%). There is no influence of headache on the activities of homework and school absence. Thus, LD should be considered the comorbidity of headache but not the cause.

Medication-overuse headache in children and in adolescents: report of a specialist centre

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Background Medication-overuse headache (MOH), according to Olesen and colleagues, could be described as “head pain presenting 15 or more days per month, with an abuse of one or more symptomatic drugs for at least 3 months, and a worsening of the headache during the same period” [1]. Epidemiological surveys conducted in Taiwan and Norwegian found respectively that 0.3% and 0.5% of adolescents could be diagnosed as MOH.

Materials and methods Retrospective study of 165 patients with primary chronic daily headache (CDH), selected among all the patients (1,100) evaluated at the Juvenile Headache Centre of Padua in the period October 2011–September 2012.

Results Patients with CDH represented 15% of all cases (165/1100) (70 males and 95 females; mean age 12 years, range 5–18 years); 16 patients with CDH presented MOH (10%).

In patients with MOH, the following drugs were overused: analgesics 50% (acetaminophen, rarely in association with codeine), NSAIDs (ibuprofen or ketoprofen) 40%, mixture of different anti-inflammatory drugs 10%; none of our patient overused triptans. The mean duration of drug overuse, at the time of the evaluation, was 5 months. The detoxification was conducted mainly in outpatient settings (90%), and rarely required a Day Hospital setting (5%) or hospitalization (5%). After drug withdrawal (follow-up: 2–4 months), 14/16 patients were “responder” (reduction in more than 50% of headache frequency); two patients remained stable.

Conclusions In our cases, the prevalence of CDH and MOH was similar to other series previously reported. Chronic headaches represent a common condition that requires global management aimed at reducing the frequency of the attacks, lowering the associated disability and improving the patients’ quality of life. On suspicion of overuse, a proper and specialized intervention should be started.

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Perfectionism and psychiatric comorbidity in children with migraine

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Introduction Children with migraine present other psychopathological disorders, specifically, in 80% of these perfectionism disorder occurs. Perfectionism is a personality trait characterized by striving for flawlessness and excessively high performance setting standards, accompanied by over-critical self-evaluations and concerns regarding the opinions of others [1]. We hypothesized that perfectionism causes the manifestation of psychological disorders such as anxiety and depression.

Objective The purpose of this study was to investigate the interaction between perfectionism and migraine in children.

Methods The sample of 100 subjects, 48 males and 52 females, aged between 8 and 14 years, with a diagnosis of migraine, was recruited for the treatment of headache from the Centre of the Department of Pediatrics and Child Neuropsychiatry of the Policlinico Umberto I in Rome. The clinical group was formed by 78 subjects with migraine without aura and 22 subjects with migraine with aura. Exclusion criteria: subjects with a diagnosis of secondary headache or tension-type headache, patients older than 14 years. The non-clinical sample, 100 subjects without migraine, 49 females and 51 males, aged between 8 and 14 years, was recruited from primary schools in Rome. We analyzed Perfectionist Self-Presentation in children and adolescents using the Perfectionist Self-Presentation Scale – Junior Form (PSPS-Jr).

Expected Results We expect that the results will show a significant association between migraine and perfectionism in children, and that this personality trait will be highly correlated with the onset of other psychopathologies.

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Therapeutic aspects of headaches

Triptan nonresponders: do they exist and who are they?

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Background Triptans represent the best treatment option for most migraine attacks, although this is not as well studied as it might be in controlled trials. Their efficacy and tolerability vary, both between agents, and from patient to patient, with about 30%–40% of patients not responding adequately to therapy. As yet unexplained, the failure of one triptan does not predict failure with another, and therefore triptan nonresponders cannot be defined as individuals who have failed a single triptan. Five clinical studies provide evidence that switching from a triptan that is ineffective to a second one can result in effective treatment in a proportion of patients. Systematic studies investigating whether there are patients who do not respond to all triptans in all formulations are lacking.

It is therefore important to identify triptan nonresponders, and evaluate the literature supporting their existence, and verify the issues to be resolved to design trials to investigate this.

Conclusions So far, no scientific data about the presence of a triptan non-responder population are available. We propose a pragmatic study design to assess the existence of this subpopulation, recognizing the complexity of the question and the likelihood that more than one issue is at play in nonresponders.

High doses of corticosteroids and verapamil in episodic cluster headache

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Introduction Corticosteroids rapidly suppress cluster headache (CH) attacks during the time required for verapamil (V) to have effect. However, it is common experience that the current use of both drugs is unsatisfactory. We report our preliminary results of an open clinical study on a series of patients (P) affected by episodic cluster headache (ECH) treated with high doses of methylprednisolone (MP) iv and verapamil (V) per os.

Methods A consecutive series of 22 P (6 females, 16 males, 40.5±14.1 years), affected by ECH (ICHD-II 2004) was followed during 33 active cluster periods (CP). Most P were recruited within 2 weeks from the beginning and more than a month before the expected spontaneous end of CP.

P received MP 250-500 mg/day iv for 5 days, then 120 mg im for 3 days, 80 mg im for 3 days and prednisone 25 mg per os for 2 days tapered in the following 8 days. Concomitantly, oral V was started up to 320-640 mg/day.

Results The 33 CP considered were interrupted within the third day from the start of MP/V administration. In 22/33 (67%) CP, no recurrence was observed during a 6 months follow-up. In 8/33 (24%) CP, recurrence was observed within the first month; but an increment of V from 400 mg/day up to 640 mg/day blocked the attacks within a week, with no further recurrence during a 6 months follow-up. In 3/33 (9%) CP, a reduction of >50% in frequency and intensity and of >75% in the length of active phase was observed.

In all our P, V was gradually tapered in not less than a month, and at least 30 days after the last attack.

Conclusions To the best of our knowledge, this is the first report about the efficacy of combined high doses of MP iv and V per os in ECH. A reappraisal of the doses and timing of these drugs with appropriate clinical trials is warranted.

Do national guidelines impact on the treatment of migraine without aura attack? Patients' responses

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Introduction Guidelines (GL) for migraine treatment were developed in 1993 by SISC, then revised in 2002 and in 2012.

Objectives To evaluate the impact of 2002 SISC GL on the current pharmacological treatment of migraine without aura (MO) attack. In previous studies, we had assessed drug use [1] before ('89-'92, n=200) and [2], after ('95-'98, n=206) the introduction of 1993 GL.

Methods We studied 1,000 consecutive MO patients (aged 38.9±13, 814 females, 186 males) who came for the first time to our Centre between 2009 and 2011. Attack drugs taken in this period were compared with those taken in the periods '89-'92 and '95-'98.

Results The most commonly used drugs are NSAIDs 78% (vs. 80% in '89-'92, 87% in '95-'98), triptans 29.8% (vs. sumatriptan available in '95-'98, 17%), combinations 25.8% (vs. 79.5% in '89-'92, 51% in '95-'98), acetaminophen 10.5% (vs. 3% in '89-'92, 9.2% in '95-'98). The most effective drugs are NSAIDs 63.5%, triptans 51.1%, combination drugs 50.8%. However, NSAIDs lose effect over time in 58.5% of patients, combination drugs in 37.2%, triptans in 10%. Undesired effects were reported by 20.2% of patients with combination drugs, 20% with ergotamine-derivatives, 16.4% with triptans, 9.9% with NSAIDs. 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), intramuscular by 1.4% (vs. 3% in '95-'98), subcutaneous by 1% (vs. 2% in '95-'98), nasal by <1% (vs. 1% in '95-'98).

Conclusions The use of triptans, although still low (30% of patients) has almost doubled, possibly also due to the introduction of new molecules; whereas that of NSAIDs is unchanged. There is a drastic reduction of combination drugs and of parenteral ways of administration.

In conclusion, SISC GL application needs to be implemented, since the current use of attack drugs still does not meet them in several aspects.

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Issues and solutions in the management of chronic headaches

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In the management of chronic headaches many problems are encountered and the solutions are only partial. To implement prevention it is recommended that patients with severe and frequent headaches receive, in addition to the diagnosis: effective treatment of the attack, early initiation of prophylactic therapy, identification and treatment of comorbidities and modifiable risk factors for progression. For acute treatment non-specific analgesic- anti-inflammatory drugs and triptans are available. NSAIDs have a ceiling of action therefore increasing the dose over the recommended dose does not increase the analgesic action but only the side effects. These medications are a good choice for perimenstrual attacks as the system of PGs seems specifically involved in the pathogenesis of menstrual migraine. It has also been suggested that COX inhibitors are protective against the development of medication-overuse headache in patients with low (<10d/mo) frequency of headache. Even the absorption of oral triptans is reduced during the migraine attack and so the result is not predictable. Several patients wake up in the last hours of the night with severe migraine attacks, with nausea and vomiting, probably already in the allodynic phase where oral triptans are ineffective. Only the injectable sumatriptan is effective in this condition.

Early initiation of prophylactic therapy is regarded as the decisive intervention to prevent chronification. Unfortunately, prophylactic drugs have limited efficacy. Approximately 50% of patients can expect a reduction of 50% of attacks. Moreover, prophylactic treatments do not significantly change the severity and length of the attacks, which is just what the patient needs. In addition, the choice among the drugs recommended is empirical, in that there are no factors predictive of response.

Sodium valproate in medication-overuse headache: a randomized controlled trial

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Objective To assess the efficacy, safety and tolerability of sodium valproate (800 mg/die) compared with placebo in patients with medication-overuse headache.

Methods This is a multicentre, randomized, double-blind, placebo-controlled study treating medication-overuse headache subjects with sodium valproate (800 mg/day) or placebo for a 3-month treatment after a 6-day outpatient detoxification regimen, with a 3-month follow-up. Primary outcome was defined by the proportion of patients having a decrease ≥50% in the number of days with headache per month (responders) from the baseline to the last 4 weeks of the 3-month treatment. Results were adjusted for age, sex, disease

duration, comorbidity and surgery. The last-observation-carried-forward method was used to adjust for missing values.

Results Nine sites enrolled 130 subjects and, after a 6-day detoxification phase, randomized 88 eligible subjects. The 3-month responder rate was higher in the sodium valproate (45.0%) than the placebo arm (23.8%) with an absolute difference of about 20% ($p=0.0431$). Sodium valproate had safety and tolerability profile comparable to placebo.

Conclusions This study supports the efficacy and safety of sodium valproate in the treatment of medication-overuse headache after detoxification.

JOINT SESSIONS

SISC – SINC (Italian Society of Clinical Neurophysiology): Up-date on the pathophysiology of migraine: the contribution of neurophysiology

Effective connectivity and cortical information flow under visual stimulation in migraine with aura

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Objective The study aims to evaluate effective connectivity patterns in EEG rhythms under repetitive visual stimulation in migraine with aura patients, in terms of non linear Granger causality and Transfer Entropy.

Materials and methods Fifteen migraine with aura (MWA) and 15 migraine without aura (MWOA) patients were evaluated interictally. All subjects were submitted to high density (65 channels) EEG during visual stimulation by black and white checkerboard gratings with two spatial frequencies [(0.5 and 2.0 cpd) at 5 and 10Hz (10 and 20 reversal/s)]. The same visual stimulation was employed to evaluate BOLD signal changes in 6 MWA and 6 MWOA.

Results MWA patients showed increased non linear Granger causality values in beta band under all types of visual stimulation, and increased information flow toward frontal regions, with respect to MWOA and controls. FMRI showed larger cortical activation in occipital and parietal zones in MWA patients in respect to MWOA.

Discussion and conclusions Our results outline important pathophysiological differences between migraine phenotypes. An increased capacity in cortical connections and transfer information may subtend the perception of aura symptoms, probably favoring the progression of cortical spreading depression.

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The role played by the cortical lateral inhibition in the habituation deficit in migraine

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Lack of habituation is the most reproducible interictal electrocortical abnor-

malty of the migraine. It could be due to deficient intracortical inhibition and/or to low cortical pre-activation by the thalamo-cortical drive. However, reduced inhibition and low cortical preactivation may not be mutually exclusive, since the latter can promote the former through a reduction of lateral inhibition. We have recently investigated lateral inhibition within the visual and somatosensory cortices in a group of migraine without aura (MO) patients compared to healthy volunteers (HVs).

We have found results favouring a migraine cycle-dependent imbalance between excitation and inhibition in the visual and somatosensory cortices that results in a heightened cortical response to repeated stimuli, i.e. a lack of habituation. We hypothesized that an interictal hypoactivity of monoaminergic pathways may cause a functional disconnection of the thalamus in migraine leading to an abnormal intracortical short-range lateral inhibition, which could contribute to the habituation deficit observed during stimulus repetition with evoked potentials.

Cortical excitability and homeostatic plasticity in pathophysiology of migraine: new evidence by study of migraine cycle

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Despite intensive research efforts, especially in the last years, the pathophysiology of migraine remains still unclear. Quite recently we showed that mechanism of homeostatic plasticity, that come into play to avoid over excitation and neural damage can be activated in migraine when facilitatory stimulation paradigms (like high frequency repetitive transcranial stimulation: HF-rTMS) are employed. Indeed, response to HF-rTMS in migraine shifted from clear greater potentiation, at low stimulation intensity, to paradoxical inhibitory responses to increasing stimulation intensity [1]. This could occur because, due to increased cortical responsiveness, the threshold for inhibitory homeostatic responses is lower in migraine and these can be more easily activated with respect to healthy controls. Indeed, in a recent study in normal subjects we found homeostatic inhibitory responses, similar to that observed in migraineurs, when excitability of motor cortical area was increased by anodal facilitatory currents. Specularly, we were able to induce in migraineurs facilitatory response pattern to rTMS, similar to that found in normal, pre-treating patients with inhibitory cathodal currents. The increased cortical responsiveness and the activation of homeostatic inhibitory response can provide the key for the understanding of many neurophysiological observations in migraine as concerns paradoxical facilitation to 1 Hz stimulation (hyperresponsivity) and paradoxical inhibition to HF stimulation (activation of inhibitory homeostatic responses). Further experiments also showed that cortical excitability and threshold for homeostatic plasticity change across the migraine cycle and this may have relevance for mechanisms underlying attack onset and recurrence.

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The diagnostic value of visual and auditory evoked potentials in migraine: a retrospective study

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Background The diagnosis of migraine is made by history and based on ICDH criteria. There are at present no reliable diagnostic tests. Many studies have found that episodic migraine patients (EM) are characterized between attacks by a habituation deficit of visual evoked potentials (VEP) and/or increased intensity dependence of auditory evoked potentials (IDAP).

Objective To determine the usefulness of VEP and IDAP tests for the diagnosis of episodic migraine.

Methods We analyzed PR-VEP (5 sequential blocks of 50 responses or 6 blocks of 100 responses) and/or IDAP recordings from 360 healthy volunteers (HV) and 624 EM (in EM interictally). Some subjects were tested both for VEP and IDAP. Thresholds were calculated by Receiver Operating Curve (ROC) analysis based on a 15% prevalence value for migraine.

Results Mean percentage habituation of VEP-5x50 and VEP-100x6 was higher in HV than in EM ($p \leq 0.0001$), and mean IDAP amplitude stimulus function slopes were steeper in EM than HV and 1.2 ± 1.1 in EM ($p \leq 0.0001$). For VEP-5x50, VEP-100x6 and IDAP – in this order – we had a global efficacy of 65.3%, 69.0%, 54.3%. In subjects who underwent both VEP and IDAP recordings, abnormality of at least one of them had a sensitivity of 83.4%, a specificity of 66.7%, and an efficacy of 81.1%.

Conclusions Taken alone, none of VEP or IDAP has sufficient diagnostic efficacy to distinguish EM from HV. However, when both tests are combined in the same patient, abnormality of at least one of them is highly predictive of migraine, suggesting that VEP and IDAP may be useful for the diagnosis of migraine.

Pain direction subtends different pathophysiological mechanisms in children with migraine

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Background In adult migraineurs, pain direction (exploding or imploding) has been associated with a different response in botulinum toxin treatment. Thus far, there has been no objective evidence in favour of the hypothesis that pain direction depends on different pathophysiological mechanisms.

Objective To investigate whether migraine adolescents with pain directed inside (imploding pain-IP) and outside (exploding pain-EP) the head have different mechanisms underlying their migrainous syndrome.

Methods Twenty migraine children, 9 with EP (11.5 ± 1.5 years) and 11 with IP (11.3 ± 1.7 years) were recruited, investigating the psychophysiological mechanisms of spatial attention. The amplitude of the N140 SEP component was measured in a neutral condition (NC), in which patients were asked to disregard the electrical stimulation, and in a spatial attention condition (SAC), in which patients had to count silently brief mechanical targets, made manually by a gauze ball on the tip of the first and the second finger of the hand ipsilateral to electrical stimulation. The N140 amplitude variations between NC and SAC were compared between both patients' groups.

Results In this study the N140 amplitude increase during SAC, as compared to the baseline, was higher in IP than in EP patients. This suggests that, as compared with the EP migraineurs, the IP patients had to use a higher amount of attentional resources to accomplish the task.

Conclusions The present study is the first to have shown neurophysiological differences, concerning spatial attention, between migraine children with either imploding or exploding pain. These results suggest that in pediatric migraine pain direction is associated with different pathophysiological mechanisms.

Brain activity associated with temporal summation of pain in episodic and chronic migraine

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Introduction Temporal summation (TS) of pain represents a form of short term neuronal plasticity which, through a temporary change in sensory neurons excitability, shifts the sensory information from tactile to nociceptive. This phenomenon is relevant in pain pathophysiology, including central sensitization and chronic pain, in which activity-dependent changes in the excitability of central neurons give rise to an abnormal TS of pain. TS of pain develops in parallel with TS of electrically induced nociceptive withdrawal reflex (NWR) of the lower limb, resulting in an objective representation of TS of pain. Facilitated TS threshold of the NWR has been detected in both episodic and chronic form of migraine [1]. We used functional magnetic resonance imaging (fMRI) to determine which brain sites play a key role in TS of NWR in episodic and chronic migraine, comparing different sets of stimulation.

Materials and methods Ten episodic migraine (1.1 IHS), five chronic migraine (1.5.1 IHS) and ten pain-free healthy subjects underwent fMRI scanning during sural nerve stimulation with one (painful), three (non-painful) or five (TS of pain) stimuli randomly delivered.

Results fMRI statistical maps identified prefrontal cortex, anterior insula and amygdala after single nociceptive stimulus and thalamus, somato-sensory, posterior insula and cingulate cortex after repetitive stimulation consistent with TS of NWR. When compared to controls, episodic migraine showed a greater activity in anterior cingulate cortex whereas chronic migraine showed a diffuse reduced pain-related activation in somatosensory and cingulate cortex.

Discussion and conclusions These results emphasized the role of the cingulate cortex in temporal processing of pain and of the anterior cingulate cortex in migraine pathophysiology. On the contrary, a dysmodulation of pain-related activity has been demonstrated in chronic migraine.

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Neuroscience and Pain Study Group

Diagnosis of neuropathic pain.

The self-sufficiency of the clinical approach

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Pain is a subjective experience that may be difficult to describe and cannot be objectively measured. Distinguishing neuropathic pain (NP) from nociceptive pain is of paramount importance because mechanisms and treatment recommendations are different. Meticulous collection of information must be the guide to the diagnostic pathway, which, associated with the findings of clinical examination will lead to the most probable diagnosis. A neurological examination must be carried out whenever a lesion of the nervous system is suspected. Considering the NP definition: “pain that appears as a direct conse-

quence of a lesion or disease that involves the somatosensory system” [1], it is pleonastic to state that the bedside sensory examination is the most important part of the clinical evaluation. The technological developments introduced into neurological diagnostics over the last decades could suggest that the neurological semeiotics is not useful anymore. However, laboratory tests for diagnosing NP are not specifically exploring NP but the nociceptive system’s integrity and function. Diseases and lesions affecting the somatosensory pathways can be painful or painless. The challenge is therefore to differentiate NP from other types of pain distinguishing if the lesion or the disease is causing the pain. Bedside examination is also the tool that can localize the damage within the somatosensory system; it may also infer the presence of other types of pathological condition, within the area of sensory abnormalities, in possible relation with the pain of our patient. Therefore, the results of laboratory tests become useful only to confirm the diagnosis of NP in the context of a clinical examination guided by a tentative diagnosis based on the pain history and distribution.

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Neuropathic pain diagnosis: we do need clinical neurophysiology

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Neuropathic pain is defined as “a pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” [1]. It is evident that, in front of a patient referring the pain of possible neuropathic nature, all our efforts should be addressed to assess the somatosensory system in order to demonstrate its “lesion or disease”. In some cases, clinical examination may be sufficient, showing clear neurological signs that demonstrate a peripheral or central somatosensory lesion. However, in other patients the simple bedside examination may not give us enough elements. Questionnaires have been prepared, focused on particular symptoms that are often present in neuropathic pain situations, such as the pain characteristics (burning, tingling) or the presence of the so-called positive symptoms (hyperalgesia and allodynia). Although these tools proved to be useful, a direct demonstration of a somatosensory system lesion can be obtained only by instrumental examination, including both neuroimaging and neurophysiological techniques. Standard neurophysiological methods, such as somatosensory evoked potentials and nerve conduction study, can be used to identify a dysfunction of the large myelinated (A β) fiber system, but they do not provide any information concerning the small myelinated (A β) and unmyelinated (C) fibers. The laser evoked potential (LEPs) allow us to record brain responses generated by the small fiber input. There has been evidence that LEP amplitude is reduced in presence of both peripheral and central neuropathic pain, while LEP amplitude is always normal (or even increased) in case of pain *sine materia*. Therefore, LEP recording represents the more reliable neurophysiological technique for neuropathic pain diagnosis.

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Lecture

The new classification of the International Headache Society – ICHD-3 beta version

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Published in June 2013, 9 years after the previous International Classification of Headache Disorders (ICHD-2), the new classification, ICHD-3, was started almost 3 years ago with the purpose of improving and better defining the criteria for the secondary headaches. Along the way it became evident to the Classification Committee that other aspects of ICHD-2 required adjustment based on the abundant literature published since ICHD-2 appearance. Therefore ICHD-3 contains several novelties also in the primary groups and in the neuralgia group.

ICHD-3 is based as much as possible on evidence, and, where this is lacking, on the best available expertise provided by the members of the working group. ICHD-3 has been published as a beta version, because a 2-3 year field-testing is expected and encouraged in order to verify the validity and usability of proposed forms and their criteria.

ICHD-3 beta has been developed in close coordination with the forthcoming International Classification of Diseases edition 11 (ICD-11) of the World Health Organization (WHO), where a good representation of headache was achieved. Also WHO Classification will be field-tested in the next few years. As a result, we will soon be able to publish not only ICHD-3 codes but also ICD-11 codes for all headache entities. That will make ICHD-3 much more useful because it is the WHO classification that in most countries is used for routine diagnostic coding, and, in many cases, determines reimbursement for patient management. It is therefore of the utmost importance that the two classifications are congruent, although the ICHD-3 will of course be more detailed than ICD 11.

There are many important new aspects and many improvements in ICHD-3 beta. For example, the diagnostic criteria for chronic migraine are now part of the main body of the classification, and double coding is recommended for chronic migraine with medication overuse. There are completely revised criteria for the secondary headaches so that diagnostic coding is now more definite and rapid. A few new entities have been added either in the main body of the classification or in the appendix, which also has been considerably expanded. The appendix now contains alternative criteria for important entities such as migraine with aura and chronic migraine. Vestibular migraine has been defined in the appendix in collaboration with the Barany Society in order to promote and facilitate research in this entity.

National headache societies are encouraged to publicize ICHD-3 beta publication in their national-language journals. Furthermore, ICHD-3 beta needs to be translated into the national languages to be adopted as much as possible in the clinical practice, by experts and non-experts.

From Birth to Adulthood

Attachment and headache in children and adolescents

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Insecure and disorganised attachments increase the risk for behavioural problems both in normative and in risk samples. The main aim of our study was to quantify the prevalence of insecure or disorganized attachment patterns in headache paediatric patients; the second aim was to assess correlations of attachment patterns with parental stress and behavioural problems.

Method Seventy-three headache patients (age range 8-11 years, 28 ma, 44 f; m.a. 9.71) were involved in the study. ICHD-II criteria diagnoses: 20 MO, 5 MA, 3 infrequent ETTH, 25 frequent ETTH, 11 CTTH, 8 chronic migraine,

1 not classified. Children's attachment was assessed using the Security Scale and the Preoccupied and Avoidant Coping Strategies. CBCL 6/18 and Parent Stress Index (PSI) were used to assess children's behavioural problems and parents' self-reported stress, respectively. Univariate ANOVA and correlation study were conducted.

Results/Discussion No significant difference was present comparing children with migraine and non-migraine headache, with the exception of Social Problems sub-scale (higher scores in migraineurs: $F=5.603$, $p=0.028$). Crossing data by all different tests by frequency of headache crises, we found an increased level of psychopathology in children with more frequent headaches. The correlation study (migraine vs. non-migraine headache) showed a moderate but in-

significant ($p=0.057$) correlation between Preoccupied strategies and Anxiety-Depression (CBCL) only in tension-type headache ($r=0.307$). In children with migraine there was a moderate and significant correlations between Somatic Complaints and Avoidant strategies ($r=0.401$; $p=.010$) and Social Problems and Preoccupied strategies ($r=0.409$; $p=.018$). The highest correlation was found between PSI and CBCL scales (suggesting that those parents who perceived a higher level of psychopathology in their children were also more stressed by their health conditions). Exploring the link between psychopathology, attachment and parental stress in different headache sub-types may offer new trajectories for the study and comprehension of migraine and non-migraine headache in children and adolescents.

Clinical aspects of headache

Chronic cerebro-spinal venous insufficiency (CCSVI) and migraine: does a link exist?

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Introduction The mechanisms of migraine chronicization (CM), with or without abuse, are still to be elucidated. MRI findings of iron accumulation in the brain, especially in periaqueductal gray and red nucleus, have been correlated with CM. Nevertheless elevated iron levels in brain tissue have been demonstrated in other neurological disorders, including multiple sclerosis (MS). Recently, Zamboni et al. (2009) suggested that an abnormal drainage of venous blood due to stenosis or malformation of the internal jugular and/or azygos veins (CCSVI) might play a role in the inflammatory processes and increased iron deposition observed in MS. Based on the common finding in MS and CM of these phenomena, one could hypothesize a possible pathogenic role of CCSVI also in CM.

Methods and results We investigated the occurrence of CCSVI in patients with CM and episodic migraineurs (EM) by an echo-color doppler combined transcranial and extracranial that studies the internal jugular veins and vertebral veins in the neck and cerebral veins deep in intracranial level, according to the Zamboni method.

We recruited 32 patients with CM (78% with drug abuse) and 27 patients with EM (37% with aura). The presence of CCSVI was demonstrated in 31% of cases of CM and in 26% of EM. In CM patients, CCSVI was correlated with the duration of headache chronicization.

Conclusions A recent study showed that CCSVI was present in 2.8% of 376 healthy subjects (CoSMo, 2012). In the light of this finding, the high rate of CCSVI positivity observed in patients with episodic and chronic migraine suggests a possible role of this factor in causing these diseases.

Migraine and hemorrhagic stroke: a meta-analysis

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Background and purpose Several studies have assessed the possible increased risk of hemorrhagic stroke in migraineurs, drawing differing conclusions. No meta-analysis on the topic has been published to date.

Methods Multiple electronic databases were systematically searched up to March 2013 for studies dealing with migraine and hemorrhagic stroke.

Results Out of 11,264 records, we identified eight studies (four case-control and four cohort studies) involving a total of 321,101 subjects, which were included in the meta-analysis. The overall pooled adjusted effect estimate of hemorrhagic stroke in subjects with any migraine versus control subjects was 1.48 (95% CI, 1.16-1.88; $p=0.002$) with moderate statistical heterogeneity ($I^2=54.7\%$; P value for Q test=0.031). The risk of hemorrhagic stroke in subjects with migraine with aura with respect to control subjects (1.62; 95% CI,

0.87-3.03; $p=0.129$) was not significantly greater, while it was greater in female migraineurs (1.55; 95% CI, 1.16-2.07; $p=0.003$) with respect to control subjects.

Conclusions The meta-analysis of the available studies suggests an association between any migraine and hemorrhagic stroke. Further studies are needed to address hemorrhagic stroke risk according to migraine type, age, gender, and hemorrhagic stroke type.

Headache and cerebral ischemia due to intracranial atherosclerotic disease

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Introduction Different studies have reported Intracranial Atherosclerotic Disease (ICAD) as one of the most important causes of stroke worldwide. Headache can occur as a first symptom during cerebral ischemia, but its prevalence at stroke onset in patients with ICAD is unknown. Our purpose was to evaluate the prevalence of onset-headache in symptomatic intracranial atherosclerosis.

Materials and methods We recruited 292 consecutive patients with acute cerebral ischemia. Epidemiological and clinical data was collected, including cardiovascular risk factors, history of migraine and presence of headache onset according to International Headache Society criteria. All patients underwent a complete extracranial and intracranial ultrasound assessment. Inclusion criteria were: 1) symptomatic 50-99% intracranial stenosis according to Baumgartner criteria; 2) confirmation by CTA/MRA/DSA; 3) persistent symptomatic 50-99% intracranial stenosis at 3 months.

Results In our cohort we found a prevalence of 20.2% ICAD, higher than in previous studies (2.24-8.1%). Among cerebro-vascular risk factors, ischemic heart disease ($p<0.05$) and the presence of more than one risk factor ($p<0.01$) were significantly related to ICAD. Among patients presenting ICAD-related ischemic event, 26.8% reported headache at onset vs. only 6.5% of those affected by cerebral ischemia not related to ICAD ($p<0.00002$). The only cerebro-vascular risk factor related to headache onset in ischemic cerebral event appeared to be a history of migraine ($p<0.000001$).

Conclusions This study has demonstrated a higher prevalence of ICAD compared to previous studies in acute ischemic stroke. Given the high recurrence stroke rate among stroke patients with ICAD and the finding of a much more prevalent onset of headache in this population, headache at stroke onset should prompt a careful search for ICAD.

Evaluation of migraine comorbidities through clinical and pharmaceutical data

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Introduction Migraine population studies report many comorbidities, mostly identified through questionnaires and based on self-reported diagnosis. Pharmacoepidemiological studies have also been performed. Our study was aimed to evaluate migraine comorbidity through the comparison of drug prescription rates of a pharmaceutical database (PD) and those of a clinical cohort (CC).

Methods Empoli Health Authority (HA11) pharmacy claims (year 2011) of the 155,829 residents aged 15-65 years, were analyzed. Triptan prescription was considered a migraine marker. The CC consisted of 681 patients aged 15-65 years, who accessed to the HA11 Headache Centre in 2011 and had a diagnosis of migraine. We evaluated if drugs not for migrainous chronic conditions (antidepressants, antipsychotics, anticonvulsants, antiasthma, antihistamines, antidiabetics, antihypertensives, antidyslipidemics, thyroid hormones, antihypertensives) were prescribed more often to migraine patients than to the general population and, we then evaluated the prescription rates in the CC.

Results According to triptan prescriptions in the PD, 1,108 subjects were considered migraine patients (MP). The prescription rates resulted different for antidepressants (22.8% MP vs. 6.8%), anticonvulsants (8.2% MP vs. 2.5%), antihistamines (9.7% MP vs. 5.6%), antiasthma (12.9% MP vs. 7.9%), antihypertensives (22.8% MP vs. 11.9%). Interestingly, beta-blockers and topiramate, both used as migraine preventive treatment, are almost totally responsible for the higher prescription rate of antihypertensives and anticonvulsants, respectively, in MP. Prescription rates for chronic conditions in the CC were similar to or significantly lower than those of the general population in the PD, with the exception of thyroid hormones (6.4% CC vs. 3.7%).

Conclusions We found no comorbidities in our migraine population. Some of the differences found with the analysis of prescriptions may be due to preventive drugs used for migraine or to a misleading diagnosis (migraine treated as sinus headache).

Primary headache and shift work: preliminary results in the study of the association in a group of workers exposed to chemical risk

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Introduction Headache is the most common pain syndrome. Primary headache involves people of working age. These aspects entail high economic costs, direct (health care spending) and indirect, related to the work world, calculated on the basis of working days lost due to illness and loss of production efficiency due to the headache accesses. About the loss of working days, the absence caused by headache in Europe involved 7-15% of the working population. The loss of productivity amounts to 35%.

Objectives This study examined the association between headache and the different types of work (shift or daily work) in a group of workers of a chemical industry.

Materials and methods Ninety-five workers (91 males and 4 females in day shift), over 18 years of age were recruited. They were divided into two groups according to whether they worked shifts (three shifts with anterograde rotation) or they worked daily (from 8.00 a.m. to 17.00 p.m.).

Results The prevalence of primary headache was higher in workers engaged in night shift than others: in this group we observed the presence of primary headache in 21 workers out of 50 (42%). In the day shift group the disease was found in 12 (26.7%): migraine without aura (51.5% of all headaches in workers), followed by episodic tension headache (42.5%) and migraine with aura (6%). Considering only males, the results showed a statistically significant

difference in the prevalence of headache in the 2 groups ($p < 0.043$ - OR 2.6). **Conclusions** The results strengthen the hypothesis that between the two events might exist a causal link.

Headache characteristics and predisposing factors in an extensive population. A cross-sectional study on 9,501 subjects

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Objectives Our aim was to examine the prevalence, characteristics and predisposing factors of different types of head pain in an extensive population.

Methods Detailed data were collected by means of a structural questionnaire from 9,501 (2,955 males, 6,546 females) residents in Italy and other countries who applied to the social network www.nomalditesta.it. Prevalence and characteristics of different pain pathologies and comorbidities and predisposing factors were statistically analysed by Student's *t*, ANOVA and Bonferroni and Chi Square test, as appropriate.

Results The following diagnoses were made: migraine (M, n=865, 9.1%), tension-type headache (TTH, n=330, 3.5%), neck and shoulder pain (NP, n=394, 4.1%), M+TTH (n=513, 5.4%), M+NP (n=3,878, 40.8%), TTH+NP (n=1,630, 17.2%), M+TTH+NP (n=1,891, 19.9%). M was chronic (CM) in 770 (11%) of the 6,784 cases where M was present, TTH was chronic in 375 (9.1%) of the 4,139 cases. Mean pain levels (VAS) were significantly higher ($p < 0.001$) for M (62.5) as compared to TTH (32.7) and NP (42.4). Days of pain were higher for NP and lower for M. However, drug consumption was highest for M alone or combined with NP. The prevalence of M was significantly higher in females ($p < 0.01$). Facial pain in cheek and preauricular region was adjunctively present in 1,323 subjects (13.9%) and its prevalence was significantly higher in females ($p < 0.01$) and in groups with superimposed pathologies. The prevalence of hypertension and psychological problems was significantly ($p < 0.001$) higher in chronic M and TTH.

Conclusions In a population of head pain patients the superposition of different pain conditions, including neck and facial pain, is a frequent finding and may have a significant impact on pain characteristics and level. Hypertension and psychological problems are predisposing factors for headache chronicisation.

Diagnostic and therapeutic errors in cluster headache: a population-based study

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Background Cluster headache (CH) is an important type of unilateral headache, but relatively rare compared with other primary headaches. The severity of the attacks predicts considerable occupational and social disabilities.

Objective The aim of this study was to identify the diagnostic and therapeutic errors in CH in order to improve the clinical and instrumental workup of these patients.

Materials and methods Our study comprised a preliminary group of 134 CH patients (106 Italians, 28 from abroad: Moldova, Bulgaria, Ukraine). All the patients were examined personally or through telephone interview by medical staff on the basis of an ad hoc questionnaire.

Results Seventy-two percent were males and 28% females (M:F ratio 2.62:1). The mean age was 42.1 ± 11.3 years. The diagnostic delay was 4.47 ± 5.8 years (range 0-30 years). The most misdiagnoses at first consultation have been observed in 77% of the cases (i.e., trigeminal neuralgia 21%, migraine without aura 19%, sinusitis 14%, other 23%).

The physician consulted prior to CH diagnosis were the following: neurologists 73%, PCP 49%, ENT 16%, dentist 5% or other physicians 5%. CH patients were treated with ineffective acute (before diagnosis 52%, after diagnosis 24%) and prophylactic treatments (before diagnosis 40%, after diagnosis 15%); alternative (27%) and invasive therapy (6%).

Conclusions Our results emphasize the necessity for improvement in education in order to ameliorate the recognition of the clinical picture and the knowledge of medical treatment of *de novo* patients with CH. The target of continuous medical education should be general neurologist, PCP, ENT and dentists. A study on a larger population of CH may further improve strategies to avoid errors.

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Migraine management in a population with chronic pain: a description of 33 cases of hypermobility type Ehlers-Danlos Syndrome

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Introduction The Ehlers-Danlos Syndromes (EDS) are a heterogeneous group of heritable connective tissue disorders. Hypermobility type is the most common variety (HT-EDS or Joint Hypermobility Syndrome). Pain is the most disabling manifestation of this disease, represented mainly by articular pain and headache. In this population of chronic pain patients we investigated if migraine features were different from the normal population.

Materials and methods We selected 33 HT-EDS patients, diagnosed according to current criteria. Controls (MO group) matched for age and gender were enrolled among migraine patients attending our Headache Clinic.

Diagnosis of headache was based on IHS criteria. We screened for a series of headache characteristics, such as age of headache onset, localization and type of pain, mean attack duration and intensity, frequency of migraine attacks/days per month, use of abortive or prophylactic medication, number of pills per month and response to abortive therapy, and examined possible differences between the two groups.

Results Significant results were the following:

- headache onset was more premature in EDS respect to MO (12.1 yo. vs. 17 yo; $p=0.005$)
- EDS patients had more migraine days/month (15.1 vs. 9.3; $p=0.01$)
- accompanying symptoms were more frequent in EDS (especially phonophobia: $p=0.02$)
- efficacy of abortive medication was almost identical between the two groups, but drug consumption was significantly higher in MO group ($p=0.001$).

Discussion and conclusions ED patients have a more severe headache syndrome in respect to normal migraineurs: they are more phonophobic, have a higher frequency of attacks, and earlier onset of the disease. Nonetheless, ED patients tend to take fewer medications/per month than the control group, and not because drugs are less efficacious.

Migraine and endocrine disorders: does a possible correlation exist?

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Background Migraine patients suffer from a variety of comorbid conditions. The International Classification of Headache Disorders (ICHD-II) included in the secondary headache group a form attributed to hypothyroidism (HT).

Materials and methods We assessed the prevalence of endocrine disorders in primary headache sufferers, by retrospectively evaluating 3,718 patients diagnosed with primary headaches, focussing on possible concurrent endocrine disorders, from 2005 to 2012.

Results The only significantly concomitant disorder found was HT (98 cases, 95 females and 3 males). The frequency of other endocrine disorders was unremarkable: 17 cases with hyperthyroidism, 13 cases with glucose homeostasis disorder, 12 with pituitary gland disorders (hyperprolactinemia), 4 with sex hormone disorders, 3 with calcium homeostasis disorder. All the patients with HT required hormonal replacement therapy. Ninety of these cases (2 males) were migraineurs and 8 suffered from tension-type headache (TTH). Therefore, the prevalence of HT was 3.0% in migraine and 1.6% in TTH. In population-based studies the prevalence of HT resulted to be <1%. Interestingly, in our clinic-based survey HT occurred after migraine onset in 87 patients (96.7%), whereas it preceded migraine in 2 migraineurs and in 3 TTH patients. For the latter subjects headache attributed to HT was ruled out, due to headache persistence after treatment with levothyroxine. For 52.0% of patients the headache showed a significant worsening after the onset of HT and hormonal replacement therapy.

Discussion In patients suffering from primary headaches, the only significantly concurrent endocrine disorder resulted to be HT. This disease was largely prevailing in migraineurs; the prevalence of HT in migraine was 3.0%, significantly higher than in the general population.

Conclusions HT should be considered as one of the various migraine comorbidities, even if possible pathophysiologic relationships remain unclear. In case of worsening of pre-existing migraine, thyroid function should be investigated to rule out a possible HT.

Weather changes and headaches: an Emergency Department retrospective study

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Introduction About half of migraineurs describe weather changes as triggers for headache onset or the worsening of ongoing headache symptoms. Aim of the present study was to assess the relative influence of some meteorological parameters on the headache attacks appraised at the Emergency Room of the Catholic University in Rome during the year 2010.

Material and methods We retrospectively evaluated the clinical data of all patients admitted at the Emergency Room of Policlinico Gemelli in Rome, during a 1-year period. The patients were diagnosed for a specific primary headache, according to the International Headache Society (IHS) criteria. Weather data were obtained from the Italian National Weather Service. Data obtained for atmospheric pressure, temperature, velocity of wind, and relative air humidity were correlated with clinical data.

Results During the 1-year period, 2,285 patients with a major diagnosis of headache were seen at the Emergency Room. The greater number of primary headaches was classifiable as migraine without aura. The migraine attacks were inversely correlated with the temperature and had a positive correlation with dampness. The attacks of migraine with aura and of tension-type headache did not correlate with all the meteorological parameters considered.

Discussion It could be speculated that any variations of meteorological pa-

rameters interfere with the neuronal excitability of the trigeminal-vascular system directly or with the structures to it correlated, facilitating the onset of the attack. In alternative, it is possible that quantitative variations of trigger factors can increase the response of migraineurs to the environmental stimuli.

Conclusions The onset and the severity of headache attacks are correlated with low temperature and elevated dampness. Our data confirm that a subgroup of migraineurs are highly 'sensitive' to the variations of some meteorological factors, that act as trigger in the attacks.

Central sensitivity syndromes and migraine: results of the application of an Italian version of the central sensitization inventory

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Introduction The term central sensitivity syndrome (CSS) has been proposed to describe these poorly understood disorders for which no specific organic cause can be found (fibromyalgia, low-back pain, irritable bowel syndrome, etc.) where central sensitization (CS) has been proposed as a common pathophysiological mechanism. Recently, Mayer et al. (2012) [1] developed a specific questionnaire for these syndromes (Central Sensitization Inventory) that showed good predictivity in evaluating CS-related symptoms. Symptoms of central sensitization have been showed to occur in migraine attacks and the mechanisms underlying these phenomena have been supposed to play a role in the pathophysiology of migraine chronification. Aim of the study was to explore the prevalence of symptoms related to CS in patients with migraine by applying an Italian version of the Central Sensitization Inventory.

Methods We studied 75 consecutive patients (66 F / 9 M; mean age: 37.5±11.4), affected by migraine (65 by migraine without aura and 10 by both with and without aura migraine), diagnosed according to IHS criteria; results were compared with a group of 30 age and sex matched healthy subjects. All subjects underwent the CSI. Responses were scored 0-4 for each of the 25 CSI items for a total scoring span 0-100. Comorbidity with other CS syndromes was also explored.

Results Patients showed scores and comorbid CSS significantly higher with respect to controls. Anxiety and IBI were the most frequent comorbid conditions. Significantly higher CSI scores were also found in patients with comorbid CSS, especially in those with anxiety.

Discussion and conclusions Application of CSI to migraine patients showed high prevalence of symptoms related to CS syndrome. This could further support the role of CS mechanisms in the pathophysiology of migraine, opening also interesting perspectives concerning relationship between migraine and other comorbid diseases.

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Evaluation of the typical duration of migraine aura: a clinically-based study

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Background In the ICHD-II, non-hemiplegic migraine aura (NHMA) duration is considered normal when it lasts between 5 and 60 minutes. A recent systematic review showed the prevalence of patients in whom the whole NHMA lasted for more than one hour varies between 11.6% and 31% [1].

Objective To evaluate the distribution of the duration of each individual symptom of NHMA and of the whole NHMA.

Methods We recruited 73 consecutive patients affected by NHMA at the Headache Centre of Pavia and of Trondheim (55 and 18, respectively). All the patients had to prospectively record the characteristics of three consecutive attacks in an *ad hoc* aura diary that included the time of onset and the end of each aura symptom and the headache.

Results Of the 73 patients recruited so far, 14 completed the diaries during three consecutive auras for a cumulative number of 42 auras recorded. Visual aura lasted for more than one hour in 13 out of 40 auras (32%), somatosensory aura in 5 out of 15 auras (33%), aphasic symptoms in 1 out of 4 (25%) and the whole aura duration in 15 out of 42 auras (35%). One patient out of 14 experienced one aura with visual symptoms lasting for 30 minutes in 2 episodes, 90 minutes in a third one.

Conclusions Our preliminary data seem to indicate that the duration of NHMA, whether single symptoms or the whole aura, may be longer than one hour in a significant proportion of migraineurs.

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Neuropsychological and psychodiagnostic aspects for models of integrated treatment in patient with chronic headaches

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Introduction Chronic daily headache, due to the continuous and debilitating pain, requires a multidisciplinary approach, because the suffering of these patients involves not only sensorial but also affective and cognitive emotional areas; therefore an integrated approach can be more effective in improving patients QOL.

Materials and methods The research involved 50 (35 F/15 M; mean age 38±/3 yrs) consecutive patients affected by chronic daily headache (including subjects with chronic migraine, chronic tension-type headache and probable psychogenic headache) that were recruited and diagnosed at the headache centre operating in our Department. Patients were assessed by clinical interview and Rorschach Psychodiagnostic Test.

Results Ninety-three percent of subjects (in particular patients with psychogenic headache) had a history of traumatic events, abuse, bereavement. The majority of patients presented an alexithymic operative style. Psychiatric comorbidity (anxiety and depression) was found in over 50% of patients with chronic tension-type headache or migraine. The Rorschach Psychodiagnostic Test showed a picture of affective dysregulation characterized by impulsivity, primitive anxiety, devitalization, depression and identity immaturity oriented towards dependence of an external source.

Discussion The emotions of the examined patients appear deprived of semantic value as a result of painful traumas at an early age, when there were no cognitive tools suitable for containing the disruptive impact of pain; when the defect of emotional regulation occurs, difficulties of connection between sensorial-emotional sphere (represented by a complex network including amygdala, hypothalamus, adrenal gland, ANS autonomic nervous system) and cognitive sphere (principally represented by prefrontal cortex), prevent the translation of those meanings and functions that the emotional-affective dimension exercises for the individual, producing unmanageable anxiety. This results in reduced capacity for mentalization, devitalization and depressive condition

Conclusions The working model of the patient suffering from headache which emerged from this research shows the need to apply integrated treatment approaches to allow the patient more suitable means of emotion regulation.

Headache and genetic thrombophilia. Preliminary results

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Introduction Thrombophilia is a condition genetically determined or acquired that predisposes to the development of venous thromboembolism and/or arterial at a young age (<50 yrs) with no apparent cause and with a tendency to relapse. Thrombophilia is a complex disorder and the genes that determine genetic susceptibility are considered to interact with external environmental factors for the occurrence of the disease [1].

Materials and methods Fifty patients referring to a clinic of diagnosis and treatment of headaches in a period of a year were enrolled. The sample included 8 males and 42 females, aged between 19 and 72 yrs, with a positive family history for cardiovascular events. Biological material analyzed: Genomic DNA extracted from peripheral blood.

Method DNA extraction, multiplex PCR amplification of the genes of prothrombin, factor V, MTHFR. Reverse hybridization of the amplified product (Reverse Dot Blot).

Mutations examined: 6, prothrombin gene G20210A, factor V gene LEIDEN, V H1299R, Y1702C, gene MTHFR C677T and A1298C.

Results All patients were positive for gene mutation: 18 double mutation in heterozygous, 22 homozygous, 3 double mutation (heterozygous + homozygous), 7 heterozygous, 1 in triple heterozygosity.

The type of headache was predominantly chronic daily headache and migraine with aura. The type of aura was sensitive and/or more types in succession. At MRI multiple gliosis: vegetative phenomena were pronounced, sleep disorders were frequent, and there was a resistance to prophylaxis and poor tolerability to triptans. We found a comorbidity for mood disorders, overuse medication, hypertension, dysthyroidism, and hypercholesterolemia. The headache was of early onset.

Discussion and conclusions The preliminary results suggest the prevalence of mutations in homozygosity or double heterozygosity. The study confirms the ongoing relationship between genetics and headache disorder.

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Headache as a clinical presentation of brain tumour in adults: results of an observational, retrospective study

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Introduction Headache is a common symptom in patients with brain tumour (BT) [1]. This observational and retrospective study was aimed to evaluate the prevalence and characteristics of headache reported as a first clinical manifestation by patients with BT consecutively admitted to our Clinic over a 2-year period (January 1, 2011-December 31, 2012).

Materials and methods Headache features were collected from BT patients' records. The diagnosis of headache was carried out according to the 2004

International Classification of Headache Disorders (ICHD-II). Records were related to BT lateralization, location, and histological features. Patient response to symptomatic drugs and headache improvement after intervention were also evaluated.

Results Seventy-two patients (36 males and 36 females) were included. Headache was referred as an onset symptom, alone or in association to other symptoms (e.g., dizziness, instability) or focal signs, by 24 out of 72 patients (33.33%). BT patients with headache were significantly younger (mean age was 52.8±12.7) than those without headache (63.9±11.1) with $p<0.0003$. Pain was more frequently bilateral (70.83% of cases) and of moderate intensity (79.16%). It was pressing/tightening in 66.7% of patients, pulsating in the remaining. Headache had a frequent presentation, i.e., at least 3 attacks/week, in 83.34% of cases. Associated symptoms were recorded in about half of the patients and, among these, nausea and vomiting were more frequent in patients with pulsating headache. In the headache group, BT location was mainly infratentorial (41.7%) followed by frontal (20.8%), occipital (16.6%), and multilobar (16.6%). A poor response to symptomatic drugs was a common finding (83.33% of cases). There was no difference in the hemispheric location between BT patients with or without headache. Furthermore, the distribution of BT histological features did not differ between the two groups, with glioblastoma as the most common type. An improvement of headache was recorded in 75% of patients after surgery, with or without radiotherapy or chemotherapy.

Discussion In our study the percentage of patients presenting with headaches is lower than reported in the literature (50-60%). Consistently with previous studies, head pain was prevalently moderate in intensity, had tension-type features and improved in about 2/3 of patients after interventions. In contrast, our patients reported frequent headaches as the first clinical evaluation, and did respond poorly to common analgesics.

Conclusions Like previous researches, our retrospective study emphasizes the need to exclude BT in patients with new late-onset headache, especially if associated with other neurological symptoms and signs.

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Pathogenetic aspects of headache

Dynamic changes in thalamic microstructure in migraine without aura patients: a diffusion tensor magnetic resonance imaging study

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Background and objectives With various methods of clinical neurophysiology, researchers have demonstrated that between migraine attacks lack of habituation during any kind of repetitive stimulation is a reproducible CNS dysfunction. This phenomenon undergoes periodic fluctuations in strong relationship with the development of the migraine cycle, since, for instance, during the attack habituation increases and normalizes. Therefore, guided by the abovementioned neurophysiological findings, we decided to focus our study on the possible migraine attack-related fluctuations over time in the diffusion tensor (DT) magnetic resonance imaging (MRI) parameters of bilateral thalami in patients affected by episodic migraine without aura. This MRI technique provides quantitative data on water molecular motion, as a marker of tissue structure.

Material and methods Twenty-four untreated migraine without aura (MO) patients underwent MRI scan (3-Tesla Siemens Gyroscan) during (n=10) and between attacks (n=14) and were compared to a group of 15 healthy volunteers (HV). We examined fractional anisotropy (FA) and mean diffusivity (MD).

Results Compared with HV, MO patients between attacks showed significantly higher FA and slightly lower MD values in the bilateral thalami ($p=0.012$; $p=0.018$, for the left and right thalamus respectively). During attacks, all MRI quantitative measurements in migraineurs were similar to those found in HV. When all patient groups (MO, MI) were combined, there was a positive correlation between the FA of the right thalamus and the number of days that had elapsed since the last migraine attack at the time of the scan ($r=0.626$, $p=0.003$).

Conclusions These higher thalamic FA values noted during the interictal period which normalized during an attack are probably related to functional plastic peri-ictal modifications in regional branching and crossing of fibres. Whether these changes could be considered as the anatomical counterpart of the cyclic functional fluctuations previously observed with the neurophysiology in migraine remains to be determined.

Cortical excitability changes in chronic migraine vs. episodic migraine: evidence by sound-induced flash illusions

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Introduction Sound-induced flash illusions represent a simple tool to evaluate the multimodal interaction of single sensorial modalities in a complex and unified percept. 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. Bolognini et al. (2011) showed that audio-visual illusions strictly depends on cortical excitability: healthy controls perceive less illusions by increasing visual cortex excitability through anodal tDCS [1]. We have already described reduced illusory perception in migraine patients, especially in the ictal period in agreement with hypothesis of cortical hyperexcitability. On such a basis, we expected chronic migraineurs to be persistently less prone to audio-visual illusions just like the episodic migraineurs in the ictal period.

Patients We included 12 patients suffering from chronic migraine with medication-overuse headache (11 F, mean age \pm SD 34.6 \pm 11.9), 32 patients with migraine with aura (MWA) and 32 patients with migraine without aura (MOA) (42 F, mean age \pm SD 32.3 \pm 16) compared to 20 unimpaired, sex- and age-matched related healthy controls (10 F, 38 \pm 18).

Methods 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. Subject had to report the number of flashes seen.

Results Illusion is present in controls and episodic migraine but not in chronic migraine; all migraine groups showed significantly less illusions with respect to controls ($p<.0001$); illusions are more reduced in chronic migraine patients overusing triptans ($p<.05$).

Discussion These results point to a condition of visual cortical hyperresponsivity in patients with chronic migraine in analogy to what has been observed in episodic patients especially during the ictal phase. This is in agreement with the view of chronic migraine as a "never ending attack". The greater effect observed in triptan overusers is in agreement with the neurophysiological finding of a reduced silent period duration (a measure of GABA_B activity) in such patients

Conclusions Sound-induced flash illusions are a sensitive tool used to evaluate changes of cortical excitability in migraine that appears to be increased during attacks and in chronic patients. Further studies on larger series are needed to confirm this result and better evaluate the role of specific drug abuse (FANS vs. Triptans).

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Central mechanisms of migraine improvement with ketogenic diet: a visual evoked potentials study

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Background Ketogenic diet (KD) is a dietetic regimen that mimics fasting in producing ketone bodies, which seems to have a potential role in treating migraine. The molecular mechanisms underpinning ketogenic diet effectiveness are only partially clear. However, from animal and human models emerges that KD might affects CNS at multiple levels: it is able to normalize cortical dysexcitability, probably via enhancement of GABA inhibition, and to reduce significantly cortical spreading depression velocity of propagation. Here, with the aim of identifying cortical electrofunctional correlates of responsiveness to short-lasting preventive intervention with KD in migraine, we investigated visual evoked potentials (VEPs) before and after KD.

Methods To find out whether ketogenic diet alters VEP habituation, we recorded VEPs (3.1 Hz reversal rate, 15 min of arc checkerboard visual pattern) before and during ketogenesis, as confirmed by urinary sticks, in 9 migraine patients. We measured VEP N75-P100 amplitudes in 6 sequential blocks of 100 sweeps and habituation as the percentage change in N1-P1 amplitude between the 6th and the 1st block.

Results After a mean of 1-month period of KD, a significant reduction of migraine frequency (from a mean of 7 to 1.9 attacks/month, $p=0.02$) and duration (from 42.6 to 18.7 hours/month, $p=0.03$) was observed. KD tended to increase VEP amplitude in block 1 and induced normalization of the interictally reduced VEP habituation (from +3% to -10%, $p=0.04$).

Discussion These findings suggest that ketogenic diet may exert its prophylactic effect in migraine through the influence on the processing of information at the cortical level. KD may be a promising therapeutic option as migraine prevention.

Lateral inhibition in somatosensory cortex of migraine without aura patients between attacks

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Background The most reproducible interictal electrocortical abnormality of the migraineur brain is the lack of habituation. It could be due to deficient intracortical inhibition and/or to low cortical pre-activation by the thalamo-cortical drive. However, reduced inhibition and low cortical preactivation may not be mutually exclusive, since the latter can promote the former through a re-

duction of lateral inhibition. Here, we investigated lateral inhibition within the somatosensory cortex in a group of migraine without aura (MO) patients compared to healthy volunteers (HVs) by stimulating two peripheral nerves simultaneously, while recording somatosensory evoked potentials (SEPs).

Methods SEPs were elicited by electrical stimulation of the right median and ulnar nerve at the right wrist separately and simultaneously (300 sweeps per condition), in 21 MO patients between attacks and in 17 HVs. We measured parietal N20-P25 amplitudes and we evaluated cortical lateral inhibition (CLI) as the ratio = $MU/(M+U)*100$, where MU is the SSEP amplitude obtained simultaneously stimulating both median and ulnar nerves (MU), and M+U is the sum of amplitudes obtained by stimulating each nerve separately (M+U). Habituation was calculated as the slope of the linear regression between the 1st and the 3rd block of 100 averaged sweeps.

Results SSEP N20-P25 amplitudes lack of habituation in MO patients ($p=0.03$). On grand-average, CLI resulted similar between groups. However, when data of HV and MO patients were combined the habituation slope was positively correlated with CLI ($r=0.331$, $p=0.04$).

Conclusions These results suggest that lateral inhibitory mechanisms within somatosensory cortex may physiologically contribute to induce lack of habituation of N20-P25 SSEPs amplitude seen in migraine patients between attacks.

Identification of new genetic variants of *KCNK18* in migraine with aura and migraine without aura

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Background Migraine with and without aura (MA and MO) have a strong genetic basis. Recently, a frameshift mutation (F139Wfsx24) in the *KCNK18* gene on chromosome 10q25.3 was reported in a large multigenerational MA pedigree. *KCNK18* gene codes for TRESK, a member of the two-pore domain family of potassium channels, expressed in dorsal root ganglion and trigeminal sensory neurons. The reported F139Wfsx24 mutation causes a complete loss of TRESK function. A functional study suggested a more complex association of other loss of function variants with migraine with aura.

Objective The aims of this study were to evaluate the frequency of *KCNK18* genetic variants in a large dataset of patients affected by migraine with and without aura, and to evaluate *in silico* their functional relevance.

Methods All three exons and intronic-exonic boundaries of the *KCNK18* gene were sequenced in 425 migraine patients (ICHD-II criteria; 255 MA, 170 MO) and 247 healthy controls. *In silico* analyses were performed using PolyPhen2 and SIFT programmes. The clinical characteristics of migraineurs carrying gene mutations were examined.

Results In 15 (5.9%) out of 255 migraine MA patients, five genetic variants (R10G, C110R, Y163Y, S231P, and F372L) were identified, while in 8 (4.7%) out of 170 MO patients six genetic variants (R10G, D46D, C110R, Y163Y, S178T, and S231P) were found. We identified only 2 mutations in controls (0.01%). *In silico* analysis suggested a pathogenetic role for two of these variants.

Conclusions Our study confirmed the presence of *KCNK18* gene mutations in migraine with aura patients and identified for the first time *KCNK18* mutations also in migraine without aura patients. The functional significance of the observed mutations and the effects on TRESK function deserve additional studies.

Effects of CGRP receptor antagonism in nitroglycerin-induced hyperalgesia

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The release of calcitonin gene-related peptide (CGRP) from trigeminal nerves plays a central role in the pathophysiology of migraine and clinical evidence shows an anti-migraine effect for CGRP antagonists. Systemic administration of nitroglycerin (NTG), a nitric oxide (NO) donor, consistently provokes spontaneous-like migraine attacks in migraine sufferers; in the rat, systemic NTG induces a condition of hyperalgesia through the activation of cerebral/spinal structures involved in pain transmission. The aim of the present study was to test the analgesic effect of CGRP receptor antagonist MK885 in two animal models of pain that are relevant for migraine: the tail flick test and the formalin test performed following 'sensitization' by NTG. The results demonstrate that systemic administration of MK885 is effective in counteracting NTG-induced hyperalgesia, in both tests. MK885 reduces the nociceptive behaviour when administered either simultaneously or prior (30-60 minutes before) to NTG. These results suggest that MK885 may represent a potential tool for the treatment of migraine by interacting with upstream mechanisms in the cascade of events that mediate the attack.

Parthenolide inhibits nociception and neurogenic vasodilatation in the trigeminovascular system by targeting TRPA1 channel

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Introduction *Tanacetum parthenium* L. (feverfew) has long been known as a migraine remedy and, according to positive results of clinical trials, it is currently recommended for migraine prevention. However, the mechanism responsible for such protective action remains unknown. Parthenolide, a major ingredient of feverfew, is a reactive molecule that can interact with nucleophilic sites of transient receptor potential ankyrin 1 (TRPA1). Thus, we hypothesized that parthenolide inhibits TRPA1 channel on peptidergic trigeminal nerves.

Methods and materials Experiments were performed *in vitro* in human and mouse cultured cells/neurons and rat isolated tissues, and *in vivo* in rats and wild-type and TRPA1-deficient mice. Electrophysiological, calcium, neuropeptide release, smooth muscle motility, allodynic and nociceptive responses, and changes in meningeal blood flow were evaluated.

Results Parthenolide selectively activates recombinant (transfected cells) or natively expressed (rat/mouse trigeminal neurons) TRPA1, and, by targeting TRPA1, activates trigeminal nerve endings. However, parthenolide behaves as a partial agonist at neuronal TRPA1 of the rat urinary bladder, desensitizes the recombinant TRPA1, and, after initial stimulation, renders peptidergic TRPA1-expressing nerve terminals unresponsive to any stimulus. These effects cause abrogation of nociceptive responses evoked by TRPA1 agonists, and inhibition of calcitonin gene-related peptide (CGRP) release from trigeminal neurons, and, in particular, of CGRP-mediated meningeal vasodilatation evoked by TRPA1 stimulants and other mechanisms.

Discussion and conclusions Peculiar features of parthenolide (TRPA1 partial agonism, channel desensitization, and defunctionalisation of peptidergic primary sensory neurons), ultimately resulting in the inhibition of CGRP release from trigeminal neurons, may contribute to the antimigraine effect of feverfew.

Visual motion processing areas in chronic migraine patients

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Introduction Many studies point out that patients suffering from migraine without aura (MO) and migraine with aura (MA) show abnormalities in visual motion perception during and between attacks. Previous studies have reported a thickening of visual motion processing areas (V3A/MT+) in MO and MA [1]. However, these changes have not been confirmed in chronic migraine (CM) [2].

Objectives The purpose of this study was to investigate regional cortical thickness/atrophy in CM (ICHD II, 2004) patients (CMP).

Methods We compared 23 CMP (age 38.7±11.5, 20 females) vs. 21 controls (age 34.9±4.7, 13 females). Cortical thickness was measured in 146 regions using FreeSurfer and volumetric T1 weighted images. Here we report on visual motion processing areas.

Results Migraineurs presented a thickening of the left occipito-temporal gyrus (12.8%, $p=0.006$), right occipito-temporal sulcus (5.7%, $p=0.048$), left inferior temporal sulcus (6.0%, $p=0.023$), right transversal temporal sulcus (12.4%, $p=0.016$), belonging to the V3A/MT+ areas.

Conclusions The role of the V3A area is particularly intriguing, since it has been suggested as the source of cortical spreading depression during the aura phase. Are MO, MA and CM, separate entities, or are they different manifestations of a similar underlying mechanism?

Our preliminary results of a thickening in the V3A/MT+ areas, not reported in other studies performed on CM, but in keeping with previous observations in MO and MA, supports the hypothesis that repetitive attacks could lead to neuroplastic changes in grey matter and emphasize the possible role of the V3A area in migraine pathogenesis.

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Dramatic remission of intractable SUNCT syndrome by occipital nerve stimulation

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Introduction SUNCT is a rare headache syndrome characterized by short-lasting unilateral neuralgiform headache associated with conjunctival injection and tearing. Even though several drugs have been successfully used, a number of cases are medically intractable. In these cases neurally destructive or cranially invasive treatments have been applied. We describe a clinical case in which complete success was obtained by the less invasive occipital nerve stimulation (ONS).

Case report A 27-year-old man was referred to our hospital because of recurrent severe facial pain superimposed on a continuous mild-to-moderate background pain. At hospital admission, he was affected by more than 100 daily, very short (5-15") attacks of sharp unbearable pain in the territory of the right trigeminal maxillary branch. Pain was accompanied by ipsilateral prominent tearing, conjunctival injection, ptosis, and palpebral oedema. Neurological examination revealed hypoesthesia in the right cheek, while

brain and orbital MRI, and MR angiography were normal. Several drugs (carbamazepine, lamotrigine, opioids, corticosteroids, indomethacin, amitriptyline, topiramate, verapamil, levetiracetam, etc.) were attempted without any improvement, and the patient could not be discharged in a 4-month period. He then underwent ONS. Immediately after the implantation, pain and autonomic phenomena disappeared, to reappear instantly if the device was switched off. Eight months later, pain recurred because of discharged pacemaker battery, and disappeared immediately after pacemaker replacement.

Conclusions The pathophysiology of SUNCT syndrome is substantially unknown, even though both trigeminal and hypothalamic involvement has been hypothesized. ONS could modulate pain, not only in the territories innervated by the occipital nerves but, also by the trigeminal nerve. In our case of intractable SUNCT, ONS displayed an astonishing efficacy; in our opinion it should be offered as first line interventional treatment in similar cases.

Case reports

Sporadic hemiplegic migraine and epilepsy: a new case report in a child

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Introduction Familial hemiplegic migraine (FHM) is a clinically and genetically heterogeneous disease. In addition to familial cases, there have been reports of sporadic cases of hemiplegic migraine (HM).

Case report An 11-year-old boy, with type 1 diabetes and mild cognitive retardation was admitted presenting weakness of left hemibody, dysarthria and confusional state. Two classical HM attacks as well as Mwo were reported in the past. No family members reported HM. In the past, brain MRI scan resulted normal. During hospitalization, he rapidly developed a left hemiclonic status epilepticus nystagmus and left tonic eye deviation. The child was sedated with propofol to control seizures. Brain MRI showed cytotoxic oedema in the right frontal-parietal regions. Seizures were controlled by levetiracetam administration; left hemiparesis improved and entirely disappeared. Brain MRI abnormalities gradually reversed. Genetic tests for CACNA1A mutations were negative. ATP1A2 and SCN1A are still ongoing. A new brain MRI showed a mild atrophy of the right hemisphere. EEG resulted normal. Flunarizine (5 mg/day) was prescribed. Two further mild HM attacks occurred in the following months. After ten months, flunarizine was discontinued with no occurrence of HM attacks. Levetiracetam was discontinued but the patient presented a generalized tonic-clonic seizure and the drug was rapidly re-titrated.

Discussion Epilepsy rarely occurs in FHM and is seen predominantly with specific CACNA1A gene mutations. Our patient presented sporadic hemiplegic migraine and epilepsy with an abrupt onset with status epilepticus.

Conclusions Epilepsy and migraine can be strictly related in selected cases.

A case of headache in a young female with Sjogren Syndrome and kidney involvement

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A 31-year-old woman came to our observation with severe throbbing bilateral headache in the fronto-temporal area, not responsive to therapy with NSAIDs. She reported intensive use of NSAIDs in the previous 2 months with

partial pain control. She suffered from Sjogren syndrome, autoimmune hypothyroidism, and she reported a history of sensory disorders in both lower limbs. Her brain CT scan was normal. Her blood tests showed renal impairment (creatinine 1.9 mg/dL) and her arterial blood gas analysis showed severe metabolic acidosis (pH 7.12, pCO₂ 17 mmHg, BE -23 mEq/l and bicarbonate 5.5 mEq/l) thus, she was treated with intravenous bicarbonate supplementation with partial benefit. In order to investigate her symptoms and to rule out a neurological involvement of Sjogren Syndrome, a MRI of the brain was performed which showed no significant abnormalities. In order to study her renal impairment we performed a kidney ultrasonography and she underwent a kidney biopsy. The renal cortex showed a diffuse interstitial, inflammatory infiltrate suggestive of acute interstitial nephritis and signs of chronic interstitial nephritis such as interstitial fibrosis and tubular atrophy. The patient was treated with potassium citrate and therapy with NSAIDs was immediately stopped. Headache improved after some weeks with resolution of the metabolic acidosis. In our opinion, kidney involvement related to Sjogren Syndrome was worsened by NSAIDs abuse causing acute interstitial nephritis and headache was caused by the consequent acidosis. Headache can be a symptom of acidosis and is possible to include this case in the group of headache attributed to disorder of homeostasis (10.7 of IHS Classification ICHD-II).

Cervicogenic headache during pregnancy: spontaneous spinal epidural haematoma

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Introduction Spontaneous spinal epidural haematoma during pregnancy is rare and may result in permanent damage if not promptly treated. Pregnancy-induced structural changes of the vascular walls and hemodynamic changes may play a role in the pathogenesis of this event.

Case report We present a case of a 34-year-old female, who at 34 weeks of gestation presented paroxysmal and rather intense unilateral head pain, spreading from the neck to the shoulders. After 24 hours the patient developed temporary inability to move her legs lasting 20-30 minutes and acral paresthesias. She was admitted, as an emergency, to the clinic: the neurological examination showed no abnormalities, standard laboratory analysis showed no coagulation disorder. An urgent MRI of the cervical spine was performed, which demonstrated a limited right posterior epidural lesion at C4-C6 level, compatible with epidural haematoma in the hyperacute stage. An emergency caesarean section was performed followed by spinal decompression and removal of the epidural haematoma without neurological sequel.

Conclusions This case study demonstrates how the presentation of a headache of recent onset, the absence of a history of headache, the type of the crisis, even in the absence of objective neurological abnormalities, can lead the decision towards undergoing instrumental tests and steer the choice in a delicate condition such as pregnancy.

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Migraine as the first clinical manifestation of hereditary hemorrhagic telangiectasia in a child

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Hemorrhagic hereditary telangiectasia (HHT) is a rare autosomal-dominant vascular disease that usually occurs in adulthood with nose bleeds as a main symptom.

We present a seven-year-old boy with severe migraine without aura. His medical history and family history were unremarkable. The neurologic examination did not highlight any neurologic deficit. A brain NMR, revealed an old ischemic lesion involving parietal and occipital lobes of the right hemisphere. The echocardiogram with contrast and the transcranial eco-color-doppler, revealed a right-to-left shunt, suggestive for a pulmonary arteriovenous fistula (PAVM), subsequently confirmed by the chest angio-CT and treated by coil embolotherapy with a significant neurological improvement. Finally the genetic test confirmed HHT.

An association has been reported between migraine and the presence of a right-to-left shunt due to a pulmonary arterio-venous malformation where the HHT is the underlying cause in about 70% of the cases. Two main assumptions have been formulated about a causal relationship between right-to-left shunt and migraine. Firstly, a genetic cause could determine both a pulmonary right-to-left shunt and migraine in patients with HHT. The other hypotheses is that substances such as serotonin or microemboli, not trapped in the pulmonary capillaries, might determine cerebral vascular instability or increased excitability of the CNS causing migraine.

An important clinical implication is that migraine can be considered a possible symptom revealing HHT in a child or young adult and that HHT patients with migraine should be screened for PAVM.

The clinical improvement in our patient after embolotherapy is a further support of the hypothesis of a relationship between right-to-left shunt and migraine.

Hemicrania continua with visual aura: first Italian case

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Hemicrania continua (HC) is a rare primary headache syndrome, characterized by a continuous unilateral headache of moderate severity, with exacerbations of severe pain associated with migrainous and autonomic features. Visual aura has been reported as a very rare atypical feature.

We report the case of a 31-year-old Caucasian man who had never suffered from headaches before and with unremarkable past medical history. He referred to our Headache Centre because of continuous unilateral right sided headache which had started 1 month before.

Constant headache was of moderate intensity, strictly localized in the right temporal-orbital region, and associated with two exacerbations per day of severe throbbing pain, accompanied with nausea, photophobia and ipsilateral autonomic symptoms, such as ptosis, conjunctival injection and tearing, lasting about 2 hours. Exacerbations were always preceded by gradual appearance of spots of flickering light in peripheral right visual hemi-field, lasting about 10 minutes. Computed tomography and magnetic resonance angiography were normal.

Indomethacin 150 mg and topiramate 75 mg per day were prescribed. Visual symptoms and continuous headache disappeared in a few days. Severe headache with autonomic symptoms reduced to one crisis per week.

After one month, topiramate was stopped due to side effects and switched to bisoprolol 5 mg. Headache frequency reduced to one moderate attack a month in the following two months, and subsequently the patient had no recurrence of symptoms. Beta blocker therapy was continued, while indomethacin was stopped.

We described the first Italian case of hemicrania continua with visual aura. The associations of indomethacin plus topiramate and indomethacin plus bisoprolol were effective.

Two cases of seizures related to migraine in children

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Introduction ICHD-II defines migralepsy at point 1.5.5 as a “migraine triggered seizure” in which a seizure occurs during migraine aura and is included among migraine's complications. In ILAE classification this entity is not recognized.

Cases description *Case 1:* A 12-year-old, female patient, affected by monthly headache referred to our Centre. Headache was diffuse or temporal, constrictive and associated with nausea, vomiting, photo- and phonophobia. Headache usually lasted between 3 and 5 hours. Sometimes visual symptoms such as scintillating scotomas lasting 10 minutes, preceded headache. She also experienced aura without headache. In three episodes visual aura was followed by a tonic-clonic seizure. EEG and brain MRI were normal. Topiramate at low dosage was introduced with efficacy. *Case 2:* A 5-year-old male suffered from headache since the age of two. Headache was throbbing, accompanied by nausea, partial loss of consciousness and urine loss. Headache lasted about 5 minutes and occurred more than one time per day. A CT scan was normal. EEG records showed generalized abnormalities in two occasions. Topiramate was started at a low dosage, with EEG normalization and reduction of frequency.

Discussion We described two cases of patients presenting headache and epileptic seizures. Epilepsy and migraine are highly related. Our cases show that it could be difficult to distinguish a comorbidity between the two diseases and a condition in which both migraine and epilepsy characteristics are present due to a common causative role.

Conclusions Migralepsy and related conditions should be considered in children with migraine and seizures.

Hallucination induced by low dose of topiramate in a migrainous girl: a case report and a revision of literature

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Introduction Topiramate (TPM) is an antiepileptic medication commonly used as a first-choice drug in the prophylactic treatment of migraine, especially in chronic and high-frequency attack forms. Although studies show that TPM is generally well tolerated, neuropsychiatric side effects, including cognitive disturbances, confusion, psychomotor slowing, concentration and/or memory difficulties, depression and mood disturbances have been widely reported. TPM-induced psychotic symptoms are also known but less frequently reported.

Case report We describe the case of a 15-year-old girl, affected by migraine without aura, who experienced a complex visual and auditory hallucination associated with a slight mood deflection, after 5 days of treatment with TPM 25 mg once a day for preventing headache. After drug discontinuation, psychotic symptoms did not appear and within two days the patient returned to her baseline mood status. Side effects to TPM were defined as ‘probable’ according to the Naranjo algorithm. During the subsequent 6 months no further similar episodes occurred.

Discussion According to the results of a systematic review of the literature in PubMed, this is the first report showing an hallucination induced by TPM at its lowest therapeutic dosage in an adolescent patient without personal medical or psychiatric history. Other two cases of psychotic symptoms induced by

low doses (i.e., 25 mg quod diem) of TPM were reported in a subject with a long history of alcoholic dependence and in a patient with bipolar disorder, respectively.

Conclusions In clinical practice we need to take into serious account the capability of TPM in producing psychotic symptoms, even at lower doses and in patients without any psychiatric illness. A slow titration to the desired dose could possibly reduce the risk of developing similar adverse reactions.

Steroid-responsive headache: main symptom of hypertrophic pachymeningitis a isolated location of Wegener's granulomatosis

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Introduction Wegener's granulomatosis is an autoimmune necrotizing systemic vasculitis.

Materials and methods A 28-year-old man presented with severe headache, resistant to NSAIDs/analgesics and responsive to steroids.

Results Two months after headache onset brain MRI showed: hypertrophic pachymeningitis. Total body CT-SCAN and blood tumor markers were negative, ESR 22 mm/h and CRP 5 mg/dL. General and neurological examinations were normal. He was treated with prednisolone (75 mg/daily) with immediate headache remittance. Prednisolone was gradually tapered and headache relapsed as dosage of 6 mg/daily was reached. Nine months later the patient presented partial seizure and therapy with levetiracetam (1000 mg/day) was started. EEG showed left temporal spikes. Lumbar puncture showed low CSF pressure, that was treated with a lumbar epidural blood patch. Headache disappeared for 4 days only. A dysimmune pathogenesis was then suspected, [elevated inflammation test and c-ANCA positive antibodies (95.9 U/mL)] and a treatment with prednisolone (50 mg/day) associated with azathioprine up to 3 mg/Kg/day was started. Progressive tapering of steroid to 6 mg/day caused headache relapse. Two years later, meningeal biopsy showed an inflammatory process mainly with B lymphocytes and plasma cells. After 28 months, the headache worsened and appeared diplopia on the left side. He underwent intravenous methylprednisolone 1 gr/day x 3 days with headache disappearance. Brain MRI showed an increased pachymeningeal thickening with enhancement and pathologic tissue in the left orbital cavity, between the superior rectus and lateral muscle. The ESR and PCR were slightly increased but autoantibodies were negative. The reassessment of previous biopsy pointed out histiocytes infiltration and granulomas with necrosis areas, suggesting Wegener's disease. He was then treated with two infusions of rituximab 1 gr twice a month with instant headache remission.

Conclusions Facing a patient with steroid-responsive headache from hypertrophic pachymeningitis associated with c-ANCA positive antibodies Wegener's disease should be suspected even in the absence of systemic vasculitis.

Efficacy of palmitoylethanolamide in a probable paroxysmal migraine

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Introduction Paroxysmal migraine is a rare form of trigeminal autonomic headache, characterized (according to IHS criteria 3.2) by strictly unilateral attacks of high intensity in the orbital, supraorbital or temporal region, accompanied by at least one dysautonomic symptom, lasting 2-30 minutes, 5 or more in number per day, completely responsive to indomethacin. Palmitoylethanolamide (PEA) is a physiological substance, an amide with

ALIA (Autacoid Local Inflammation Antagonism) effect that modulates mastocyte reactivity. PEA has a cannabinergic effect reducing prostaglandine synthesis and increasing anandamide levels.

Case report A woman 63-year-old with a medical history of bilateral thromboflebitis at 20, colecistectomy at 52, hypothyroidism from 59, affected by HCV hepatitis presented to our Centre. From the age of 60, she experienced various active periods (4-5/year) of 3-15 days characterized by 5-8 attacks per day of intense stabbing pain lasting 2-5 minutes, strictly unilateral on the right side, localized in frontal, ocular, temporal and periauricular region. No dysautonomic accompanying symptoms were referred. Neurological and general exams were normal. Blood tests demonstrated a low level of C reactive protein; brain angioMR was normal; brain MR showed microvascular hyperintensity areas in white matter. After diagnosis of probable (not all IHS criteria was fulfilled) paroxysmal migraine, we prescribed treatment with palmitoilethanolamide 600 mg two times/day, for 8 months. During this period headache did not appear; one month after discontinuing therapy, headache appeared with the same symptoms, therefore, treatment was started again with complete resolution.

Discussion and conclusions Our case is the first (according to Medline search) treated with palmitoilethanolamide, previously used in treatment of neuralgiform pain such as trigeminal neuralgia. The relative safety of this drug should recommend its use as a first step in treatment of headaches with a certain involvement of trigeminal nerve.

Headache in childhood and adolescence

Vit D deficiency, headache and overweight in children: a retrospective analysis

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Introduction According to recent observations, there is a worldwide vitamin D insufficiency. A number of observations suggest a link between low serum levels of vitamin D and higher incidence of chronic pain and other conditions, such as obesity [1].

Materials and methods We retrospectively analyzed 118 charts of children referred to the Headache Centre of the Neuropsychiatric Clinic of the San Salvatore Hospital and subjected to Day Hospital for further investigations between 2012 and 2013. Any type of headache, according ICHD-II criteria, was included. We collected serum levels of Vitamin D in 80 of the patients. Moreover, we calculated BMI. Descriptive statistics as well as chi-squared, logit regression and ANOVA were performed.

Results One hundred and eighteen patients (46.6% males vs. 53.3% females) were included. The mean age of patients was 10.5 ys (SD=2.78); the mean level of serum Vitamin D was 19 ng/ml (SD=9.8). The patients were affected by MWA in 26.2%, MWOA in 55%, and TTH in 30% of cases. Eleven patients received a double diagnosis. Of the total sample, 57.5% had vitamin D serum levels <20 ng/ml. Vit D <20 ng/ml was found in 64% of overweight children vs. 53% of children with normal weight. Female sex was positively related to high frequency of headache ($p<0.05$). MWOA is negatively related to serum Vit D levels ($p<0.05$). Furthermore, BMI is positively related to daily frequency of headache, regardless of the diagnosis of MWOA, MWA or TTH ($p<0.01$).

Conclusions In our sample Vit D deficiency is prevalent in children suffering with MWOA and Vit D deficiency is present in more than half of the total sample. Furthermore, our analysis shows high prevalence of daily headache in overweight children.

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Cardiovascular risk in children and adolescents with migraine

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Introduction The association between migraine with aura (MA) and stroke has been evaluated in adults, however the link between these entities is currently unknown. We investigated family history of juvenile vascular diseases in the families of migraneous patients to evaluate the possible liability in developing such events in young subjects with MA.

Material and methods In a retrospective study we evaluated 495 patients (348 with migraine without aura (MO) and 147 with MA, based on ICHD-II criteria) [1] and 150 healthy controls. Hospital record databases were screened to obtain data. We considered positive a family history of thromboembolic events (TE) or myocardial infarction (MI) in young age (≤ 50 years). Statistical analysis: Fisher's exact Test, Odds Ratio (OR) and 95% confidence interval (CI), $p<0.05$.

Results Occurrence of TE in first degree relatives of MA, MO and control subjects showed that respectively 6.12%, 2.30% and 1.33% had thrombotic events in young age; 6.80%, 2.30% and 2.00%, had MI ≤ 50 years. Comparing MA patients to controls, juvenile TE in relatives was associated with increased risk of MA in children (OR 4.8 (IC 1.02 - 22.7), $p=0.034$); a higher number of patients with positive family history of MI was observed in MA (OR 3.5 (IC 0.96 - 13.2), $p=0.050$). The relation was confirmed comparing MA and MO groups: the risk of developing MA was more than doubled in patients with familiar history of TE (OR 2.7 (IC 1.04 - 7.33), $p=0.054$) and tripled with familiar history of MI (OR 3.1 (IC 1.19 - 8.02), $p=0.031$).

Discussion and conclusions For the first time, we identified a significant correlation with familiar history of vascular diseases in juvenile age in children and adolescents with MA; such subjects, based on literature data available for adults, already presented an increased risk of stroke.

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Alexithymic characteristics in pediatric patients with primary headaches

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Introduction Alexithymia is a personality construct that reflects difficulties in verbal expression of emotions and limited ability to use fantasy. The aim of the study was to establish the prevalence of alexithymia among two samples of children affected by primary headache. Moreover we tried to find a correlation between alexithymia in children and their mothers.

Materials and methods This study involved 47 subjects (11 males, 36 females, aged from 8 to 17 years) suffering from tension-type headache (TTH) and 42 subjects (18 males, 24 females, aged from 8 to 17 years) suffering from migraine (M). The alexithymic construct was measured using the Alexithymia Questionnaire for Children and the Toronto Alexithymia Scale [1].

Results Higher rates of alexithymia were observed in the children suffering from TTH than M patients ($p < 0.05$). We also found a correlation between TAS-20 scores obtained by the mothers of M patients and their children.

Discussion and conclusions This study has an element of novelty because studies investigating the alexithymia in 2 subgroups of primary headache in developmental age are lacking. The results of this study demonstrated that patients suffering from TTH are more alexithymic than M patients. Furthermore a child's alexithymia may correspond to a mother's deficient emotive competence.

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Observational study of preventive treatment of migraine in children and adolescents: preliminary results

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Introduction Migraine is a frequent and regular disabling condition in childhood. Therefore, when headache is frequent (>1 a week) or causes substantial disability, the Italian guidelines suggest including, in addition to the symptomatic, a preventive therapy in the pharmacological strategy. Several drugs have shown good efficacy in preventive migraine treatment in childhood, but there is no information about their trend over time. The goal of this study is to evaluate the efficacy (reduction of attacks) of the prophylactic drugs at the end of the treatment and its long-term effect (>6/12 months).

Methods The observational study examined 30 patients (12 M and 18 F; two age groups 5-11; 12-18) affected by migraine (27 MWA; 3 MWOA). The sample was divided into two groups defined by similar PedMIDAS score and age: 15 of them practiced prophylactic therapy (flunarizine or topiramate) for about 3 months; whereas the others practiced only acute treatment. Data were analyzed by unvaried analysis (chi-square test).

Results At the end of the treatment the subjects treated with preventive therapy showed a statistically relevant reduction of attacks ($p < 0.05$: 8 patients treated and none of the untreated). The first long-term results showed that therapeutic efficacy lasts over time.

Conclusions This study confirms the efficacy of preventive therapy in subjects affected by migraine, as already described in the literature. Presently, we have enlarged the population sample and the first results obtained show a better reduction of attacks in long-term treated subjects compared to untreated subjects.

Intellectual functioning and headache in children: the interictal evaluation

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Introduction The purpose of this study was to assess the cognitive functioning of children affected by headache, pinpointing the differences in in-

telligence style between subjects affected by MoA and subjects with TTH.

Methods The study population consisted of 147 children (mean age: 10.82±2.17 years) with headache, recruited from the Headache Centre for Developmental Age, Child and Adolescent Neuropsychiatry Clinic, Second University of Naples. Cognitive profiling was performed using WISC-III throughout the sample. According to the ICHD-II criteria for pediatric age, subjects were divided into MoA group (n=75; 43 boys, 32 girls) and TTH group (n=72; 49 boys, 23 girls). The control group was composed of 137 typical developing subjects recruited from schools in the Campania region.

Results No difference in full intelligence quotient was found between the groups, but the children with TTH had a lower verbal intelligence quotient and a higher performance intelligence quotient than the controls and children with MoA. Factor analysis data showed that the children with MoA seemed to have lower perceptual organization than the children affected by TTH [1].

Discussion and conclusions To our knowledge, studies on cognitive functioning in children affected by headache in the interictal phase are scarce, and our results suggest a new perspective in the understanding of the neuropsychological aspects of young headache patients.

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VEP habituation distribution in the families of migraine children

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Introduction In spite of the bulk of studies showing reduced visual evoked potential (VEP) habituation in adult migraineurs, this abnormality has never been demonstrated in children with migraine. VEP habituation can be assumed as a marker of the visual cortex excitability, whose abnormality in migraineurs is related to the genetic background of this disease. In pediatric age, it is debated whether the presence of migraine in the families of young migraineurs is due to a hypothesized genetic background or is a consequence of the "psychological environment". The aim of our study was to investigate whether neurophysiological or psychological elements are segregated in families of migraine children.

Methods We studied 11 children (2 siblings) with migraine without aura and their parents. 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.

Results VEP habituation was significantly lower in both patients and migraineur parents than in non-migraineur parents (two-way ANOVA: $F=14.7$, $p < 0.001$). As for the psychological tests, no significant difference was found "between groups" when we compared the Internalizing ($p=0.5$), Externalizing ($p=0.3$) and Total scales scores ($p=0.1$).

Conclusions This is the first study showing a reduced VEP habituation in migraine children. Our results suggest that the familial distribution of the disease is due to a genetic background, while the "psychological environment" does not have a significant influence.

Neurofibromatosis type I and migraine in childhood: a new therapeutic perspective

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Introduction Neurofibromatosis type 1 (NF1) is a rare genetic disease, associated with many neurological comorbidities, such as headache. Despite the high prevalence of headache in this population, little data exists regarding the classification of headaches experienced by patients with NF1.

Objective Aim of the study was to verify the efficacy and safety of nutraceutical complex containing Ginkgolide B/Coenzyme Q10/Riboflavin/Magnesium for the prophylaxis in a sample of children affected by NF1 presenting migraine without aura symptoms.

Methods Ginkgolide B/Coenzyme Q10/Riboflavin/Magnesium complex was orally administered as prophylactic therapy twice a day for 6 months to 18 school-aged patients affected by NF1 and presenting symptoms of migraine without aura (MoA) (10 M; mean age: 8.4 ± 1.65). Each patient kept a journal to record: number, intensity (according to VAS scale), duration of attacks and concomitant symptoms. In addition, the Ped-MIDAS scale was administered to assess migraine-related disability. To verify the efficacy of the association, we tested the starting frequency (T0) of headache after 6 months (T1) and then we calculated the migraine frequency delta percentage to express the decrease in monthly frequency.

Results A reduction ($p < 0.001$) in all migraine outcomes (frequency, duration, intensity and disability grade) was reported after the period of treatment [1].

Discussion and conclusions Nutraceutical complex containing Ginkgolide B/Coenzyme Q10/Riboflavin/Magnesium for the prophylaxis of migraine also in NF1 subjects, pinpointing the importance of considering the migraine symptomatology as the therapeutic target and not the basic pathology as impediment for a correct management.

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Cognitive profile in new onset headache in children

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Introduction Primary headache is a common clinical condition that includes migraine (with or without aura) and tension-type headache, as more common types among idiopathic headache in children [1]. There are few available data on cognitive profile in pediatric headache.

Material and methods A prospective, controlled study aimed at evaluating the cognitive profile in children with idiopathic headache was conducted at the Pediatric Neurology, Sant'Andrea Hospital. We investigated 17 patients between the ages of 6 and 15 years (9 females and 8 males). All data about history, physical and neurological examination, awake and sleep-EEG, prick test, cognitive assessment by WISC-R, the characteristics of headache and analysis of all confounding variables, such as obesity, hypertension, psychological distress, psychiatric and respiratory disorders, were collected.

Results Children with headache enrolled in the study did not show cognitive deficits, even better, 52.9% of them had high total IQ values. Eleven (64.7%) children showed a significantly higher verbal IQ compared with the performance IQ. In addition, the whole sample had an excellence in the sub-sector termed "similarities" which is an index of "ability of abstraction, generalization and inductive reasoning".

Conclusions The preliminary data of our prospective study (17 children investigated until now) showed that children seem to have a specific cognitive profile characterized by high skill in a "specific" verbal sub-test (similarities). To confirm these findings, a larger pediatric sample should be investigated.

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Children's headache: drawings in the diagnostic workup

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Introduction Drawings have been used in the developmental age to recognize psychological insights and pain perception; however, in few studies drawings were used for headache assessment. The aim of the present study was to evaluate the effectiveness of drawings in childhood headache assessment.

Method We collected 67 headache subjects (33 males and 34 females), 6-14 years of age (mean age: 10.7; SD: ± 2.37), admitted to the Child Neuropsychiatry Unit of Parma in a period of 22 months. At the first visit the child was asked to draw his own headache, without any further suggestion or time limits. Clinical diagnosis was made according to the ICHD-II. Drawings were analyzed independently by two child neuropsychiatrists blinded for clinical data and were categorized as migraine or tension-type headache (TTH). The diagnosis based on drawings was compared to the clinical one. Cohen's K-score for interrater agreement and sensitivity (Se), specificity (Sp), positive predictive value (PPV) for both types of headache were evaluated.

Results Thirty-seven subjects were clinically diagnosed with migraine (55.2%) and 30 with TTH (44.8%). K-score was 0.84 (excellent agreement 0.81-1.0 according to Landis). Drawings showed a Se=85.71% and 81.48%, a Sp=81.48% and 85.71% and a PPV=85.71% and 81.48%, for migraine and TTH respectively.

Discussion The presence of severe/pounding pain (but not its localization), photophobia, phonophobia and neurological focal signs in drawings was highly predictive of migraine. Other symptoms (gastrointestinal symptoms and crying) were less frequently drawn, but almost always associated with a correct diagnosis of migraine. Instead, in the TTH group drawings there was a paucity of pain-associated symptoms.

Conclusions Our study demonstrated the usefulness of drawings to disentangle migraine and TTH. We suggest the inclusion of this non-invasive and child-friendly instrument in the diagnostic assessment of childhood headache.

Childhood migraine as parental stressor

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Background To date, no reports are about the impact of childhood migraine as parental stressor. The aim of this study was to evaluate the prevalence of maternal stress in a large pediatric sample of MoA individuals.

Methods The study population consisted of 218 children (112 boys, 106 girls) mean age 8.32 ± 2.06 years (range 6-13) suffering from MoA and 405 typical developing children (207 boys, 198 girls) mean age 8.54 ± 2.47 years.

Mothers of children in each group answered the Parent Stress Index-Short Form (PSI-SF) questionnaire to assess parental stress levels.

Results The two groups were matched for age ($p=0.262$), gender ($p=0.983$), and BMI adjusted for age ($p<0.106$). Mothers of MoA children reported higher mean PSI-SF scores related to the Parental Distress domain ($p<0.001$), Dysfunctional Parent-Child Interaction domain ($p<0.001$), Difficult Child subscale ($p<0.001$), and Total Stress domain than mothers of controls ($p<0.001$). No differences between the two groups were found for Defensive Responding subscale scores [1].

Conclusions Our study may be the first to highlight the presence of high levels of stress in parents of children affected by migraine without aura.

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Alexithymia, headache and eating disorders in childhood and adolescence

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Introduction This study examines the relationship between alexithymia, primary headache and eating disorders in childhood and adolescence. The aim was to investigate if headache and eating disorders represent the somatic translation of the inability to identify and express their emotions.

Sample recruitment: the sample was composed of 46 subjects, 26 females and 20 males, aged 10 to 18 years.

Materials and methods The alexithymic construct was measured using the Italian version of the Toronto Alexithymia Scale (TAS 20, 1996). Primary headache was diagnosed according to the International Headache Classification (ICHD-II, 2004) criteria, while eating disorders were diagnosed according to the SAFA-test (in particular the SAFA-P subscale, specific for psychogenic eating disorders, 1999).

Results Twenty-eight subjects were affected by tension-type headache (12 males and 16 females) while 18 subjects by migraine (8 males and 10 females); there was no significant differences among the males and females in alexithymia prevalence; alexithymia was present more in tension-type headache patients than in migraineurs, with statistical significance ($p<0.05$). The SAFA-test showed that tension-type headache patients present risk factors for eating behaviour and higher prevalence of depressive disorders compared with migraineurs, males have lower pathological eating behaviours compared to female. The SAFA results showed that while in migraineurs there were issues related to body acceptance, patients with tension-type headache had behaviours that tended towards "perfectionism".

Conclusions There is no real relationship between alexithymia, headache and eating disorders, however it is clear that the inability of the children to identify and describe their emotions, could be a potential risk factor in the development of psychosomatic symptoms, such as headache and eating disorders, and the development of psychological and behavioural characteristics such as a tendency towards perfectionism and feelings of inadequacy.

Migraine with aura in children: a retrospective analysis

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Introduction Few studies have reported migraine with aura in the pediatric population [1].

Methods We analyzed charts of children affected by headache referred to the Headache Centre of Bambino Gesù Pediatric Hospital between 2000 and 2011. We analyzed the clinical features of headache as well as 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 were included in the study. The mean age of headache onset was 9.5 years. Headache following aura symptoms was classified according ICHD-II criteria but we used proposed revised criteria not including duration of attack to re-classify patients, demonstrating an improvement in the diagnosis. Aura was classified in preictal (67.3%), ictal (22.7%) or pre and ictal (10%). Aura duration was in the most cases comprised between 5 and 30 minutes but we recorded also aura duration shorter than 5 minutes (15.5%) and longer than 2 hours (3.6%). The shorter was the aura duration, the lower was the attack frequency ($p<0.05$). Duration of aura was shorter in the youngest children ($p<0.001$). Visual aura with positive symptoms (scintillating scotoma) showed a significant correlation with a shorter duration of the migraine attack.

Discussion 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 that should be further investigated.

Conclusions Our study, although retrospective, may be useful to improve our current knowledge of migraine with aura in children.

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Headaches and comorbidities in children

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Introduction Comorbidity is the coexistence of two or more clinical conditions in the same subject and at the same time. This term underlines not the accidental presence of two diseases, but a coincidence statistically significant in the population [1]. This study, conducted in a large sample, aimed to verify the differences within the different types of primary headache among patients with and without comorbidity

Materials and methods The sample was composed of 715 patients, 315 M and 400 F, aged between 3 and 18 years. The patients were divided into 3 groups on the basis of the age. The following disorders were verified: psychiatric disorders as reported by parents, (patients with a diagnosis already performed), as sleep disorders, internalizing and externalizing disorders through the CBCL (the two versions of the Child Behaviour Checklist of Achenbach and Rescorla, 2001); the academic performances and learning disorders by Cornoldi test; organic disease, such as, allergic, neurological (epilepsy, febrile seizures, syncope), auxoendocrinological and gastrointestinal diseases, infections and ear sinusitis. Also, we evaluated the symptoms of periodic syndrome.

Results The diagnosis more represented was migraine without aura. In 81% of the sample almost one comorbidity was present and we found a difference among the three age groups ($p<0.01$). The most present comorbidities, but equally distributed between M and TTH were allergic disorders and sleep disorders. Psychiatric disorders and obesity were higher in TTH, syncops and epilepsy among migraineurs. The specific learning disorders (SLD) were present in 13% of patients and were prevalent in the CDH group. By analyzing the troubles of the periodic syndrome: abdominal pain, motion sickness were prevalent in migraineurs ($p<0.001$).

Conclusions Psychiatric and organic comorbidities were equally represented in the various types of headache, with the exception of CDH where psychiatric disorders prevailed.

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Developmental coordination disorder and pediatric migraine: an observational study

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Introduction Developmental coordination disorder (DCD) is a very common problem among children, with a prevalence ranging up to 19%. The aim of this study was to evaluate the presence of motor coordination impairment in a population of children affected by MoA, and its role as putative risk factor for motor skills impairment.

Methods This observational study was performed in the Clinic of Child and Adolescent Neuropsychiatry of the Second University of Naples. MoA was diagnosed according to the International Classification of Headache Disorders (ICHD-II) criteria. The study population consisted of 27 patients affected by MoA (16 females, 11 males) (mean age: 8.7±2.15 years) and 59 typically developing children (34 females, 25 males) (mean age: 8.0±2.1 years). The whole population underwent a clinical evaluation in order to assess the total IQ level, the visual motor integration skills, and the presence of DCD.

Results MoA children had more impairments in motor coordination ($p<0.001$) and visual motor integration ($p<0.001$) than control group [1].

Discussion and conclusions To our knowledge, this is the first study to assess the association of poor motor coordination and MoA in children using objective measurements. These findings suggest a new perspective in the management of migraine disease in children, pinpointing that the relationship between DCD and migraine could represent a not yet understood or identified comorbidity, even if further reports are necessary, and that migraine probably could be considered not only a painful syndrome in future.

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Migraine in children and adolescents: does a “psychological marker” exist?

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Introduction A characteristic set of psychological features has been observed among migraine sufferers, but studies comparing migraine and non-migraine headache are missing. Studies on adults evidenced that the presence of psychiatric disorders is more related to frequent headache crises [1] than to headache sub-types. Main aim is to analyse if migraine differs from non-migraine headache in several psychological domains.

Method Fifty headache patients (age-range 7-12 years, 37% male, m.a. 9.78, SD:1.28) and 50 healthy controls (m.a. 9.45; SD:1.89), matched by age and gender, were enrolled. Children's attachment was assessed using Security Scale and Preoccupied and Avoidant Coping Strategies. CBCL-6/18 and Parent Stress Index were used to assess respectively children's behavioural

problems and parents' self-reported stress. ICHD-II criteria had been used for diagnoses (21 migraine with/without aura vs. 29 non-migraine headache).

Results In the comparison with their peers, headache children presented a higher rate of internalizing ($t(49)=5.09$, $p<0.001$), externalizing ($t(49)=3.65$, $p=.011$) and total problems ($t(49)=4.65$, $p<0.001$). The risk for internalising problems was higher for children with migraine ($n=23$, $t(49)=1.98$, $p=.05$). Specifically, parents of migraineurs reported more stress than children without migraine, reaching the significance along the Parent-Child Domain ($t(40)=2.01$, $p=.05$). In headache children, the effect size of the correlation between attachment scales and behavioural problems showed a moderate association between avoidant strategies and internalising behavioural problems ($r=.31$). Specifically, this was true to a higher extent for children with migraine ($r=.38$). No differences had been found according to the frequency of the crises.

Discussion and conclusions Migraineurs showed psychological characteristics that differentiated them from non-migraineurs. Not only behavioural problems (Internalizing), but also higher levels of stress in parents and more maladaptive coping strategies are shown by migraine than non-migraine patients. The hypothesis of a “psychological marker” differentiating migraineurs needs further study for the several related implications.

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Chronic headaches

Thalamic involvement in migraine chronification process

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Background Decreased high-frequency somatosensory oscillations (HFOs), reflecting thalamo-cortical activity, and lack of habituation of low-frequency (LF-) somatosensory evoked potentials (SSEPs) to repetitive sensory stimulation characterize episodic migraine between attacks. Here, we study conventional LF-SSEPs and HFOs in episodic migraineurs who developed chronic migraine (CM).

Methods Thirty-four episodic (15 interictally [MOii], 19 ictally [MOi]) and 19 CM patients underwent right median nerve SSEPs. The patient groups were compared to a group composed of 20 healthy volunteers (HV) of comparable age and gender distribution. We measured the N20-P25 LF-SSEP 1st amplitude block and habituation, and, after applying a band-pass filter (450-750 Hz), maximal peak-to-peak latency and the amplitudes of the early and late HFOs.

Results Reduced early HFOs, lower 1st block LF-SSEPs and lack of habituation characterize MOii. Initially higher SSEP amplitudes and late normal habituation characterize both CM and MOi patients. After the digital filtration, both patient groups showed shortened latency peaks and normalization of early HFO amplitudes with increased late HFOs. When data of MO and CM patients were combined, the monthly number of days with headache negatively correlated with the LF-SSEP slope ($r=-0.385$, $p=0.006$), which in turn negatively correlated with the 1st amplitude block ($r=0.568$, $p<0.001$).

Conclusions Our results in chronic migraine show abnormalities that are also reported during attacks in episodic migraineurs, namely initial response sensitization and late habituation. From the HFO analysis emerges that this sensory sensitization may be explained by an increase in the strength of the connections between the thalamus and cortex compared to episodic migraine between attacks.

Chronic migraine in the Emergency Department: a two-year prospective study on the efficacy of a dedicated acute Headache Centre

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Background Chronic migraine (CM) is often underdiagnosed in the Emergency Department (ED) and rarely referred to a Headache Centre.

Objective To evaluate the effectiveness of a dedicated Acute Headache Centre (AHC) in improving management and disability of patients with CM referring to the ED.

Methods We performed a two-year prospective analysis of all patients with non-traumatic headache visited in the EDs of Trieste and referred to the AHC. Patients with AHC diagnosis of CM were enrolled. Causes of presentation, multiple admittances, diagnostic tests, consulting visits, therapies, length of stay into the ED, ED diagnosis, and MIDAS scores, were analyzed using SPSS 14.0.

Results Out of 398 patients totally admitted in AHC, 39 patients (9.8%) (87.2% F and 12.8% M; mean age: 40 ± 14 years) were enrolled. Nine patients (23.1%) had previous multiple admittances in the ED. Severity of pain was the most frequent cause of presentation (51.3%). ED diagnoses were NOS headache (76.9%), primary headache (23.1%), only one patient had a diagnosis of CM. Eleven patients (28.2%) underwent a CT of the skull. Consulting visits were required in 59% of cases. Twenty-two patients (56.4%) received multiple therapies in the ED, the most frequent being NSAIDs (35%). Prophylactic treatment was rarely initiated in the ED (7.7%). The mean length of stay in the ED was 240 ± 220 minutes. Thirty-six percent of patients were overusers. All the patients were properly treated in AHC, mainly with symptomatic (triptans, 56.4%) and prophylactic (antiepileptics, 41%) therapy. The mean MIDAS total score at the first AHC visit was 111 ± 63 , and was decreased at the three-month follow-up visit (47 ± 38).

Conclusions Chronic migraine is frequent in the ED, widely underdiagnosed, scarcely responsive to acute treatment, and rarely properly treated. A high percentage of CM had multiple admittances in the ED. A dedicated Acute Headache Centre is effective in identifying and in specifically treating CM, resulting in a significant reduction of disability.

Impact of body mass index on drug consumption in medication overuse patients

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Background A percentage of migraine patients develop chronic daily headache due to medication overuse [medication-overuse headache (MOH)]. Since MOH is a disabling health problem, identifying patients at risk for its development is crucial. Weight gain seems to play a role in headache transformation, although the underlying mechanisms are not yet clearly understood. Here, with the aim of identifying a worsening factor in MOH, rather than of detecting a specific risk factor for disease development, we investigated whether body mass index (BMI) and other clinical features might predict monthly drug consumption that is the hallmark of disease.

Methods We recruited 119 consecutive MOH patients and we collected their clinical variables. Pearson's correlation test was used to search for correlations. Linear regression, using step-wise model, was used to determine the best predictive model for monthly drug consumption, with systolic and dias-

tolic blood pressure, BMI, age, age at the onset of the disease, monthly number of days with headache, duration of the chronic and of the overuse phase, and type of overused drug considered as independent variables.

Results The monthly drug consumption correlated positively with the BMI ($r=0.299$, $p=0.004$). At multiple regression analysis, only the duration of the chronic phase and the BMI emerged as significant independent predictors of analgesic drug consumption (Beta=0.293, Cohen's $f^2=0.093$; Beta=0.290, Cohen's $f^2=0.158$ respectively).

Discussion These findings showed a strong influence of BMI in the MOH most characterized clinical feature, i.e. the number of monthly tablets intake, once more supporting the idea that MOH is a substance abuse disorder. Although the exact mechanisms of weight gain promoting medication overuse are unknown, our data underlined the fact that patients still in an episodic phase should be encouraged to maintain their weight (if normal) or decrease it (if overweight).

Aggressiveness and impulsiveness in chronic and episodic cluster headache

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Introduction Psychiatric and psychological comorbidity of cluster headache (CH) has received much less attention than in migraine or tension-type headache. Most of the hypotheses on personality characteristics, psychological features and coping style of CH, such as those regarding impulsiveness and aggressive behaviour have not yet been validated by solid observational data. **Objective** The aim of the study was to investigate whether patients with CH have higher levels of aggressiveness and impulsivity compared to healthy volunteers.

Materials and methods Seventy-nine CH patients (73.5% episodic form ECH, 26.5% chronic form, CCH) attending two headache clinics were asked to fill in the Aggression Questionnaire (AQ, a self-report scale exploring the aggressiveness in its multidimensional aspects – verbal aggression, physical aggression, anger and hostility) and the Barrett Impulsiveness Scale (BIS, a self-report scale exploring impulsiveness in three different “keys”: attentional, motor and non planning). Data regarding ECH were collected in both the active and remission phase. Control group included 80 sex- and age-matched healthy volunteers.

Results Physical aggression scores were significantly higher in CCH than in controls (19 ± 2 vs. 14.8 ± 1 , $p < 0.05$) whereas anger scores were significantly higher in both active ECH (17 ± 1.2) and CCH (19 ± 2) than in controls (14.8 ± 1 , $p = 0.04$). The attentional key scores of BIS were significantly higher in both ECH and CCH patients than in controls (17.8 ± 1 , 18 ± 2 and 14.3 ± 1 , respectively, $p < 0.0001$). In the 33 ECH patients completing the questionnaire in the active and the remission phase no significant difference was found as regards to both AQ and BIS indexes.

Discussion Our data suggest the presence of trait-dependent higher levels of aggression and impulsivity in CH patients specifically regarding the physical aggressiveness, anger and the attentional key dimensions.

Efficacy of a detoxification protocol in medication-overuse headache: report from a multicentric multinational study

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The management of medication-overuse headache (MOH) is often difficult and no specific guidelines are available as regards to the most practical and effective approaches. In this study we defined and tested a consensus protocol on a large population of MOH patients distributed in different countries. The protocol was based on evidence from the literature and on the consolidated clinical expertise and publication records of the members of the consensus group. A total of 377 MOH subjects were enrolled in 4 Centres from Europe (Italy, Denmark, Germany, Spain) and 2 Centres in Latin America (Argentina, Chile). The majority of patients were treated according to an outpatient detoxification programme. The post-detoxification follow-up lasted 6 months.

The procedure yielded a positive outcome in terms of responders - defined as MOH subjects who reverted to an episodic pattern of headache and no longer overused reductions of days of headache. At the last evaluation performed 6 months after detoxification, 65.8% of subjects were responders and around 2/3 of subjects were no longer overusers. When comparing the outpatient vs. the in-patient procedure, no significant difference emerged as regards to the percentage of responders and of relapsers, although a higher frequency of drop-outs was observed in the outpatients approach.

The present findings support the adoption of the proposed consensus protocol for its proved effectiveness and adaptability to different countries and healthcare approaches.

Influence of the type of primary headache on the outcome of medication-overuse headache following detoxification

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Background Medication-overuse headache (MOH) results from the chronicification of primary headaches, usually migraine and tension-type headache or both, as a consequence of the progressive increase in the intake of symptomatic drugs.

Methods In the multicentre controlled study COMOESTAS, we enrolled, detoxified and followed up 501 MOH patients for 6 months.

Results Before the enrolment, the primary headache, confirmed by the diary, was episodic migraine (M) in 306 subjects, tension-type headache (TTH) in 35 subjects, mixed type (MT, migraine plus tension-type headache)

in 160 subjects. At 6-month follow-up, 90.2% of the subjects were no longer overusing acute medications (cured) and 67.5% also reverted to an episodic pattern of headache (responders), while only 7% relapsed in overusing. The percentage of responders was statistically higher in the M group. No significant differences were detected between groups as regards to the percentage of subjects who were cured or the percentage of responders. M and MT patients showed a greater reduction in headache frequency ($p < .003$). The frequency of acute medication intake was reduced similarly in all groups, with no significant differences.

Conclusions Our results indicate a very good prognosis for detoxified patients, with a higher rate of responders in migraineurs. It seems that TTH more rarely evolves toward MOH, but, when it does, it is more difficult to revert it back to the episodic pattern. Behavioral factors, associated to the type of original headache, should be taken into account for the outcome of MOH.

Onabotulinumtoxin “A” for chronic daily headache: a retrospective cohort study

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Introduction Chronic daily headache (CDH), a primary headache including chronic migraine (CM) and medication-overuse headache (MOH), is often associated with relevant disability and affects 4% of the general population worldwide. Botulinum toxin type A has been studied as a prophylactic treatment for migraine and recently (PREEMPT 1 and 2 trials) onabotulinumtoxin was found effective in CM and particularly in MOH. In 2013 in Italy an extension to the BOTOX® (onabotulinumtoxin A) licence for the prophylaxis of chronic migraine was approved.

Material and methods We retrospectively reviewed clinical charts of patients with CDH refractory to pharmacological treatment, recruited in the AOU Careggi Headache Centre between 2010 and 2012, who, after signing informed consent, received treatment with onabotulinumtoxin A.

Results Fifty-six patients, (80% female), mean age 52 years (18-78), were treated (mean length of treatment 1 year) with onabotulinum toxin A with the injection paradigm fixed sites and fixed dose in the pericranial muscle and follow the pain sites with a total dose of 155 (n=49) or 195 U (n=7). At baseline 15 patients had tension-type headache (TTH), 37 patients migraine without aura, 1 migraine with aura and 3 a mixed type of CDH. Diagnosis of MOH could be posed in all patients. Forty-four patients (76%) reported a persistent good response to treatment, (decrease of intensity and frequency of attacks, n=23; decrease of frequency, n=11; decrease of intensity, n=10). All patients referred a decrease in analgesic consumption. Twelve patients reported no change in headache frequency or intensity.

Conclusions BOTOX® could represent a useful treatment for patients affected by CDH.

Multimodal approach in chronic migraine

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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 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; sphenopalatine 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; NSR 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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Non-invasive vagus nerve stimulation (nVNS) for acute treatment of chronic migraine and medication-overuse headache

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Introduction Central and peripheral neurostimulation procedures have been recently investigated in patients with chronic primary headaches refractory to standard therapies. The majority of these procedures are highly invasive and controlled trials are sparse. The *Gammacore*® device is a portable non-invasive stimulator that produces a mild electrical signal transmitted to the vagus nerve through the skin. Preliminary studies suggested that patients with migraine and cluster headache experienced a reduction in the frequency and severity of their headache symptoms with non-invasive vagus nerve stimulation (nVNS).

Objective The aim of this study was to evaluate the safety and the efficacy of treatment with nVNS in patients with chronic migraine and medication-overuse headache (CM/MOH) during the detoxification period and in a 6-month follow-up period.

Methods Ten patients (9 females, 1 male, mean age ± SD: 58.5±9.4 yrs) with CM-MOH were enrolled in the study. Patients underwent a 5-day in-patient detoxification period, according to a standard protocol. Headache attacks during the detoxification period and in the 6-month follow-up period were treated with repeated nVNS. The clinical characteristics of headaches were recorded in a diary.

Results At present, about 65 migraine attacks per month were treated with nVNS. At two hours, headache response rate was 68%, with 36% free pain patients. A highly significant ($p<0.001$) reduction in the use of acute drug treatment was observed. No major adverse event was reported.

Accurate psychiatric preoperative evaluation is needed in patients with chronic refractory migraine eligible for neurostimulator implantation

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Introduction Implantable central and peripheral neurostimulation is an invasive treatment for patients affected by chronic migraine refractory to conventional pharmacological therapy [1]. Being neurostimulation potentially complicated by side effects as infection or neurological damage, patients have to be highly motivated and compliant to benefit from treatment.

Material and methods Eighty-five patients with untreatable chronic migraine were selected. Before implantation patients underwent psychological evaluation (MMPI-2) to evaluate mental health and motivation. Potential risk due to implantation are: benefit not achieved, infections, neurological damages, muscular stimulation and pain, break or dislocation of catheter with lost of function, damage or need of substitution, haematoma or seroma. Of the 85 selected patients, 31 were excluded because of psychiatric comorbidities, 35 refused implantation and 19 were finally implanted.

Results Of the 19 patients treated with neurostimulation, 16 had no complications with efficacy and benefits to treatment. However, 1 patient had to discontinue treatment for the occurrence of infection in the surgical site; 2 patients had no compliance to treatment, maybe due to underestimation of existing psychiatric diseases.

Summary and conclusions In our cohort we observed just a major medical side-effect which led to removal of the device, but more than 10% of subjects discontinued therapy due to low psychiatric compliance to the therapy. Since the implantation of a neurostimulator is an invasive procedure, and in our cohort we also observed a major complication, an accurate psychological and psychiatric preoperative evaluation is needed to avoid implantation in non-compliant subjects with psychiatric comorbidities.

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Psychopathological aspects in patients with medication-overuse headache

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Background Psychiatric comorbidities are commonly observed in medication-overuse headache (MOH) patients and are considered important risk factors for the chronification of head pain [1].

Objective This study aimed at assessing the prevalence of psychopathological disorders in patients with MOH, comparing them to patients with episodic migraine without aura (EM) and healthy subjects (HS).

Materials and methods Overall, 88 of the 130 MOH patients screened in the controlled randomised clinical trial *SAMOHA* (*Sodium valproate in the treatment of Medication-Overuse Headache*: a 6-day detoxification protocol was followed by a 3-month prophylactic treatment utilizing placebo/sodium valproate, at nine Italian headache centres) 127 EM patients and 102 HS were included in the study. The presence of psychopathological disturbances was evaluated using the following tests/questionnaires: Migraine Disability Assessment (MIDAS), Migraine-Specific Quality of Life Questionnaire (MSQ), Leeds Dependence Questionnaire (LDQ), Beck Anxiety & Depression Inventory (Beck-A and Beck-D), Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and Modified Mini-International Neuropsychiatric Interview (Modified-MINI).

Results The mean ages (SD) were 43.2 (9.5), 41.3 (11.1) and 39.2 (13.1) for MOH, EM and HS, respectively. There was a significant prevalence of females (76.0%) in all groups. MOH and EM patients had a similar frequency of Beck-D categories ($p=0.1879$), while the HS group had normal values in most cases. Analysing results obtained from Beck-A, Y-BOCS and the MINI scale, a significant higher frequency of psychopathological comorbidities in MOH patients compared to both EM patients and HS group was observed. Univariate analysis showed higher mean values for LDQ score in MOH patients compared to the EM and HS groups ($p<0.0001$ and $p<0.0001$); furthermore, EM subjects had higher scores when compared to HS ($p<0.0001$).

Discussion and conclusions These data confirm the presence of psychiatric comorbidities in patients with MOH, which can contribute to the chronification of pain as well as to the impairment of patient's quality of life, a worse prognosis and a decreased response to treatment: all of which inflict higher health care costs. Therefore, the assessment of psychiatric risk factors should be included in the work-up and management of all MOH patients.

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Short-term psychodynamic psychotherapy versus pharmacological treatment in chronic headache: an observational study

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Introduction About 2-5% of the general population suffers from chronic headache, frequently associated with medication-overuse headache (MOH). Drug withdrawal, followed by prophylactic medication, is the treatment of choice for MOH but there are yet no standardized therapeutic protocols. We demonstrated that a combined pharmacological and short-term psychodynamic psychotherapy (STPP) approach was effective in MOH (Altieri, 2009). Aim of the present observational study was to evaluate if STPP alone might be beneficial in chronic headache.

Methods Patients were recruited according to the ICHD-II criteria. At the first visit, patients were informed of the possibility to choose between a psychotherapeutic or pharmacological treatment, and MOH patients were advised to discontinue the drugs of abuse. They underwent a standardized neurological, psychiatric and instrumental work-up. HIT-6, MIDAS and Depression and Anxiety Hamilton were also acquired. The STPP group underwent 4 meetings in two weeks followed by two months of psychotherapy. The pharmacological group was treated with sodium valproate 600 mg/daily. Follow-up visits were planned at 2, 4 and 8 weeks.

Results We recruited consecutively 60 patients with chronic headache (87% with MOH). STPP protocol was chosen by 35 patients (58%) whereas the remaining did the pharmacological one. There were no significant clinical differences between the two groups.

After 2 months, the STPP group showed a significant decrease in attack frequency (-47%, $p<0.001$), pain intensity (-24%, $p<0.001$) and drug intake (-77%, $p<0.001$). Similar results were observed in the pharmacological group. HIT-6 and Depression and Anxiety Hamilton scores were improved as well in the STPP group.

Conclusions STPP alone may be effective in the treatment of chronic headache as well as valproate therapy. This observation underlines the need of a multidisciplinary approach in treating chronic headache.

Evaluation of the relationship among patients with chronic headache and partner

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Objectives Few studies evaluate the relationship between patients with chronic headache and their partners [1]. So, the main objective of the study was to assess if there was a common relational model among patients with chronic headache and their partners. The secondary objective was to assess the mental representation that the partner has with regard to headache, and the social support perceived by the patient.

Materials and methods Twelve patients with chronic headache and partners who referred to the Headache Centre of the Policlinico of Modena were enrolled. Data collection was carried out using a semi-structured interview (narrative interview). All interviews were audio-recorded, transcribed and qualitatively analyzed according to the model of the Interpretative Phenomenological Analysis.

Results The patients recognized "the emotional closeness of partners" but not the effective support. The perceived social support offered by the significant person was not a source for approaching difficulties and limiting headache. Only patients that had an "open" interaction with their partners, above all, in negative situations, better managed the disease and showed a better adaptive response.

Discussion and conclusions Negative communication with partners is a source of stress and could aggravate perception of pain. A group intervention for patients and partners would be desirable to improve perception of social support and to suggest a potential coping strategy for the management of chronic headache.

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Chronic migraine: an observational, retrospective, multicentre study conducted by the SISC Triveneta Group

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Background Chronic migraine (CM) is a complication of migraine that arises as headache attacks increase in frequency, typically over months to years. Estimates of the worldwide prevalence of CM range approximately from 1.4 to 2.2%, imposing substantial burdens on individual sufferers and their families and, more broadly, upon society.

Materials and methods We retrospectively evaluated 4,583 patients referred to our Headache Centres over the last year.

Results Among these patients, 710 (15.5%) were diagnosed with chronic headache. The most commonly diagnosed chronic headaches were: medication-overuse headache (MOH, 41%), CM (32%) and chronic tension-type headache (20%). Most patients were referred by family practitioners (46%), but several individuals (33%) reported spontaneously. The waiting times averaged 5.1 months for the first examination and 4.4 months for the follow-up visit, respectively. A priority referral for chronic headache was available in 5 of the 9 Centres. On average, the patients with MOH had been overusing acute symptomatic drugs for 30 months. The overused drugs were: combination medications (32%), triptans (27%), non-steroidal anti-inflammatory drugs (21%), and simple analgesics (20%). All the authors of this survey stated that detoxification should always be the first consideration in overusing patients. The detoxification treatment was performed as in-patients in 25% of cases, and as outpatients in the remaining cases, 15% in day hospital, and 60% in day service setting, respectively.

Discussion In our Headache Centres the patients with chronic headache disorders represented more than 15% of all cases. MOH appeared to be more common than CM. The first step in the management of CM complicated by medication overuse should be the withdrawal of the overused drugs.

Conclusions Although CM is highly disabling and prevalent, it remains a poorly understood, underrecognized, undertreated, and underfunded disorder. These findings indicate that there is a significant need to improve the management of CM.

Chronic headache and medication overuse: analysis of patients and medical interventions

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Introduction The lack of standardized approaches makes the evaluation of the outcome of the process of care in patients with chronic headache and medication overuse more difficult than is the case for episodic headaches. The aim of this study was to critically analyse both the characteristics of chronic headache patients and the way they are managed.

Methods We reviewed all the medical records of patients admitted to the Day Hospital of the Headache Centre in the second semester of 2012.

Results Eighty female patients (mean age 52 years) had been admitted to the Day Hospital; 42% of them had already been hospitalized at least once, even in the 3 previous years. The headache had started as episodic with menarche in 38% of patients and it had become chronic on average after 22 years. All patients overused prescription medications: 70% NSAIDs; 49% triptans; 19% combination of indomethacin, prochlorperazine and caffeine; 7.5% combination of codeine and paracetamol; 6.3% combination of butalbital, propyphenazone and caffeine; 6.3% tramadol. Fifty-two percent of the patients had previously taken at least three prophylactic treatments. During hospitalization several lab tests and consultations had been carried out.

Discussion Medication overuse no longer appears as a consequence of the barriers that the headache patients, particularly migraine sufferers, encounter in accessing health care facilities. In fact, most of the patients examined were taking prescription medications, prophylactic treatments and were regularly followed by the Centre and by other specialists for years.

Conclusions Patients with chronic headache and medication overuse are now intensely medicalized without decisive benefits and with the risk that their condition becomes crystallized even more so, as chronic and intractable. This categorization could impede the research of different and more effective interventions by physicians and patients.

Therapeutic aspects of headache

Comparison of frovatriptan versus other triptans in the acute treatment of migraine with aura attacks: pooled analysis of double-blind, randomized, cross-over, multicentre, studies

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Background Approximately 20-30% of people suffering from migraine, experience particularly disabling attacks with aura. Presently no data are available on the efficacy of treating migraine attacks while experiencing signs and symptoms of aura. In this retrospective, pooled analysis of individual data from randomized, double-blind, cross-over, multicentre studies, we evaluated the efficacy of frovatriptan vs. other triptans administered at the onset of a migraine attack with aura (IHS criteria).

Materials and methods Eligible subjects were randomized to frovatriptan 2.5 mg or rizatriptan 10 mg, frovatriptan 2.5 mg or zolmitriptan 2.5 mg, frovatriptan 2.5 mg or almotriptan 12.5 mg. Each patient was asked to treat 1 to 3 attacks with each drug in no more than 3 months, before switching to the other treatment. One hundred and seventeen attacks treated during aura in 56 subjects of the intention-to-treat analysis (mean age±SD: 40±10 years; 91% females) were considered.

Results Pain free at 2-hours did not significantly differ under frovatriptan and comparators [30% vs. 17%; OR: 0.47 (0.19, 1.14), $p=0.091$]. Also pain free episodes at 4-hours were similarly distributed between treatments [frovatriptan: 51% vs. comparators: 40%; OR: 0.64 (0.31, 1.34), $p=0.237$]. Conversely, rate of relapse at 48-hours was significantly ($p=0.002$) less in frovatriptan-treated attacks [67% vs. 90% comparators; OR: 0.22 (0.08, 0.61)]. Additionally, at 48-hours from drug intake, headache intensity was reduced significantly ($p<0.05$) more by frovatriptan than by comparators (76% vs. 58%).

Conclusions Frovatriptan seems to have a similar immediate efficacy, but a more sustained effect and a better tolerability than the other triptans in migraine with aura attacks.

Efficacy of frovatriptan vs. other triptans in week-end migraine: pooled analysis of three double-blind, randomized, crossover, multicentre, Italian studies

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Background Migraine attacks may often occur during days off and evidence

on the efficacy of antimigraine drugs in these weekend migraines is limited. In the present study we evaluated the efficacy of four different triptans in weekend vs. workday migraine attacks through a pooled analysis of individual data from three Italian, randomized, double-blind, cross-over studies.

Materials and methods Subjects with a history of migraine with or without aura were randomized to frovatriptan 2.5 mg or rizatriptan 10 mg, frovatriptan 2.5 mg or zolmitriptan 2.5 mg, frovatriptan 2.5 mg or almotriptan 12.5 mg. Each patient had to treat 1 to 3 attacks with each drug in no more than 3 months. For this retrospective analysis patients with at least one migraine attack without aura on any Saturday or Sunday were selected.

Results One hundred and eighty-eight (54%) of the 346 patients of the intention-to-treat analysis had weekend migraine and were included in the analysis. A total of 569 attacks occurred during the weekend and 1281 during workdays. The proportion of pain free at 2-hours did not significantly differ between weekend and workday attacks for frovatriptan (26% vs. 27%) or for the comparators (34% vs. 32%). Also, pain relief episodes were similarly distributed between weekend and non-weekend attacks (frovatriptan: 40% vs. 42%; comparators: 49% vs. 43%, $p=NS$). Conversely, rate of relapse at 48-hours was significantly ($p<0.05$) less during weekend attacks for frovatriptan (17% vs. 30% workdays), while this was not the case for comparators (weekends 34% vs. workdays 40%, $p=NS$).

Conclusions Our study provides the first evidence that frovatriptan may represent a particularly favourable option for treating weekend migraine attacks.

Relapse in acute migraine treatment: comparison of frovatriptan with other triptans

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Background Beside pain-free and abrupt relief from pain, relapse is a very important outcome parameter for treatment of acute migraine attacks. The International Headache Society (IHS) defined relapse as the most important measure of drug efficacy in clinical trials after pain freedom at 2-hours. We have compared the relapse rates of frovatriptan with those of rizatriptan, zolmitriptan, and almotriptan by pooling together data from three double-blind, randomized, controlled, cross-over trials, with an identical design.

Materials and methods Patients aged 18-65 years with migraine with or without aura (IHS criteria) and having experienced one to six migraine attacks per month for six months prior to entry into the study, were enrolled. Patients had to treat three consecutive migraine attacks with frovatriptan 2.5 mg and three with a comparator (rizatriptan 10 mg, zolmitriptan 2.5 mg and almotriptan 12.5 mg).

Results Three hundred and forty-six patients were included in the intention-to-treat analysis. They treated 987 attacks with frovatriptan and 986 with another triptan. Pain-free at 2-hours did not differ between frovatriptan (30.0%) and the other triptans (34.2%, OR=1.20; CI=0.98-1.46; $p>0.05$). The rate of 24-hour relapse was lower under frovatriptan than under other triptans: 16.2% vs. 23.2% (OR=0.64; CI=0.43-0.95; $p<0.05$). This was the case also for 48-hour relapse rate, which was 26.7% under frovatriptan and 39.7% under comparators (OR=0.55; CI=0.39-0.77; $p<0.001$).

Conclusions Frovatriptan has a lower recurrence rate than the compared triptans and this difference is clinically relevant. The low relapse rate of frovatriptan is likely explained by its specific pharmacological properties with a long half-life time.

Nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen for episodic tension-type headache: a trial sequential analysis (TSA)

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Introduction Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are widely used in the treatment of episodic tension-type headache (TTH). Randomized controlled trials (RCTs) comparing these drugs have given conflicting results. Trial sequential analysis (TSA) is a relatively new statistical technique that improves the interpretation of meta-analyses differentiating cases of demonstrated futility (i.e., proof of no incremental effectiveness) from cases of inconclusive results (i.e., no proof of incremental effectiveness).

Methods We applied TSA to re-analyze the 6 RCTs included in the meta-analysis by Yoon et al. [1]. The end-point was the rate of patients with less than 50% pain relief (failure rate). Assumptions of TSA included two-sided testing, risk of type 1 error=5%, and power=80%. The reference effect was set at a failure rate of 36.2% (equal to the cumulative arithmetic rate of the 6 acetaminophen arms). Two values of relative risk reduction (RRR) were tested (RRR=33% and RRR=20%); accordingly, two separate TSA were carried out.

Results The cumulative number of included patients from the 6 RCTs was 2,162. The TSA based on the assumption of RRR=33%, was inconclusive (the optimal information size was estimated at 2,851 patients). The other TSA (assumption: RRR=20%) was inconclusive, too. The optimal information size was estimated to be of 8,087 patients.

Discussion and conclusions To reach a conclusion based on an anticipated relative difference of 20% in failure rates, another 6,000 patients would be needed to appropriately settle this therapeutic question. Future RCTs are therefore needed to investigate the relative effectiveness of NSAIDs vs. acetaminophen.

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Dexketoprofen trometamol in the acute treatment of migraine attack: a phase II, randomized, double-blind, crossover, placebo-controlled, dose optimization study

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Background Migraine is a disabling disease that significantly affects the quality of life. NSAIDs are indicated for treatment of mild-moderate attacks or when triptans are contraindicated/ineffective. In the present study we evaluated efficacy and tolerability of dexketoprofen 25 mg (DKP25) and 50 mg (DKP50) compared to placebo (PLB) for migraine treatment.

Materials and methods This randomized, double-blind, single-centre, cross-over, placebo-controlled study was performed in 93 patients with at least one migraine attack per month in the preceding 6 months. Participants were enrolled and randomized to DKP25, DKP50 and PLB. Primary endpoint was pain-free at 2h after drug intake. Secondary end points were pain-relief episodes at 2h, any functional disability, the presence of accompanying symptoms and tolerability.

Results Seventy-six patients (mean age 40.5±10.9 and 61% female) com-

pleted the study. At baseline, mean number of attacks/month was 3.7 ± 1.3 , with a mean duration of 15.4 ± 13.5 h.

The rate of pain-free at 2 hours was higher in DKP50 group than in PLB group (34% vs. 15%, $p < 0.05$).

DKP25 and DKP50 improved headache relief at 2h compared to PLB (DKP25: 57%; DKP50: 65%; PLB: 25%, $p < 0.001$), and reduced the disability (DKP25 vs. PLB: 40% vs. 24%, $p = 0.045$; DKP50 vs. PLB: 46% vs. 24%, $p < 0.0004$). The proportion of patients with recovery of photophobia and phonophobia after 2 hours was higher with DKP25 (46% and 52%) and with DKP50 (72% and 44%) compared to PLB (24% and 24%, $p < 0.05$). Resolution of nausea was higher with both doses of DKP (62–64%) compared to PLB (33%). The recurrence of AE was similar to placebo.

Conclusions Both doses of DKP were effective for acute migraine treatment. Both DKP dosages were well tolerated.

tDCS treatment: first experience in drug resistant migrainous patients

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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. A multicentre observational study using (tDCS) in the treatment of migraine has been carried out. **Material 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, University of Padova and Pavia Headache Centre. Patients with a history of acute neurological, psychiatric or medical disease, family history of epilepsy, pregnancy, cardiac pacemaker or previous surgery involving implants in the head were not included in the study. Patients underwent electrical (n=30) or sham (n=30) stimulation, in 5 treatment sessions every other day for 10 minutes. The present study included a follow up at t30, t60, t90 and t120. For each patient headache frequency, duration and intensity (VAS), headache days per month and the response to symptomatic therapy were evaluated; and also a list of the 5 main precipitating factors was collected.

Results Primary endpoint was the reduction of at least 50% of the headache clinical parameters. Secondary endpoint was the assessment of the plausibility of decreasing threshold of cortical excitability by evaluating response to triggers.

At t30 a reduction of at least 50% of the parameters evaluated in almost 75% of the patients treated with tDCS was observed, while, at t60 the benefit was maintained for approximately 30% of treated patients.

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 efficacy both of pharmacological treatment and tDCS treatment.

Conclusions tDCS has been introduced as a non invasive tool to guide neuroplasticity and to modulate cortical function by tonic stimulation with weak direct currents. Studies involving patients affected by chronic pain confirm that tDCs can produce long-lasting pain relief.

Efficacy and tolerability of antiepileptic drugs in epilepsy and migraine diseases

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Background Both migraine and epilepsy are chronic disorders characterised by transient and recurrent neurological symptoms. The two disorders often occur together and share some clinical-therapeutic characteristics. In clinical practice, differences emerge for the tolerability, safety and side effects (SEs) of drugs used for both disorders, which seem to be disease-related. Therefore, we interviewed patients treated with anti-epileptics drugs (AEDs) suffering from epilepsy, migraine, or both diseases.

Methods We collected the SEs associated with valproic acid (VPA), topiramate (TPM) and lamotrigine (LTG) use for the prophylactic therapy of migraine, epilepsy as well as both disorders.

Results Over the last year, we interviewed 243 out-patients (pts): 93 with epilepsy (E-pts), 90 with migraine (M-pts) and 60 patients with both diseases (EM-pts); all three groups received valproic acid (VPA), topiramate (TPM) or lamotrigine (LTG) that have proven to be effective in about 80% of all cases. Overall, 60.2% of all patients have reported SEs; these have been more frequent in M-pts (more than 86%) compared to E-pts (45%). TPM has been the most widely used drug for migraine prophylaxis. Its most frequent SEs include paresthesias (in 50% of M-pts and 28% of E-pts) and language disorders. Whereas, weight gain has been recorded in 54% of M-pts taking VPA compared to 16.3% of E-pts. In addition, more than 25% of M-pts and 15% of E-pts have suspended medication because of significant SEs.

Discussion Our data confirm the safety and effectiveness of AEDs in clinical practice but highlight the relevance of SEs in determining discontinuation [1]. Greater prevalence of SEs, due to AEDs in migraineurs compared to E-pts, has been demonstrated even if AED (VPA, LTG and TPM) dosage has been markedly lower than those used in E-pts.

Thus, the mechanisms which underlie the different prevalence of SEs in migraineurs and epileptics need to be further investigated.

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Diagnostic-rehabilitative pathways in cervicogenic headache, tension-type headache and migraine: randomized controlled trial between pharmacological and physiotherapy approaches

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The aim of this study was to verify the efficacy of an individual physiotherapy treatment based on a protocol assessment of cervical spine disorders in headache patients. Patients with cervicogenic or tension-type headache (CeH, TTH) and migraine that were not taking a pharmacological prophylaxis in the last 3 months were enrolled at the Headache Centre of Trieste.

CeH and TTH underwent a combined protocol of postural advice, exercises and manual therapy versus a control group with Laroxyl; migraine underwent Documentation Based Care protocol of strengthening and mobilization versus a topiramate prophylaxis control group. A follow-up at six months was carried out.

The physiotherapy protocol involved: 4 CeH, 7 TTH and 15 migraine patients; the control group involved: 4 CeH, 14 TTH and 19 migraine patients. CeH: 2 patients of the physiotherapy group abolished the symptoms completely, as confirmed at follow-up. Three patients of the control group had significant improvements in frequency and duration but symptoms were not eliminated. TTH: pain intensity improved only in the physiotherapy group ($p = 0.0156$);

frequency had comparable improvements in both groups ($p=0.0156$ and 0.0005), while duration improved only in the control group ($p<0.0001$).

Migraine: pain intensity improved in both groups with comparable results ($p=0.0156$ and 0.0195); while the other parameters improved only in the control group ($p<0.0001$ and 0.0026).

There were significant improvements at the Questionnaire NPDS-I in TTH and ESA ($p=0.0156$ and 0.098) and 50% of CeH had a score of 0 at the end of the physiotherapy treatment. The individualized physiotherapy treatment yielded positive results in patients with CeH, comparable results with the pharmacological prophylaxis in TTH and limited results in migraine.

Treatment of drug-resistant headache and cranio-facial pain by occipital nerve stimulation

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Introduction Many targets for treating headache disorders and cranio-facial pain syndromes with neurostimulation have been described; recently good outcome has been reported with subcutaneous leads placement at C1 level and stimulation of the greater occipital nerve [Occipital Nerve Stimulation (ONS)]. **Materials and methods** From January 2008 to January 2012, we implanted leads for ONS in 15 patients with chronic drug-resistant headache and cranio-facial pain syndromes: occipital neuralgia (4 cases), cervicogenic headache (1 case), TACs (6 cases: 3 chronic cluster headache, 2 chronic paroxysmal hemicrania, 1 SUNCT), migraine (2 cases) and transformed migraine (2 cases). In 8 cases lead was implanted bilaterally. External stimulation trial of 7-15 days was performed. Twelve patients obtained pain improvement $>50\%$ and significant improvement in QoL (4 occipital neuralgia, 1 cervicogenic headache, 3 chronic cluster headache, 2 chronic paroxysmal hemicrania, 1 SUNCT, 1 transformed migraine): they underwent neurostimulator implant. Stimulation parameters were 1.5-9.0 Volts, 30-60 Hz, 90-400 microsec, bipolar configuration, cyclic mode. Follow-up was 3-48 months, average 21 months.

Results Up to now 8 patients (66.6%) are "responders" (pain improvement $>70\%$) and 4 patients (33.4%) are "remittent" (complete or nearly complete pain control). Best results were achieved in occipital neuralgia, cervicogenic headache and trigeminal autonomic cephalalgias (TACs). Among TACs chronic cluster headache showed delayed improvement of attacks with maximal effect after months: higher voltage of stimulation (5-9 V) and consequent early battery depletion. Complications were 3 lead migrations, 1 skin erosion and 2 subjective tension perception in cervical area.

Conclusions Occipital nerve stimulation is a safe and well tolerated possibility of treatment for selected patients with severe headaches and cranio-facial pain syndromes resistant to medications and other conservative therapies.

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Latest breaking news in basic science of migraine

Abnormal synaptic morphology and neuronal Ca^{2+} -homeostasis in migraine mutant mice

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Background Familial hemiplegic migraine (FHM) is caused by gain-of-function mutations (e.g., S218L) of $Ca_v2.1$. Excitatory neurotransmission may be enhanced, and, *in vivo*, FHM1 mice show enhanced susceptibility to cortical spreading depression (CSD). CSD, the electrophysiologic event underlying migraine, is a transient disruption of membrane ionic gradients that propagates across cortex.

Objectives To assess neuronal structure and intracellular Ca^{2+} -levels ($[Ca^{2+}]_i$) at baseline, during and after CSD in transgenic mice for familial hemiplegic migraine.

Methods *In vivo* 2-photon microscopy images of cortical layers were obtained 5 weeks after intracortical injection of the genetically encoded Ca^{2+} -indicator Yellow Cameleon (AAV2-YC3.6), in female wild type (WT) and S218L transgenic mice. YFP/CFP ratios were measured, and exact $[Ca^{2+}]_i$ can be determined because YC3.6 is a FRET based indicator. SD was evoked by KCl (300 mM). Before and after CSD, we assessed a cortical volume of 600x600x100mm depth. During CSD, we performed singleplane timecourse movies 30-40 mm deep.

Results At baseline, $[Ca^{2+}]_i$ was higher in S218L. During CSD, $[Ca^{2+}]_i$ abruptly increased by ~3-fold, and then declined to a plateau. The onset of calcium increase, peak and plateau $[Ca^{2+}]_i$ were higher in S218L, in both axons and dendrites. Acute and transient structural changes of neurons during CSD (e.g. density, diameter, or duration of dendritic beading) did not differ. We found structural differences in neuropil, at baseline and after CSD. At baseline, the average area of an axonal varicosity was larger in S218L. Ten minutes after CSD, the density of axonal varicosities increased, and their area decreased. The percentage of mushroom type spines increased. In S218L, the diameter of dendritic spine head increased.

Conclusions FHM1 mutations increase $[Ca^{2+}]_i$ at baseline and during CSD, and alter axonal morphology as well as lasting structural changes after CSD.

Changes in glutamatergic neurotransmission within the migraine cycle: evidence by repetitive transcranial magnetic stimulation (rTMS)

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Introduction Although some neurophysiological studies have showed 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 rTMS in order to indirectly study presynaptic mechanisms of glutamatergic neurotransmission across the different phases of the migraine cycle.

Methods Fifty migraine with aura (MwA), 50 migraine without aura (MwoA), 10 chronic migraine (CM) patients and 20 healthy subjects underwent suprathreshold (120% 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 with episodic migraine were studied whatever the phase of the migraine cycle: interictal, preictal, ictal or postictal.

Results In the interictal phase, both in MwA and MwoA patients, MEPs responses changed according to attack frequency showing: increased facilitation in patients with a lower attack frequency and paradoxical inhibitory response in those with higher attack frequency, as compared to controls. A significant greater inhibitory response was recorded during the ictal and post-ictal phase as well as in CM patients. Conversely, in the pre-ictal phase, we ob-

served a facilitatory response to the trains similar to that of normal subjects. No significant differences were recorded between MwA and MwoA patients.

Discussion and conclusions Our results support the hypothesis that in migraine a transient increase in the threshold for inhibitory homeostatic mechanisms could favor the onset of a migraine attack. The strong activation of inhibitory homeostatic mechanisms of glutamate release could be involved, in patients with episodic migraine, in the resolution of the migraine attack and in preventing further attacks. In CM patients these mechanisms could become ineffective due to an excessive lowering in the attack threshold.

A history of migraine accelerates infarct growth in stroke patients

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Background Migraine is an independent stroke risk factor, particularly in otherwise healthy persons. A migraine history increases stroke risk, especially in young females suffering from migraine with aura (6-fold). Recent animal experiments suggest that migraine mutations increase brain vulnerability to ischemia via excitatory mechanisms [1]. Migraine mutant mice develop higher number of ischemic depolarizations and accelerated infarct growth during hyperacute stroke, with worse outcomes. Anti-excitatory treatment prevents this severe stroke phenotype.

Objectives To assess acute stroke evolution in patients with a documented migraine history.

Methods We retrospectively analyzed lesion volumes on diffusion-weighted imaging (DWI), and the volume of perfusion defect on perfusion-weighted imaging (PWI) using mean transit time (MTT), from consecutive patients in Massachusetts General Hospital stroke database (years 2003-2012). Measurements were done blinded to migraine status.

Results A total of 155 stroke patients had reliably documented presence or absence of a migraine history. Stroke patients with a migraine history were younger and more often female, compared to those without. Migraineurs less frequently had coronary artery disease or diabetes. The frequency of posterior circulation lesions was significantly higher in migraineurs. Otherwise, groups were comparable. In patients with PWI scans, DWI-PWI mismatch was calculated on spatially co-registered DWI and MTT maps, as a marker for viable tissue at risk for infarction. In migraineurs, a larger area of the perfusion defect showed DWI changes, resulting in smaller DWI/PWI mismatches. Indeed, a larger proportion of migraineurs showed no mismatch (i.e., DWI/PWI>0.9; without aura $p=0.011$, with aura $p=0.002$), indicating that the entire perfusion defect was already infarcted.

Conclusions Our data show that a history of migraine, particularly with aura, is associated with accelerated acute infarct growth. A prospective case-control study is warranted to confirm and extend these data. With regard to stroke treatment, data suggest a shorter therapeutic window for acute stroke interventions in migraineurs, due to rapid loss of salvageable brain tissue.

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Quadripulse repetitive transcranial magnetic stimulation on visual cortex for chronic migraine prevention: a pilot-trial

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Background Chronic migraine can be compared to a “never ending attack” [1] with normal habituation of visual-evoked cortical potentials and an increase cortical preactivation level.

Quadripulse repetitive transcranial magnetic stimulation (QP rTMS) is able to durably modify the excitability of the underlying cortex.

Methods We recruited 10 patients suffering from chronic migraine with and without medication overuse (ICHD-2 1.5.1; 2 8.2). All had stable preventive treatment for at least 2 months.

We applied QP rTMS with a 50ms ISI (4 pulses at 20 Hz every 5 s for 30 minutes – intensity of stimulation: 80% of phosphene or 90% of motor thresholds) over the visual cortex (Oz), twice a week for 4 weeks. Patients filled in a headache diary before (T0), during (T1) and after treatment (T2).

Results A majority of patients improved significantly after QP rTMS therapy. Migraine days decreased on average from 20/month at T0 to 11/month at T1 (-47%, $p<0.05$) and severe attacks were reduced by 54% ($p<0.05$). At T2 the clinical improvement remained stable with 48% reduction compared to baseline ($p<0.05$). There were no adverse events. Interestingly, medication overuse did not modify the response to QP rTMS therapy.

Conclusions This pilot trial demonstrates for the first time that 2 weekly sessions of inhibitory QP rTMS can be effective in the preventive treatment of chronic migraine. The therapy significantly reduced migraine days and 70% of patients reversed from chronic to episodic migraine. These results indicate that a large sham-controlled trial is worthwhile in chronic migraine.

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Sleep deprivation enhances susceptibility to cortical spreading depression

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Background Many factors that modulate migraine (e.g., sex hormones, migraine prophylactic drugs) have been shown to also modulate in the same direction susceptibility to cortical spreading depression (CSD), the electrophysiologic event underlying migraine. Changes in sleep rhythm and sleep deprivation are well-known migraine triggers. Sleep deprivation modulates neocortical excitability both in humans and in animal models. Sleep deprivation can facilitate the migraine chronification and trigger attacks.

Objectives To investigate the effect of sleep deprivation, a well-known migraine trigger, on CSD susceptibility.

Methods Acute sleep deprivation was induced for 6h or 12h starting with daylight, using the “gentle handling method” [1] in male Sprague-Dawley rats (340±40g). Control group was kept in the same environment but undisturbed to allow sleep. Following sleep deprivation, rats were anesthetized, and femoral artery cannulated to monitor arterial blood gas and blood pressure. Rats were intubated and ventilated to maintain a normal systemic physiologic state. CSD susceptibility was assessed by measuring the frequency of CSDs evoked by topical KCl (1M), or using the direct cathodal stimulation intensity threshold (bipolar electrode, 1-800mC). Amplitude, propagation speed, and duration of CSD were also recorded. All experiments were done blinded. Data are mean ± standard deviation.

Results Sleep deprivation increased the frequency of CSDs ($p=0.01$ and 0.007 , 6h and 12h sleep deprivation, respectively) and decreased the electrical CSD threshold ($p=0.095$ and 0.037 , 6h and 12h sleep deprivation, respectively) in a duration-dependent manner compared to controls. Other CSD parameters and systemic physiology did not differ between groups.

Conclusions In keeping with other migraine modulators, sleep deprivation enhances CSD susceptibility to explain its mechanism as a migraine trigger. Our data underscore the importance of CSD as a migraine substrate that can be targeted therapeutically.

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Diffuse noxious inhibitory controls are differentially modulated by attention to the pain intensity and the early electrodermal activity to a laser-heat stimulus

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Introduction Diffuse noxious inhibitory controls (DNIC) is a physiological system, inhibiting a phasic pain by the heterotopic application of a counterirritation pain. DNIC seems to be altered in migraine and tension-type headache. Attention and stimulus salience influence widely pain modulation. However, the role of attention in DNIC modulation is still controversial. **Material and methods** Three control (1st, 3rd, 5th) and three counterirritation (2nd, 4th, 6th) blocks of ten pain stimuli were alternated in a multi-block design. Test-pain was delivered by Thulium-YAG laser on the left hand while counterirritation by foot submersion in 4°C water. Participants were split into 2 groups according to an attention-demanding task. High-attention (HA, $n=23$) group rated every laser pulse during all blocks; low-attention (LA, $n=20$) group gave an estimate of stimuli painfulness per block. Individual salience to pain was measured by electrodermal activity (EA). Behavioral pain scale (VAS) and N2-P2 laser-evoked potentials (LEPs) were used to record response to test-pain and calculate VAS-DNIC and LEPs-DNIC separately.

Results HA group showed a lower VAS score in 1st, 2nd and 3rd blocks vs. LA group ($p<0.01$). The higher pain reduction, associated to a greater DNIC ($p=0.02$), was found in the 2nd (counterirritation) block in HA group vs. LA group. A negative correlation between EA in 1st block and following LEPs-DNIC ($r=-0.21$; $p=0.03$) was found: the higher the EA value, the lower LEPs-DNIC.

Conclusions HA group showed a high pain reduction of VAS score, possibly due to the higher cognitive-demanding task. Conversely, DNIC-mediated analgesia seems to be independent from attention and proportional to the early EA. The pain reduction in 2nd block seems to be due partially to attention and partially to DNIC suggesting a cooperation of these two mechanisms.

Neuroscience and Pain

Nocebo effect dissociates the laser-pain rating from the N2/P2 laser evoked potential amplitude

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Introduction The present study aimed at investigating whether LEP amplitude and subjective perception of laser-pain could undergo placebo effect.

Materials and methods Ten subjects underwent either a conditioning placebo session (CNS) or a learning placebo session (LNS). At time 0 (baseline), LEPs were acquired from both right and left hand stimulation. At time 1, Vaseline was applied on the right hand and subjects were informed that they were receiving an hyperalgesic cream. In CNS, LEPs were recorded from both right and left hand using the same stimulus intensity as in the baseline. In LNS, right hand LEPs were recorded initially by a stimulus intensity increased surreptitiously, so as to make the healthy volunteers believe that the hyperalgesic treatment really worked. Then, Vaseline was applied again and right and left hand LEPs were recorded at the same stimulus intensity as in the baseline. After each LEP recording, subjects were asked to rate laser-pain, by using a 101-points numerical rating scale (NRS).

Results In CNS, laser-pain rating to right hand stimulation was increased after placebo treatment, as compared to baseline. On the contrary, in both CNS and LNS the N2/P2 amplitude change induced by placebo treatment, as compared to the baseline, was not different for both right (experimental) and left (control) hand stimulation.

Conclusions Our results support the hypothesis that LEP amplitude cannot be considered as an objective measure of laser-pain perception.

Brain activity associated with temporal summation of pain in healthy subjects

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Introduction Temporal summation (TS) of pain represents a form of short term neuronal plasticity which, through a temporary change in sensory neurons excitability, shifts the sensory information from tactile to nociceptive. This phenomenon is relevant in pain pathophysiology, including central sensitization and chronic pain, in which activity-dependent changes in the excitability of central neurons give rise to an abnormal TS of pain stimuli. TS of pain develops in parallel with TS of electrically induced nociceptive withdrawal reflex (NWR) of the lower limb, resulting in an objective representation of TS of pain. We used fMRI to determine which brain sites play a key role in TS of NWR, comparing different sets of stimulation.

Materials and methods Ten pain-free healthy subjects underwent fMRI scanning during sural nerve stimulation with one (painful), three (non-painful) or five (TS of pain) stimuli randomly delivered.

Results fMRI statistical maps identified several brain regions with single nociceptive stimulus dependent activation, including prefrontal cortex, anterior insula and amygdala and with repetitive stimulation dependent activation consistent with TS of NWR, including thalamus, somatosensory, anterior and posterior insula and cingulate cortex.

Conclusions These results show that brain activations associated with TS of NWR occur in areas involved in somatosensory processing as well as in cognition and affect, and are prominent in cingulate cortex that serves pain modulation and could be involved in the development of chronic pain.

Peripheral and central nervous contribution to gastrointestinal symptoms in diabetic patients with autonomic neuropathy

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Introduction To explore the role of diabetic autonomic neuropathy (DAN) in patients with long-standing diabetes mellitus (DM), we investigated psychophysical responses and neuronal activity recorded as evoked brain potentials and dipolar source modelling.

Methods Fifteen healthy volunteers and 14 type-1 DM patients with DAN were assessed with a symptom score index characterizing upper GI abnormalities. Multichannel electroencephalography was recorded during painful electrical stimulation of the lower oesophagus. Brain activity to painful stimulations was modelled using Brain Electrical Source Analysis.

Results Diabetic patients had higher stimulus intensities to evoke painful sensation ($p \leq 0.001$), longer latencies of N2 and P2 components (both $p \leq 0.001$), and lower amplitudes of P1-N2 and N2-P2 complexes ($p \leq 0.001$; $p = 0.02$). Inverse modelling of brain sources showed deeper bilateral insular dipolar source localization ($p = 0.002$). Symptom score index was negatively correlated with the depth of insular activity ($p = 0.004$) and positively correlated with insular dipole strength ($p = 0.03$).

Discussion and conclusions DM patients show peripheral and central neuroplastic changes. Moreover, the role of abnormal insular processing may explain the appearance and persistence of GI symptoms related to DAN.

Heterogeneous phenotypes in a family with Nav 1.7 new mutations

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Background and aims The literature currently suggests that voltage-gated sodium channels mutations play a major role in the pathogenesis of some neuropathic pain, and in Small Fibre Neuropathy (SFN)

Methods We describe a family carrying Nav 1.7 mutation (exon 15 2794A>C M932L, exon 16 2971G>T V991L, exon 25 4612T>C W1538R). The father is asymptomatic while the daughter complained of severe neuropathic pain for years, with paroxysmal crisis, positive sensory signs (allodynia, hyperesthesia) and autonomic complaints.

Results The clinical, neurophysiological and neuropathological evaluations were consistent with SFN only in the daughter, by studying Thermal Quantitative Sensory Testing, Laser Doppler Flowmetry, Laser Evoked Potentials, Nerve Conduction Study (NCS) and skin biopsy.

Conclusions The heterogeneous phenotypes observed in the two carriers of the same complex mutations, together with the different results obtained by instrumental examinations, can confirm the possible role of unknown epigenetic, environmental aspects or gene modifiers.

Prevalence and characteristics of neuropathic pain in traumatic brachial plexopathy

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Objectives Aims of the study were: 1) to assess the prevalence and the characteristics of neuropathic pain (NeuP) in traumatic brachial plexopathy (TBP); 2) to evaluate the quality of life (QoL) in TBP by using dedicated scales.

Methods We collected 107 patients (85 M, 22 F; mean age: 42.4±12.3) with TBP. All patients underwent a detailed clinical examination, clinical questionnaires and neurophysiological tests (EMG). Chronic pain was defined in presence of pain in the last 30 days. The intensity of pain was assessed with the Numerical Rating Scale. In all patients with pain the DN4 questionnaire was performed; in patients with a DN4 score ≥ 4 , NPSI, Beck Depression Inventory and Quality of life scale (SF-36) were fulfilled.

Results NeuP prevalence was 56%. Paroxysmal pain and paresthesia/dysesthesia had higher values at NPSI. TBP patients with chronic pain had worse SF-36 scores, with a strong correlation between QoL and NeuP.

Discussion To define different types of pain may have a great impact in a new classification strategy for NeuP. In TBP sensory profiles assessment of NeuP could play an important role in a successful pain management; therefore, results of this study could be crucial to plan future clinical trials with the aim to evaluate the efficacy of NeuP pharmacological treatment in TBP.

Pain in stroke patients: characteristics and impact during rehabilitation treatment

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Introduction A previous study on post-surgical orthopaedic rehabilitation showed pain may delay the rehabilitation pathway.

Objectives The main objectives of this study were: a) quantification and characterization (nociceptive/neuropathic) of pain in a wide sample of patients undergoing post-stroke rehabilitation; b) evaluation of occurrence of interaction between pain and rehabilitation process.

Materials and methods We studied 106 patients, 52.6% males, mean age 70.9 yrs (SD: 12.9), range 32-91. The intensity of pain was assessed by using Numeric Rating Scale (NRS); moreover, pain features were dissected through DN4, a discriminative tool to investigate the occurrence of neuropathic pain. The health-related quality of life was measured by using the Italian version of the Short Form 36 Health Status Survey (SF36). In order to evaluate whether the pain interfered with the rehabilitation act and plan, data derived from a specifically designed structured questionnaire for the physiotherapist were acquired.

Results In one third of the sample the Pain Assessment in Advanced Dementia Scale was used to measure pain (for cognitive/language impairment); about half of them (48.5%) presented a score of ≥ 3 . Patients with normal cognitive/language 24.7% referred a NRS ≥ 3 and 8.2% had a DN4 ≥ 4 (meaning neuropathic origin of pain). In 32.9% of cases pain influenced rehabilitation treatment (in particular 46.2% modified, 50.0% slowed down and 3.8%

stopped rehabilitation programme). Moreover 74.1% (20/27) complained of pain during the rehabilitation session. In 65.4% of the cases pain caused a reduction of the attention of the patient during rehabilitation treatment.

Discussion The results show pain is an important element in the rehabilitation of stroke patients. In many cases pain may contribute to limit the attention of the patient during rehabilitation treatment.

Conclusions Preliminary data from the study on Don Gnocchi rehabilitation centres, showed that pain has a relevant role in the rehabilitation treatment.

Sensory profiles in diabetic neuropathic pain: a tool for stratification of patients according to their underlying pathophysiology?

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Background Neuropathic pain (NP) a frequent complication of diabetes mellitus (DM), but its pathophysiology is unclear. Pain sensory profile (SP) (i.e., the subjective and objective sensory changes associated with pain) may represent a tool for stratifying patients with diabetic NP according to the underlying pain pathogenesis.

Aims To explore subjective and objective SP of patients with diabetic NP and to define them according to the clinical and demographic variables, examine the role of small vs. large fiber involvement.

Results We recruited 53 patients and collected their clinical and demographic variables, NP subjective and objective SP and electrodiagnostic data. Serum cytokines were examined in a subgroup of patients in an attempt to correlate them to SP. Negative QST signs were significantly higher in patients with NP. Cluster analysis documented different subgroups of DM patients according to their subjective and objective SPs. Serum cytokines were correlated to large nerve fiber damage.

Conclusions Despite their clinical heterogeneity, patients with diabetic NP may be clustered according to their SP. These clusters may represent a key for better understanding the pathophysiology of diabetic NP and to stratify the patients for future therapeutic trials.

Processing of nociceptive input in patients with schizophrenia: preliminary results

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Introduction According to previous studies schizophrenic patients have a reduced perception of pain.

Objectives We aimed at assessing pain thresholds and nociceptive pathway function in schizophrenic patients by using Quantitative Sensory Testing (QST) and Laser evoked potentials (LEPs).

Methods We planned to enroll 30 patients with a diagnosis of schizophrenia and 30 age and sex matched healthy controls. At present we have enrolled 8 schizophrenic patients and 10 healthy controls. All subjects underwent QST and right hand LEPs.

Results Although QST parameters did not show statistical significance between schizophrenic patients and normal controls, the cold pain threshold approached the statistical significance ($p=0.08$, unpaired t -test). Conversely,

the amplitude of all LEP components was significantly lower in patients than in controls ($p<0.05$).

Conclusions These preliminary data suggest that schizophrenic patients have an abnormal processing of nociceptive input. These abnormalities might reflect a dopaminergic dysfunction.

Quantification of epidermal nerves by immunofluorescence and bright-field microscopy: a comparative study

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The assessment of epidermal nerve fiber density (ENF) in skin biopsy has been accepted as an objective and reliable technique to diagnose SFN. Two different methods, bright-field microscopy and immunofluorescence with or without confocal microscopy, are currently used in the clinical practice to quantify ENF. Overall, from previous published reports, normal values of ENF with immunofluorescence are higher than those obtained with bright-field microscopy, but no study has been specifically designed to compare the two methods. The aim of this study was to evaluate the agreement between the two techniques of ENF analysis. We recruited 63 subjects, 20 healthy controls (12 men and 8 women, age 41.6 ± 11.3 years, range 27-68) and 43 patients affected by small fiber neuropathy (21 men and 22 women, age 57.7 ± 14.4 years, range 22-82) from three Centres (Milan, Rome and Telese Terme). We obtained 2 adjacent skin samples (about 2 mm apart), using a 2.5 or 3 mm punch, from distal leg, after local anesthesia with lidocaine. One sample was immediately fixed in Zamboni for immunofluorescence and the other in 2% PLP for bright-field microscopy. Following standardized procedures, samples for immunofluorescence were processed and analyzed in Telese, whereas samples for bright-field microscopy were processed and analyzed in Milan and Rome. Mean ENF density (f/mm) was 13.4 ± 4.5 with immunofluorescence and 6.0 ± 2.1 with bright-field microscopy in normal subjects and 9.0 ± 4.6 with immunofluorescence and 4.0 ± 2.6 with bright-field microscopy in SFN. The mean ratio between the two methods was 2.2 ± 0.3 in controls and 2.8 ± 1.4 in patients. We found a significant agreement between the two methods (overall $p<0.001$, $r=0.83$; in controls $p<0.001$, $r=0.90$; in patients $p<0.001$, $r=0.77$). Our study demonstrates that the two techniques are comparable, even considering the biological variability that has to be taken in account when two different skin samples within the same area are analyzed. We also confirm that the values of ENF density obtained with immunofluorescence are higher than the ones obtained with bright-field microscopy.

Laser evoked potentials habituation in irritable bowel syndrome

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Introduction The mechanisms of most chronic pain syndromes are only partially understood. Intense and/or long-lasting afferent barrage can strongly contribute to central sensitization and often seems to be associated with abnormal endogenous pain modulation. Many patients with chronic pain dis-

orders show evidence of increased facilitation and decreased or absent inhibition of pain. Majority of Irritable Bowel Syndrome (IBS) patients have both rectal and somatic hypersensitivity. Local rectal anesthesia reduces rectal and somatic pain in irritable bowel syndrome patients, supporting the possibility that visceral hyperalgesia and secondary cutaneous hyperalgesia is the result of central sensitization dynamically maintained by input from the GIT. The aim of this study was to evaluate the cortical responses to laser stimuli and pain modulation in patient with IBS.

Materials and methods Fifteen outpatients with a IBS diagnosis and 15 controls subjects were examined. We registered 62 channels laser evoked potentials while patients received three trains of 21 laser stimuli at 10-12 sec ISI delivered on the right hand and right periumbilical region. We evaluated habituation by comparing the average of the first group of seven stimuli with the last group of the same series. Psychopathological assessment was performed with Stai I, Stai II, BDI, MAF, MOS, SF36 and Dn4 scales.

Results We found a normal N2-P2 amplitude and latency after stimulation of periumbilical region with a reduction of habituation in both sites.

Discussion and conclusions These results can be expression of a central sensitization that appears to involve this pain hypersensitivity syndrome which may share the same mechanism underlying fibromyalgia and other chronic pain conditions.

Neurophysiological study of cutaneous silent period in demyelinating and axonal polyneuropathies

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Introduction Cutaneous silent period (CSP) is a pause in voluntary muscle contraction following painful cutaneous nerve stimulation which allows to study small-myelinated fibres. We investigated CSP in patients with demyelinating and axonal polyneuropathy (PNP) and explored correlation between CSP changes and neuropathic pain.

Materials and methods Eighty demyelinating PNP patients, 178 axonal PNP patients and 265 controls underwent clinical (neurological examination, Medical Research Council Score, DN4-Questionnaire,) and electrophysiological (motor root conduction time, compound muscle action potentials, sensory nerve action potentials and CSPs of the ulnar nerve) investigations. Another parameter showing the difference between the CSP latency and the MRCT, was also calculated, in order to evaluate the conduction of the afferent fibre network.

Results In the demyelinating PNP group, all electrophysiological latencies were longer with respect to the axonal PNP group and the controls ($p=0.0001$); axonal PNP group had shorter CSP duration with respect to the controls ($p=0.0001$). Axonal PNP patients suffered from painful sensations more than the demyelinating PNP patients ($p=0.02$) but CSP parameters were not different among painful and painless patients.

Conclusions Our findings confirm in a large number of patients that CSP evaluation is effective to study small-fibres dysfunction in the afferent sensory pathway in both axonal and demyelinating PNP. The lack of correlation between shortened CSP duration and presence of neuropathic pain suggest that neuropathic pain could be influenced primarily from plasticity change in the spinal cord.

Spinal direct current stimulation is able to modulate the temporal summation of pain at spinal level in healthy subjects

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Introduction To best characterize the potential analgesic effect of spinal Direct Current Stimulation (sDCS), we investigated the effect of sDCS on the temporal summation threshold (TST) of the lower limb nociceptive withdrawal reflex (NWR) that develops in parallel with the temporal summation of pain and reflects the level of facilitation in pain processing at spinal level. **Subjects and methods** Ten healthy volunteers underwent recordings of TST before sDCS stimulation (baseline) and immediately (T0), 30 minutes (T30) and 60 minutes (T60) after DCS offset. sDCS treatment (2 mA, 15 minutes) applied in correspondence of spinal process of the tenth thoracic vertebra and to the right shoulder. Each subject underwent three treatment conditions (anodal, cathodal and sham) tested randomly in a double-blind, cross-over design, with an inter-session elapse of at least one week. The terms of anodal or cathodal refers to the electrode positioned at the spinal level.

Results TST was significantly increased at T30 and T60 minutes after anodal sDCS, whereas cathodal and sham stimulation left TST unchanged across sessions.

Conclusion and discussion Our data demonstrated that sDCS is able to modulate TST in healthy volunteers. In consideration of our hypothesis these results may suggest a possible application of sDCS in chronic pain conditions.

Usefulness of the association of laser evoked potentials and skin biopsy for the diagnosis of neuropathic pains with similar clinical presentation and different pathophysiological mechanisms: two case reports

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Case 1 A 77-year-old female patient with chronic, spontaneous pain on the left side of her face, after trigeminal radiofrequency rhizotomy for treatment of classical trigeminal neuralgia.

Method (1) The tactile, pin-prick and warm sensations were investigated using respectively a soft brush, a needle, and a thermal roller (40°C); (2) the A-delta fibre pathways were assessed by YAP laser evoked potentials (LEPs); (3) the epidermal innervation was evaluated by neurodiagnostic skin biopsy (NSB) using indirect immunofluorescence.

Results The results showed, in the painful area: (1) anaesthesia to tactile, pin-prick and warm stimuli (2) absence of LEPs; (3) a slight reduction of the epidermal innervation. This case report describes a typical pattern of "anesthesia dolorosa" and is suggestive for a deafferentation pain with preganglionic lesion.

Case 2 A 71-year-old female patient with sudden, unilateral episodes of spontaneous pain on the right side of her face.

Method It was identical to that used in case one.

Results The results showed, in the painful area: (1) tactile, pinprick and warm severe hypoesthesia; (2) LEP absence; (3) severe reduction of epidermal innervation. This case report describes a symptomatic trigeminal neuralgia with ganglionic or postganglionic lesion.

Conclusions The two cases indicate that the contemporary use of NSB and LEPs is useful to discriminate neuropathic pains presenting with similar clinical characteristics but with different pathophysiological mechanisms such as deafferentation, preganglionic damage (case one) and peripheral, ganglionic or postganglionic damage (case two).

Circadian hyperactivity of the lower limb nociceptive system in idiopathic restless legs syndrome: a CO₂ laser evoked potential study

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Introduction The idiopathic form of restless legs syndrome (RLS) is a common sensorimotor disorder involving nociceptive system. Aim of the study was to assess the nociceptive system during the night and afternoon in idiopathic RLS patients, by recording the laser evoked potentials (LEPs).

Material and methods We studied 11 patients (mean age 53.40±18.59 years; 6 males, 5 females) affected by idiopathic RLS. LEPs were recorded to stimulation of the right foot, hand and perioral region. LEPs were recorded at night (between 9:00 PM and 11:00 PM) and in the early afternoon (between 1:00 PM and 3:00 PM). Two consecutive averages (20 trials each) were obtained for each stimulation site. LEPs were recorded from 3 recording electrodes placed at Cz, Fz, and T3 sites of the 10-20 International System. The results were compared with 11 control subjects age and sex matched (mean age 55.3±18.7 years).

Results In RLS patients, we found a significant increase of N1, as well as N2-P2 amplitude after foot stimulation during nighttime session ($p=0.016$ and $p=0.008$, respectively) when compared to daytime. The N1 and N2/P2 amplitude after hand and face stimulation was not significantly different comparing the two sessions ($p>0.05$).

Discussion We did not find any impairment of the nociceptive system in RLS. However, there is a prevailing activity of the Delta nociceptive system of lower limbs during nighttime.

Conclusions These findings suggest, in idiopathic RLS, a circadian disinhibition in the central processing of the lower limb Delta-fiber inputs.

Botulinum toxin for muscle cramps associated with diabetic neuropathy: a double-blind, placebo-controlled study

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Introduction Muscle cramps are painful, involuntary, paroxysmal muscle contraction observed in several neurological and metabolic diseases other than in a number of physiological conditions including muscle fatigue, pregnancy, and in the elderly. The association of muscle cramps with diabetes mellitus (DM), as well as with diabetic peripheral neuropathy, has been known for several years. No pharmacological treatment has shown to provide adequate relief in reducing cramp-associated pain. Botulinum toxin type A (BoNT/A) has demonstrated to be effective in reducing cramp frequency and severity in patients with benign cramp-fasciculations syndrome. The aim of the present study was to evaluate the effect of BoNT/A in reducing the severity and the frequency of occurrences of cramps in patients with diabetic neuropathy.

Methods In this double-blind, randomized trial, 30 patients with diabetic neuropathy and frequent leg cramps underwent BoNT/A injections (n=15) or an equivalent dose of normal saline (n=15). *Primary outcome*: variation in the mean intensity of cramping pain (on a scale from 0 to 10). *Secondary outcomes*: variations in the number of occurrences; variations in the electrophysiologically measured *Cramp Threshold Frequency* (CTF); variations in the Cramp Severity Scale (CSS). Patients were evaluated before, and at week 1, 4, 8, 12, 16, 20 after injections.

Results All the outcome measures showed significant changes in the treated group as compared with placebo. The effect appeared at week 1, and persisted until week 16, disappearing at week 20.

Conclusions BoNT/A can be a safe and promising treatment for painful cramps associated with diabetic neuropathy.

Clinical aspects of headache

Temporary aphasia in migraine with aura

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Background Temporary aphasia (TA) can be experienced during aura by migraine with aura (MA) patients. They are not very frequent and very little information exist about them.

Objectives To investigate some aspects of TA in MA patients, in particular: 1. to analyze speech disorders characterizing TA; 2. to find out if subjects suffering from MA with TA show a different emotional experience compared to patients suffering from MA without TA.

Materials and methods Subjects suffering from MA (ICHD-II) with and without TA were selected from patients referring to the Headache Centre in a 3-month period (October-December 2012).

State-Trait Anger Expression Inventory (STAXI), 9 scales of the battery of psychological tests CBA 2.0 and Conversational Analysis Profile for People with Aphasia (CAPP) were used for the study.

Results Twenty MA patients (13 females, 7 males, mean age 43.5 yrs), 10 with TA (Group A) and 10 without (Group B), were included in the study. Group A subjects were administered all tests, while group B subjects only psychological ones. On the basis of CAPP data the most frequent speech disorders in TA are failure in finding words, production of phonemic paraphasias, circumlocutions and apraxic errors. Less frequent disorder is a tendency to use non fluent and telegraphic language style. According to the results of the psychological tests no differences were observed between the two groups.

Conclusions This is one of the first studies on this aspect of aura. It identified more clearly the different types of speech disturbances appearing during aura in MA sufferers. It also showed that the presence of this kind of disturbances does not produce the onset of negative feelings in these patients. These results would benefit from a replication on a larger sample.

Fatigue and migraine without aura: a study investigating occurrence and correlation with the main descriptors of disease

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Introduction Fatigue is a commonly reported symptom in several neurological disorders, however data concerning fatigue in migraine patients are limited and heterogeneous; the aim of this study was to assess the occurrence of fatigue in episodic migraine patients and to evaluate the existence of a possible correlation between the presence of fatigue, parameters of disease and comorbid mood or anxiety disorders.

Methods One hundred consecutive migraine without aura patients (IHS criteria, 2004), were enrolled at the Headache Centre of Pisa University; patients with episodic migraine, without migraine preventive treatment and/or overuse of symptomatic drugs were enrolled. Fatigue was assessed using the Fatigue

Severity Scale; moreover, migraine-related disability, mood and anxiety disorders were evaluated, respectively, by means of MIDAS (Migraine Disability Assessment Score), GAD-7 (Generalized Anxiety Disorder 7-item scale) and PHQ-9 (Patient Health Questionnaire 9-item scale).

Results Forty-four percent of migraine patients had a FSS score greater than 27, i.e., indicative of excessive fatigue; the statistical analysis, carried out by means of the Spearman coefficient ρ , demonstrated the existence of a significant correlation between FSS score and monthly frequency of migraine attacks (ρ 0.196; $p < 0.05$), migraine related disability (ρ 0.376; $p < 0.01$) and depression (ρ 0.491; $p < 0.01$). Moreover, the correlation data, also corrected for depression, confirmed a significant correlation between fatigue and migraine-related disability (ρ 0.031; $p < 0.05$).

Discussion The results of this study seem to support the hypothesis that migraine itself could be related to a condition of fatigability and showed that fatigue in episodic migraine patients correlates with a more severe-disabling migraine clinical picture. Studies suggested that, irrespective of cause, fatigue has a major impact on daily functioning and quality of life patients, therefore its identification might play a crucial role in the perspective of an individually tailored management of migraine patients in order to improve clinical outcome.

Photophobia is associated with allodynia during migraine without aura attack

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Background Allodynia is a phenomenon of central sensitization associated with more functional disability and severity of migraine. Allodynia is positively related to headache frequency, attack duration, illness duration, and unilateral pain. Conversely, little is known if some of the common accompanying symptoms of the migraine pain are more present in allodynic migraineurs.

Objective To investigate the occurrence of the common accompanying symptoms of migraine without aura in allodynic patients.

Materials and methods One hundred and fifty-six consecutive migraineurs without aura were recruited. Other primary headaches comorbidity and migraine prophylaxis were exclusion criteria. Each patient was interviewed following a structured questionnaire including the presence or not of photophobia, phonophobia, osmophobia, nausea/vomit, throbbing pain, unilateral pain, autonomic signs. Allodynia during the migraine attack was measured using the Allodynia Symptoms Check-list 12 (ASC-12); χ^2 test with continuity correction or Fisher's exact test was used for categorical variables.

Results Twenty-nine patients (18.6%) were non-allodynic, 48 (30.8%) mild-allodynic, 44 (28.2%) moderate-allodynic, and 35 (22.4%) severe-allodynic. Photophobia is significantly more frequent in allodynic patients than in non allodynic ones ($p = 0.034$).

Conclusions A higher degree of critical light susceptibility is present in allodynic migraineurs without aura. We suggest that allodynia is a clinical expression of a broader central sensitization that could lead to a cortical hyper-reactivity to sensorial stimuli.

Migraine and epilepsy: comorbidity or “ictal epileptic headache”?

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Introduction The comorbid migraine/headache and epilepsy has been debated for more than 100 years. The not completely investigated epidemiological aspects in childhood, contributed to improve the confusion about available data to establish a significant “not random” association between headache and seizure. It is believed that a significant association of these events could be explained by the autonomic manifestations so frequent in childhood, as demonstrated by the peculiar “Panayiotopoulos syndrome”.

Clinical Cases Here we describe two cases which could be considered a model of our proposed IEH criteria. At the onset they had an intensive migraine without aura, associated with sub-continuous occipital EEG abnormalities. After 8 and 10 months, both patients of 9 and 14 years-old, respectively, showed identical events, followed by a motor-sensitive generalized seizures.

Discussion Since 1950, Italian, German and English researchers, have suggested that headache could be the sole ictal epileptic manifestation [1]. Only recently this nosological entity has been taken in consideration, with the proposal of new published criteria [1] to identify patients with Ictal Epileptic Headache (IEH), whose frequency has not been elucidated, if marginal or just “underestimated”. The concept of “migralepsy” (a headache followed by symptoms and signs characteristic of an epileptic seizure) coined by Lennox and Lennox in 1960, in our opinion, led to a delayed identification of IEH because the headache phase that precedes, in migralepsy, the epileptic seizure, in many cases is an IEH followed by other ictal events.

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Headache in the elderly: disease or symptoms of disease? The fine line between primary and secondary headaches as a diagnostic problem especially in Emergency

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Introduction Headache is an uncommon problem in the elderly. It may be an expression of a long history of migraine or a secondary form when there is an acute or recent-onset. Eighty percent of headaches are primary forms while the remaining 20% are secondary forms. Of these, 33% concerns the population older than 70 years [1]. In Italy, admittance to the Emergency Department (ED) for headache in the elderly is represented by a number ranging between 1.2 and 4.5%. Of these patients about 23% required neurological evaluation of which 4.3-6.4% presented secondary headaches.

Materials and methods We report our experience related to data about patients over 65 years of age evaluated in the ED of Humanitas Gavazzeni (Bergamo). In particular, we analyzed the request of evaluation for headache and the diagnosis at discharge.

Results Among all requests of neurological examination, 21% were for headache; 5% of them evidenced secondary headache and were represented in most cases, by headache due to hypertension, cerebrovascular disorders and post-traumatic damage. The appropriate diagnosis, at discharge was estimated at about 80%. In the remaining 20% we had observed a different diagnosis at follow-up evaluation, due to a second level examination (MR, EEG, etc.).

Conclusions Patients over 50 years of age with headache should be investigated to exclude a secondary form. However, it is important to carefully con-

sider all cases in the elderly and in the ED. Generally, the primary forms are better classified. Nevertheless, secondary headaches need proper procedures for a correct definition and diagnosis, which can sometimes be made during the follow-up evaluation.

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Cluster headache in the elderly is more common in women than in men

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Background Cluster headache (CH) is considered a disorder of young men which predominantly begins at age 20 to 40 years, the mean age being 31.5 years. It is well known that CH affects more frequently men than women, the gender ratio ranging in various studies from 4.4:1 to 2.5:1.

Materials and Methods We evaluated patients with CH aged 65 years and older. For the last 16 years we have observed 254 patients suffering from CH. Out of these cases, 42 patients (16.5% of the whole population) were older than 65 years.

Results In this group of elderly patients, 24 were females (57.1%) and 18 were males (42.9%). We diagnosed 4 patients with CH (only one bout, according to the International Classification of Headache Disorders second edition, ICHD-II), 24 with episodic CH, and 14 with chronic CH. The onset occurred in ages 35-44 years for 21.4% of cases, in ages 45-54 years for 16.7%, in ages 55-64 years for 28.6% and after the age of 65 years for 33.3%. Notably, in the latter subgroup, the females significantly prevailed, accounting for 78.6% of cases.

Discussion This study, confirming our previous results, demonstrates that CH can begin in geriatric age. Moreover, with regard to onset of CH, we found a significantly higher number of females in the group of patients older than 65 years.

Conclusions In CH patients over the age of 65 years, females represented the great majority of cases, in contrast with the evident male preponderance in the previous ages. Apparently peculiar to the female distribution, an increased frequency of CH appears to occur in middle-age and elderly patients. To our knowledge, we report the patient with the oldest age at onset (a 93-year-old woman) and the largest case series of CH elderly patients published in the literature to date.

Borderline personality, anxiety-mood disorders and migraine: clinical implications

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Introduction Recent clinical studies have shown that, among personality disorders, the borderline personality disorder (BPD) is mostly associated to a negative impact on migraine clinical features and its management.

Patients and methods We evaluated a sample of 50 consecutive ICHD-II migraine patients with DSM IV-Axis I diagnosis (mood and anxiety disorders) detected by the MINI Structured Neuro-Psychiatric Interview and a group of 50 consecutive migraine patients without psychiatric disorders matched for age, gender and type of migraine (with aura, without aura, episodic, chronic).

At baseline, we assessed some demographic variables and migraine clinical features: headache days (the number of days over the 30-day period during which they experienced a headache), headache severity (4-point scale: 0 - none, 1 - mild, 2 - moderate, 3 - severe), disability and quality of life (by MIDAS and HIT-6). We administered to all patients the Diagnostic Interview for Borderline Patients (DIB), by Gunderson et al., a semi-structured interview which evaluates five areas of functioning: social adaptation, impulse-action patterns, affects, psychotic symptoms and interpersonal relations [1].

Both groups were treated for their migraines via a uniform pharmacological management programme.

Follow-up was conducted at 3^o and 6^o month. At month 6, as measures of outcome: Headache activity (the sum of all headache severity ratings divided by the number of headache days experienced over the target period), and Disability/Quality of life were considered.

Statistical analysis of data was carried out by the Mann-Whitney test and the χ^2 test with Yates's correction as indicated.

Results Among the group of migraineurs with psychiatric Axis-I Disorders, high scores (over 7) to DIB, indicating the presence of borderline personality disorder, were found in patients with bipolar disorder II (66%) and panic attack disorder (52%). The analysis of the specific areas of functioning, assessed by DIB, showed that subjects with high scores to areas "impulse-action patterns" and "affects" (such as anger and similarities) reported significant worsening rates on outcome migraine measures and greater headache disability.

Conclusions The comorbidity migraine-personality disorders/traits should be more deeply explored. A primary point to clarify is the relationship migraine-borderline personality disorder and, among Axis I-Axis II disorders, the comorbidity bipolar disorder II-borderline personality disorder with migraine, for the relevant implications on clinical course and management of migraine.

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Adjustment and pre-existing psychiatric disorders prevalence among headache patients accessing a pain clinic in southern Italy

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Background Several studies have shown that correlation exists between headache and psychiatric disorders such as mood disorders, anxiety disorders, adjustment disorders, somatoform disorders and addictions. Also, personality disorders and certain personality traits are considered related to headache. Mental health problems are generally seen as reactive to the chronic pain condition, but there are studies suggesting they might be, in some cases, headache predictors and risk factors.

Objectives The present study was performed in order to investigate if correlations exist between headache and psychiatric disorders among the population of headache patients accessing to the "Pugliese - Ciaccio" Hospital pain clinic in Catanzaro (Italy). Moreover, aim of this study was to investigate the temporal relationship between headache and mental health problems.

Methods We collected data from 141 patients accessing for the first time the "Pugliese - Ciaccio" Hospital pain clinic from February 2012 to November 2012; patients were referred for headache problems by their family doctor or other specialists; the study sample was composed of 110 females and 31 males aged from 18 to 80 years with a mean age range from 31 to 40 years; we assessed headache using ICHD-II criteria and screened mental health conditions using DSM-IV criteria based clinical interviews; Data were analysed using GNU/PSPP Statistical package for counting frequencies and correlational tests.

Results The majority of the headache patients was diagnosed with a psychiatric condition (56.74%); the most frequently diagnosed mental health prob-

lems among headache patients were anxiety disorders (26.24%) such as Generalized Anxiety and Panic Disorder, mood disorders such as Dystimic and Cyclothimic Disorder, adjustment disorders (7.80%); furthermore there was a prevalence of pre-existing (47.52%) rather than reactive psychiatric disorders (9.22%) among headache patients.

Conclusions Our study indicates that psychiatric disorders are prevalent among the headache patients population accessing our pain clinic and that mental health problems might constitute pre-existing conditions rather than reactions to chronic pain. It is therefore necessary to assess headache patients with psychological tools for mental health problems and personality traits in order to adjust their therapeutic programme. Thus, multidisciplinary interventions according to the bio-psycho-social model of health care should be used when taking care of chronic headache patients.

The compliance of migrainous patients: is there a role for Attention-Deficit Disorder detecting Brown Scale?

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Background Compliance in migraineurs is unsatisfactory, probably because of comorbid depression, anxiety, chronic nature and beliefs in its benignity. Adult Attention-Deficit Disorder (ADD) has a prevalence of 3-4% in the general adult population, and recent findings suggest a comorbidity with migraine. It presents with restlessness, dysphoria, lack of concentration, failure to plan daily activities and negative psychosocial impact. Brown Scale is a validated one for ADD initial detection.

Aim To investigate a relationship between scores in ADD Brown Scale and compliance in migraine.

Materials and methods We cross-sectionally screened patients seen at the Centre in November 2012 with BDI, STAI and Brown Scale for ADD. All patients were required to fill in a headache diary.

Inclusion criteria: migraine with or without aura (ICHD-II), >18 yrs, follow-up >1 year. **Exclusion criteria:** other headaches, psychiatric comorbidity, lack of comprehension of Italian.

Compliance was evaluated and scored on a 4-step grid according to data from the diary and therapy adherence of the previous year. Brown Scales were evaluated after compliances scores, to avoid interpretation bias. A regression analysis was used to treat data.

Results We included 60 patients (48 females, 12 males, mean age: 46.78 yrs). Average scores of Brown, BDI, STAI were 35,23, 9,6038, 41,9057 and 45,2453, respectively. Higher score at Brown Scale was predictive of worse compliance in completing headache diary ($p < 0.05$, β -coefficient -0.292), but not of worse therapy adherence. All results were controlled for sex, age and BDI and STAI scores.

Conclusions ADD is a condition comorbid with migraine. Higher scores at Brown Scales could be a predictive factor for poor compliance in reporting in the headache diary, our best tool to evaluate effectiveness of preventive and acute therapy. These results would benefit from a replication in a larger sample.

Headache care objectives and outcomes in a tertiary centre in the Italian Region of Calabria

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Objective This study was performed to determine headache characteristics and patients attitude towards an accessed tertiary care headache centre in Catanzaro;

other objectives were to evaluate previous prescribed treatments, health care seeking previous pattern and adherence/response to provided treatment.

Background The characteristics of primary headache patients accessing a tertiary centre are different from those found in services directed to the general population. Daily or near-daily headaches as well as overuse of symptomatic medications are much more frequent in these centres.

Methods Four hundred and thirty clinical records of patients accessing the Headache centre in Catanzaro from September 2010 to December 2012 were reviewed. Retrieved data included sex, age, headache diagnosis, previously taken drugs; prophylactic treatment response was defined as a greater than 50% reduction in headache frequency in 4-6 weeks. Acute treatment response was defined as 2 hours pain free status and no pain recurrence in the following 24 hours. Headache episodes were recorded in a detailed diary.

Results The average headache duration found among our 430 patients in their life time (75% females; age range 18-72 years) was 22.2 years; 61.3% of patients reported headache in 3 or more days per week. Symptomatic medications were overused by 45.6% of patients; patients were diagnosed with migraine (57.8%), medication-overuse headache (35.6%), tension-type headache (5.4%) and cluster headache (2.8%). Two or more prophylactic medications were prescribed to a large portion of patients (75%). In an intention-to-treat analysis of subjects, a significant improvement (52.8%) resulted in headache frequency in 4-6 weeks of preventive treatment.

Conclusions The population of our tertiary care centre was mainly composed of migraineurs and chronic migraineurs with symptomatic medication overuse. Multiple triptans use was the most frequent pattern of symptomatic medications use, perhaps due to the large number of previous neurologist consultations. This pattern differs from the recommended treatment guidelines followed by most monotherapy prescribing physicians. Clinically based studies on these parameters are useful to better investigate treatment options for the headache patients population in a tertiary care centre.

Headache in emergency settings: assessing diagnosis accuracy for neurology outpatient services

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Introduction As many as 90% of individuals have at least one headache/year. In emergency settings, approximately 5% of patients with headache have serious underlying neurologic disorders. Therefore, it is imperative that headache be diagnosed rapidly and accurately. The International Headache Society Classification of Headache indicates fourteen types of head pain. Since this is a non-specific symptom which can instead refer to several neurological diseases, the neurologist should be as precise as possible in formulating a diagnosis. It is essential to properly orient the diagnostic and therapeutic course that the patient will have to take.

Objectives This study examined the amount of correct diagnoses made during outpatient visits in emergency settings; a diagnosis is correct when it complies with the above-mentioned classification.

Materials and methods The data refer to 1,748 patients seen in one year. At first we analysed the number of headache diagnosis compared to that of other disorders. Among the diagnosis of headache we searched how many were correct and how many incorrect. Finally, in the group of incorrect diagnosis we evaluated which measure the neurologist set up: diagnostic procedures, treatment, or both.

Results The diagnosis of headache was made in 22.4% of the patients. One hundred and fourteen diagnoses were correct. The remaining 278 were reported with a generic term "headache" or "atypical facial algia". One hundred and ninety-eight required check-ups, 44 were prescribed a therapy, 36 re-

quired check-ups and prescribed treatment. Finally, 3 patients were registered without a diagnosis of any kind.

Conclusions The results demonstrate the need for a greater segmentation in the assessment of urgency to guide the clinician to the proper diagnostic and therapeutic course.

Disability in migraine: are motherhood and pregnancy a side of the dice?

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Introduction Migraine (M) is a frequent problem and a leading cause of disability, particularly in women. However, M influence on women reproductive choices appears under-investigated.

Aim Our study aims to evaluate the influence of headache on reproductive choices and perceived ability in motherhood.

Methods We interviewed 135 women affected by M without (84%) and with (16%) aura, aged 21-71 years, using a semi-structured questionnaire. We collected data about intensity of attacks and frequency, fertility, pregnancies, abortion/miscarriage and number of children. We asked if their condition of headache sufferer could influence the decision of facing pregnancy and perceived ability in motherhood.

Results Among the 135 women interviewed, 43 (32%) were post-menopausal vs. 92 (68%) who had their menses; 35 (26%) were nulliparous vs. 100 (74%) who had had at least one pregnancy; 93 (69%) were mothers vs. 42 (31%) who did not have children; 35 (26%) experienced miscarriage or chose abortion at least once; 67 (50%) had less than 5 attacks/month, 37 (27%) had 5-14 attacks/month, 31 (23%) had ≥ 15 attacks/month. Pain intensity was low (NRS 1-4) in 4 (3%), moderate (NRS 5-7) in 55 (41%), high (NRS 8-10) in 76 (56%). Among our 135 patients, of those who wanted another child (44; 33%) 13/44 (30%) considered their headache a problem for a pregnancy; a single patient interrupted a pregnancy because of the headache.

Among patients who did not want a pregnancy or further pregnancies (91; 67%), 13/91 (14%) listed headache among the causes for this choice.

As a whole, 69/135 (51%) deemed that headache could interfere with their performance in maternal role.

Conclusions Our preliminary results show a negative influence of M on the choice of pregnancy and self-perception as mothers.

The Cephalalgic Day Service: quantitative approaches for planning and management of clinical services

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Introduction "Day Service" is a novel hospital service organization available for outpatients with complex pathological profiles. According to the relevant clinical specialty, some standard outpatient clinical service packages have been defined following specific clinical guidelines. In this work, we focused on Day Service planning and management for chronic headache patients.

Objective The main aim was to make more effective and efficient the patient flow, by ensuring that for each patient admitted all the required clinical services were delivered during the planned period. To this end, we designed and developed an optimization model-based solution approach, by taking into account all the relevant issues involved in the problem.

Materials and methods Within Day Service, the related clinical services are planned in advance and delivered typically on a monthly basis for elective patients. In this context, a strategic decision concerns the optimal clinical management of patients, and, in particular, the implementation of efficient and effective patient admission and clinical services scheduling procedures, by tackling different requirements regarding the availability of the hospital resources.

Results The proposed approach has been validated within the Headache Day Service Unit of the Neurology Division of Pugliese-Ciaccio General Hospital, Catanzaro.

Conclusions The obtained results confirmed the effectiveness of the proposed approach, since it allowed a more efficient planning of clinical service and management by making the best use of available hospital resources.

Unilateral or bilateral migraine pain: does it affect the migraine clinical picture?

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Introduction It is well known that migraine pain may differ concerning its localization, i.e., strictly unilateral, unilateral side alternating, bilateral or both, however it remains unclear whether pain location might affect migraine clinical presentation; this study was carried out in order to assess possible differences in the migraine clinical picture in a sample of unilateral compared to bilateral migraine pain sufferers.

Methods Two hundred and one consecutive migraine patients (IHS criteria, 2004) were recruited; patients with migraine preventive treatment or overuse of symptomatic drugs were excluded. Data regarding pain features (unilateral/bilateral, quality and severity), presence of photophobia, phonophobia, osmophobia, nausea and vomiting and dopaminergic prodromal symptoms were collected.

Results Eighty-nine patients had unilateral pain, 74 bilateral and 38 both unilateral and bilateral migraine attacks; patients with unilateral versus bilateral pain were compared. Pain quality was pulsating in 73% of unilateral versus 72.9% of bilateral migraineurs and also accompanying symptoms did not significantly differ between the two groups (photophobia 86.5% vs. 83.7%; phonophobia 85.3% vs. 82.4%; osmophobia 56.1% vs. 63.5%; nausea and vomiting 83.1% vs. 77%). Prodromal dopaminergic symptoms were respectively reported by 71.7% of unilateral vs. 78.1% of bilateral migraineurs. Moreover mean attacks severity, evaluated by means of a ten point analogic scale, was 8.4 in unilateral pain versus 8.2 in bilateral migraine; allodynic features during the attacks were finally reported by 78.7% of unilateral versus 83.7% of bilateral patients.

Discussion Pain lateralization remains one of the most intriguing speculative aspects of headache research; in clinical context it is not clear if pain location affects the migraine clinical picture. The results of this study, although preliminary and carried out in a limited sample of migraineurs, seem to show that the migraine picture is not affected by pain localization; further studies are certainly necessary in order to better understand the biological basis of migraine unilateral/bilateral presentation.

Headache, migraine and epilepsy: a proposal of terminology in relation to the possible associations

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Background The association between a headache attack and an epileptic seizure has different possibilities, some with unclear or discussed terminologies. The ICHD-II defines three kinds of association: 1) Migraine-triggered seizure (“migrralepsy”), 2) Hemicrania epileptica, 3) Post-ictal headache. We discuss these terminologies and propose new definitions.

Results On the basis of the data of the literature, we propose the following definitions.

A) *Pre-ictal migraine and migraine-triggered seizure*: conditions characterized by a migraine attack, with or without aura, and a seizure occurring during or within (conventionally) 1 hour after the migraine attack. The preferential use of the term “migraine-triggered seizure” depends on the possibility of actually demonstrating whether migraine plays a role in precipitating an epileptic seizure. A differentiation from occipital epilepsy is mandatory.

Pre-ictal headache is to be used when the criteria for migraine are not met. The term “migrralepsy” has not been used univocally, and may therefore lead to misinterpretation.

B) *Epileptic headache* (EH, or “Ictal epileptic headache”) is characterized by headache (whether migraine or not) with onset, and cessation if isolated, coinciding with a scalp or deep EEG pattern of epileptic seizure, featuring two variants: A) “Pure” or “isolated” [1], “Isolated epileptic headache (IEH)”, or B) headache followed without discontinuity by other epileptic manifestations, thus actually being an epileptic seizure beginning with headache as an “aura”. “Hemicrania epileptica” is a very rare variant of EH, characterized by ipsilateral location of headache and ictal EEG paroxysms. C) *Post-ictal headache*: tension-type headache or migraine occurring (conventionally) within 3 hours following a seizure (ICHD-II criterion). D) *Interictal headache*: a comorbid condition, to be differentiated by the above reported peri-ictal and ictal headaches.

Conclusions The aforesaid definitions inferred from the cases reported in the literature can be a guide for an up-to-date of the terminology.

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Correlation between allodynia and migraine severity

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Background Allodynia, perception of pain from non-nociceptive stimuli, is a clinical sign of central sensitization. It has been reported that allodynia correlates with migraine attacks severity. Also, severity of migraine has been hypothesized to contribute to the development of allodynia.

Objectives To evaluate the relationship between allodynia and degree of migraine severity to better understand mechanisms related to central sensitization induced migraine.

Methods This retrospective analysis recruited 94 patients; baseline information on pain level was recorded using diaries completed by the patients while baseline allodynia was assessed with specific screening tools. The relationship between allodynia and migraine severity was analyzed by Fisher exact test and chi-square test.

Results At baseline 46% of patients experienced allodynia. Allodynia relates to both degrees of migraine severity (moderate pain baseline $p=0.1807$; severe pain baseline $p=0.5830$). Patients reporting a severe level of migraine pain experienced significantly more allodynia (53%) than patients with a moderate level of pain (44%).

Conclusions The results according to this study demonstrate that allodynia correlates with migraine severity. This retrospective analysis suggests that migraine severity is a significant factor in predicting central sensitization experienced by migraine patients.

Is patent foramen ovale a co-morbidity of migraine with aura? A combined and simultaneous sonography study with related MRI findings

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Introduction PFO is a common finding present in 20-34% of the population and is generally asymptomatic. Several conditions such as stroke, migraine, decompression illness and systemic arterial-embolism have been associated with PFO with contradictory results. It is known that the incidence of PFO in patients with migraine with aura (MA+) is about 50%. Migraineurs have a 5 times higher risk of posterior-circulation-infarcts than the normal population and often have white matter brain lesions on MRI. Migraineurs PFO+ have an increased risk of paradoxical embolism and greater lesion-load on MRI.

Method and results We retrospectively analysed the data of 120 consecutive patients subjected to transcranial doppler sonography (TCD) for cryptogenic stroke, migraine, syncope and others. We used agitated saline test with TCD and simultaneous execution of transthoracic echocardiography. Transesophageal echocardiography was extended to PFO+, right-left shunt was detected in 36 of 44 (81.8%) patients with cryptogenic stroke, in 8 of 28 (28.57%) pts with migraine (53.3% MA+) and in 3 of 48 (6.2%) pts with other diagnosis. All 8 PFO+ patients with migraine were affected by MA+ and showed multiple spots in the white matter on RMN. Others 7 MA+ (6 with multiple spots) and 13 with tension-type headache (2 with multiple spots) were negative

Discussion PFO was found in 81.8% of patients with cryptogenic stroke, in 53.3% MA+ and in 28.57% of all migraine. Migraineurs without aura were all PFO- and MRI-.

Conclusions The combined and simultaneous ultrasound approach optimized the diagnosis of PFO. The prevalence of PFO is significantly greater in pts with cryptogenic stroke and migraineurs with aura in our study as in the literature. All patients positive for PFO and with a diagnosis of migraine with aura showed multiple spots in the white matter at RMN. The increased risk of stroke found in epidemiologic studies in patients with migraine with aura may be partly explained by an increased propensity to paradoxical cerebral embolism.

ARTE Cluster Project: cluster headache - from pain to inspiration...

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Introduction "Let a sufferer try to describe a pain in his head to a doctor and language at once runs dry. There is nothing ready made for him. He is forced to coin words himself, and taking his pain in one hand and a lump of pure sound in the other (as perhaps the people of Babel did in the beginning), so to crush them together that a brand new word in the end drops out".

With these words Virginia Woolf expressed in a definitive way (and like no others will ever do), the difficulties encountered by the headache sufferers in communicating their pain. This barrier of communication is well known to both patients and headache specialists, and plays a crucial role in underestimating the disability induced by the headache disorders.

In the words of the US writer J.C. Oates, art is at its essence "a tool for creating empathy among human beings". ARTE Cluster is a project of Alleanza Cefalalgici Cluster whose aim is to collect artistic material to be used for promoting the activities of the association and to raise awareness about CH patients' sufferings. The aim of this study was to investigate the educational, artistic and therapeutic value of the paintings included in ARTE Cluster.

Materials and methods In 2011 we solicited CH patients' associations and figurative artists, throughout the world, to join to the ARTE Cluster Project. Here we present a narrative analysis of artwork collected in the last two years.

Results ARTE Cluster Project now includes 210 paintings (95 produced by cluster headache sufferers and 115 by artists inspired by the disease). Taken as a whole, the exhibition expresses the full range of physical and psychological aspects related to CH with a prevalence of themes dealing with exhaustion, torture, isolation and fear.

Discussion CH represents a powerful source of inspiration for artistic expression. Art has proven to be able to create powerful icons of the disease that communicate about CH much more than single words can do and that may be used as educational tools to sensitize people and physicians about the dramatic sufferings of CH patients. An impressive number of CH patients demonstrated artistic talent (12 of them were professional artists) possibly for the therapeutic aspect of the creative process of art making or for a natural artistic talent.

Coming soon www.alcecluster.cefalea.it.

Communication and the headache patients: social and deontological aspects

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The authors performed a preliminary review of the aspects regarding the social costs of headaches as a useful reference point for assessing the "weight" of this disease in the economic and social context. Focus is then put on the mechanisms regarding the communication process, underlying the weaknesses and criticalities concerning the doctor-patient relationship.

Two current aspects in the information process were also analysed, i.e., in particular, the obligations of the doctor and online network.

Case reports

A case of cluster headache treated with rotigotine: clinical and neurophysiological correlates

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Background Chronic cluster headache (CCH) is characterized by recurrent bouts of facial pain lasting up to 180 minutes in the absence of a long remission period. Some patients with CCH seem to be unresponsive to common pharmacological treatment and are addressed to surgical procedures. Drug-resistant CCH is a clinical challenge for physicians

Methods We report the case of a 43-year-old male patient with treatment-resistant CCH, who improved with administration of transdermal rotigotine. We also evaluated the nociceptive blink reflex habituation that was reduced before the treatment (as is usual in CH patients) and normalized by transdermal rotigotine.

Discussion Since in our patient rotigotine has proven to be effective in treating chronic cluster headache and normalizing trigeminal system excitability, we suggest that this innovative dopamine agonist drug could represent a further therapeutic option in the treatment of drug-resistant CCH.

Bilateral cluster headache: a case report

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Introduction Cluster headache (CH) is a unilateral headache usually confined to the one side, which exceptionally shifts side from one bout to another, but is confined to one side during a single bout.

Case Description We report on the case of a 58-year-old male, smoker, admitted to our clinic for clinical events present for more than 4 months. He referred episodes, mostly nocturnal feeling of “electric shocks” to the head, lasting a few seconds, which were followed by a feeling of “numbness” over the same area for approximately 1 hour, accompanied by a feeling of general malaise and nausea. After about 15 days, he started to develop a clinical picture characterised by perception of oppression and bilateral retro-ocular burning, lasting a few seconds, followed by pain of varying intensity (moderate to severe): associated with conjunctival hyperemia, tearing, eyelid edema and blurred vision, of variable duration (from 15 to 60 minutes) but not accompanied by runny nose, sweating or other symptoms. Frequency of events gradually became daily. All tests performed including neuroimaging (brain MRI and angiographic MRI), ECG, carotid Doppler ultrasound, ruled out secondary causes. Results of routine hematologic tests were normal as well as the screening for autoimmune (including testing for ANA, ANCA, LAC, ACA), inflammation (ESR, CRP) and thrombophilia conditions. The patient responded very well to oxygen therapy but did not benefit from prophylactic therapy with verapamil, which has been empirically proven. Therefore, topiramate (titrated up to a dose of 50 mg/day) was administered which brought about a significant reduction in the intensity and frequency of headache episodes.

Conclusions To our knowledge, this case is the third in the literature reporting bilateral CH [1, 2]. Thus, in the case of atypical clinical presentation with an unsatisfactory treatment response, secondary underlying diseases need to be fully excluded.

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Idiopathic intracranial hypertension: a case report

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Introduction Intracranial idiopathic hypertension (IIH) is a clinical entity nowadays of uncertain etiology.

A primary contribution to the understanding of pathophysiology of IIH derives from the recent techniques of neuroimaging (in brief, a chronic interference in cerebral venous flow of liquor).

Case report M.C. is a 26-year-old female patient, suffering from a continuous headache which had started six weeks before, gradually worsening, characterized by total head pressure with throbbing pain behind both eyes and a pulse-synchronous tinnitus. The pain had intensity moderate-severe, did not change with physical activities and was drug-resistant. In the previous days, she reported diplopia and disartria, both resolved after a brief time. An urgent CT scan of the head resulted negative. II degree obesity.

All the routine exams (chemical blood and clinical tests) were normal except for a bilateral papilloedema with normal visual function at the eye examination and empty sella at the MR imaging. The patient refused to perform a lumbar

puncture. The diagnosis was idiopathic intracranial hypertension. She was treated medically with acetazolamide (500 mg/die) and a weight reduction programme. The symptoms progressively resolved.

Discussion Neuroimaging examinations ruled out secondary causes of elevated intracranial pressure. The presence of empty sella can be considered a “late” sign, related to the persistence of intracranial hypertension. Obesity would have an additional role in the increase of intracranial pressure.

Conclusions The patient’s refusal to have a lumbar puncture does not allow a definite diagnosis: its execution is considered fundamental by current classifications (ICHD-II and Modified Dandy Criteria), necessary to exclude secondary causes. The lumbar puncture can be used as an efficient long-term treatment when practiced in a repetitive way.

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Idiopathic pseudotumor cerebri: is it a benign condition?

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Introduction Pseudotumor cerebri (PC) is characterized by headache, papilloedema, intracranial hypertension (beyond 200 mmH₂O), normal cerebrospinal fluid (CSF), neuroimaging and neurological examination (with the exception of papilloedema and sixth nerve palsy).

In children, PC is rare and often due to identifiable conditions. If a cause is not identified the condition is known as idiopathic intracranial hypertension. A multidisciplinary approach for prompt diagnosis and a correct treatment is necessary to avoid the complications of PC.

Case description A 12-year-old female, with a normal body mass index, presented with diplopia and headache, without vomiting, for ten days. On admittance, sixth nerve palsy was noted. Ophthalmologic examination showed papilloedema, while brain MRI was normal. An angio CT scan of the skull revealed no abnormalities. A lumbar puncture (LP) revealed normal CSF composition with a pressure of 230 mmH₂O. Visually evoked potentials showed a P 100 delayed latency. Extended blood tests and endocrine evaluation were performed and acetazolamide was started. Ten days after, the girl experienced bilateral visual loss, worse in the left eye. Methylprednisolone was begun and cerebral angiography with liquor extraction was performed. A subcutaneous reservoir, connected to the lateral ventricles, was applied on the skull and a further CSF extraction was performed after 2 days. Medical treatment was continued and after 20 days the girl showed a complete recovery of the 6th nerve palsy and papilloedema. Headache episodes were no longer referred.

Conclusions The term benign intracranial hypertension should be avoided for the possibility of serious complications. Our report shows that a multidisciplinary approach is needed to avoid permanent optic atrophy.

Atypical presentation of ophthalmoplegic migraine in adult

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Introduction Ophthalmoplegic migraine is an extremely rare disorder characterized by childhood onset, recurrent crises of migraine and paresis of one or more ocular cranial nerves (OCNs). According to ICHD-II criteria the diagnosis is achieved when at least two attacks are accompanied with, or followed within 4 days of onset by paresis of one or more OCNs. Paresis be-

comes permanent in 30% of the cases and is rarely encountered in the adult. A contrast enhancement of the affected nerves is frequently reported in the literature (86% of patients) at Computed Tomography (CT) [1]. The most credited hypothesis about pathophysiology indicates a recurrent demyelinating neuropathy, which promotes the activation of the trigeminal-vascular system.

Case report A 53-year-old woman, deaf-mute from birth, was referred to our Hospital because of the persistence of vision disturbances and migraine-like headache over the last two months. After the first attacks, the patient reported a left convergent squint, that became permanent with recurrent crises. Neurologic examination revealed the paralysis of the left sixth cranial nerve. She reported a history of migraine without aura from childhood. Laboratory tests were in the normal range, except for a mild hypercholesterolemia. After injection of contrast agent, magnetic resonance imaging (MRI) did not reveal brain or ocular diseases, and no significant areas of enhancement were noted. A therapy with steroids and amitriptyline resulted in a reduction of number and intensity of crises. However, ocular paresis persisted.

Discussion The adult onset of opthalmoplegic migraine, as in our case, is rarely reported in the literature. All diagnostic criteria for this condition were fulfilled in the patient; however, the absence of contrast enhancement of the affected cranial nerve may question the most credited hypothesis (recurrent demyelinating neuropathy), and raises the need for new theories that could explain this rare disease.

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Recurrent headaches and “incidental findings” on brain MRI: to wait or to intervene?

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Introduction Incidental findings on brain magnetic resonance imaging (MRI) are common. An asymptomatic brain lesion, identified “incidentally” during the course of brain scanning for an unrelated reason, is called “incidentaloma”. Radiological appearance can be misleading with overlap between non neoplastic lesions (i.e., cortical dysplasias, hamartomas, infectious or inflammatory lesions). Pediatric incidental brain tumors represent a growing dilemma for treatment/management: “Wait and See” or “Pro Intervene” [1]. The strategy “*primum non nocere*” is indicated for T2-hyperintense lesions, areagent to contrast and with negative MRI-perfusion, spectroscopy and/or positron emission tomography (PET). Early neurosurgery, however, could be preferable for growing and/or symptomatic lesions, or if PET is positive.

Case Report Two children diagnosed with a primary headache (ICHD-II, 2004): respectively a boy (7 years old) with a headache pattern suggestive of migraine without aura and a girl (12 years old) diagnosed with episodic tension-type headache. Both patients presented a prolonged history of recurrent headache and a normal neurological examination; the family history was positive for migraine. Brain MRI of both children showed small bright white matter lesions (hypointense on T1-weighted image, hyperintense on T2-weighted image and fluid-attenuated inversion recovery) in the frontal left cortex, areagent to contrast and stable at the short term follow-up.

Conclusions The differential diagnosis of headache, the hypothesis of the nature of the cortical lesion detected by MRI, and the controversial clinical management are all points of controversy which need to be further investigated.

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Cavernous sinus dural arteriovenous fistula successfully treated with coil embolization: case report

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Introduction Cavernous sinus dural arteriovenous fistulas (cDAVFs) are abnormal arteriovenous shunts in the dura of the cavernous sinus. Predominant symptoms are diplopia, pulsatile exophthalmos, glaucoma, chemosis, conjunctival injection, visual loss, headache, tinnitus, transient ischemic attacks, recurrent syncopes and seizures. cDAVFs are also a risk factor of intracranial hemorrhage. Management includes mainly transarterial or transvenous embolization.

Case Report C.G., 66-year-old woman, four months before observation began suffering from a continuous pulsating headache localized in occipital and left fronto-parietal and periorbital regions, with eyelid oedema, conjunctival injection and diplopia to left lateral gaze because of left fourth and sixth cranial nerve paresis. Analgesics were ineffective, as amitriptyline, pregabalin and betametasone. One month before observation she started suffering from tinnitus and loss of hearing in left ear and mild dysphonia. Cerebral MRI and angiography and subsequent cerebral arteriography disclosed a left cDAVF. The headache was diagnosed as 6.3.3 Headache attributed to cDAVF, following ICHD-II. The patient underwent transvenous embolization through left inferior petrous sinus and occlusion of the fistula by filling left cavernous sinus with platinum coils, without complications during the procedure.

Results After embolization, pulsating headache, tinnitus and diplopia subsided, whilst a continuous mild compressing pain in left periorbital and parietal region persisted. Cerebral arteriography showed complete occlusion of the lesion. After one year follow-up complete remission of clinical symptoms and no recurrence of the fistula were detected.

Discussion The decision to treat cDAVFs depends mostly on the drainage pattern and clinical symptoms. Endovascular management of cDAVFs can be accomplished either by occlusion of arterial feeders and venous drainage via arterial route or by retrograde transvenous occlusion of the sinus harbouring the fistula. In this case, transvenous endovascular coil embolization provided successful occlusion of the lesion and complete disappearance of clinical symptoms, without side effects.

Conclusions Transvenous embolization with coils proved to be a safe and effective management for patients with cDAVFs.

ONS and chronic cluster headache: a case report

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Background Occipital nerve stimulation (ONS) is emerging as a promising treatment for patients with medically intractable, highly disabling chronic headache disorders, including cluster headache.

The mechanism of action is poorly understood, though recent data suggest that ONS could restore the balance within the impaired central pain system through slow neuromodulatory processes in the pain neuromatrix.

Materials and methods A patient with medically intractable CCH [1] was implanted with a octapolar lead for ONS and a retrospective assessment of her clinical outcome was obtained. The most proper recommendations about the criteria were followed for the use of neurostimulation in primary headaches.

Surgical technique A double stage procedure was used to allow an intraoperative trial of stimulation. An octapolar electrode are placed superficial to the

cervical muscle fascia, transverse to occipital nerve trunk at the level of C1, usually using fluoroscopic guidance.

The second part was performed after twenty days. A subcutaneous left subclavicular pocket was created for implantation of the IPG (rechargeable EON Mini, St. Jude Medical Neuromodulation).

Results After a follow-up of 5 months the patient reported an improvement of 70%, with a reduction in attack frequency and intensity. The patient used continuous bilateral stimulation; the range for amplitude was 0–5.5 volts, pulse width 480 sec, and frequency 40 Hz. Occipital paresthesia was often referred as fastidious; in the postoperative period, she refers muscle recruitment, neck stiffness and skin discomfort.

Conclusions ONS offers a safe, effective option for some patients with CCH that have traditionally been treated with cranially invasive or neurally destructive procedures. More studies are required to evaluate and understand this novel therapy.

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A combination of occipital and supraorbital neurostimulation for the treatment of refractory chronic migraine: a case report

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Background A proportion of chronic headache patients become refractory to medical treatment and severely disabled. Neurostimulation is being increasingly utilized as a treatment modality. Action potentials are elicited by depolarizing nerve fibres with electrical impulses produced by a current generator device called neurostimulator. It can be used percutaneously with implantable neurostimulators and electrodes positioned over the spinal cord.

Findings A 48-year-old female patient presented with a long-life history of chronic migraine and tension-type headache. After developing a medication refractory headache, on February 2012 she underwent an operation for the implantation of an occipital nerve stimulation device, a form of peripheral nerve stimulation with positioning of electrodes in the occipital area. After a period of validation, the patient referred that in frontal area she did not receive benefit through electrical stimulation. For this reason, on November 2012, she received a second implant of a supraorbital neurostimulator, a kind of device in which electrodes are positioned in the frontal area of the head and operate with a low-frequency electrical current. On January 2013, due to damage of the device, it was changed and on March 2013, because of a malfunctioning in the battery power system, it was changed again with another model device of the same type.

Conclusions At present, thanks to the stimulation effect, the patient refers a resolution of the migraine problem but there is a persistence of the tension-type headache.

Headache in childhood and adolescence

Epidemiological and clinical features of pediatric migraine in a tertiary centre

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Introduction Migraine is one of the most common kinds of headache in childhood, severely impacting families and children. The aim of this study was to report demographic and clinical features of migraine in our Centre.

Material and methods A retrospective study was performed over a 6-year period (January 2006–August 2012). Hospital record databases were screened for the diagnosis of migraine with (MA) or without aura (MO), based on ICHD-II criteria [1]. Statistical analysis: Fisher's Test or Mann-Whitney U-Test, $p < 0.05$.

Results Migraine was diagnosed in 522 children (294 males; mean age (interquartile range): 10 (3) years). One hundred and seventy-four (33.3%) patients had MA, 348 (66.7%) had MO. Twenty-seven more patients experienced just one episode of migraine, thus a definite diagnosis was not reached. Most of the diagnoses were made between 9 and 14 years of age. After stratification into 5 groups for age, we observed a progressive increase of diagnoses in females, with a peak after 15 years, and a rise of MA. A significant difference between MO and MA was found regarding sex ($p = 0.000$) and age at diagnosis ($p = 0.000$): patients with MA were older and more frequently females. In both groups, patients usually presented infrequent, severe attacks (<1-3/months) lasting <2 hours, associated with nausea and/or vomiting, photophobia and phonophobia. These symptoms were more frequent in MO, as well as osmophobia. Subjective vertigo was more frequent in MA. Visual auras were the most common (87.07%), followed by sensorial (44.21%) and language (15.64%). Confusional state was observed in 10.88%. A positive family history of headache was found in >88% (first degree relatives usually affected).

Discussion and conclusions This study highlights epidemiologic and clinical features of pediatric migraine in our Centre and provides some insight into the pattern of this kind of primary headache in children and adolescents, reflecting available data of literature.

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Evolution of headache in childhood: prognostic factors and clinical features

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Observation of 330 patients referred between 2004 and 2005 to the Centre, only 240 subjects, that fulfilled precisely IHS criteria, were extrapolated. Among these, those patients responding to the following characteristics were taken into consideration:

- 1) Migraine: at least 2 attacks/month.
- 2) Tension-type headache (TTH): at least one attack/week.

Both characteristics in the 3 months prior to the first observation.

One hundred and twenty patients were evaluated from the clinical point of view and underwent assessment for the presence of any psychiatric comorbidity with DSM IV and YSR. These patients were all contacted in 2012 and of these 76 subjects (40 m, 36 f) were double-checked and underwent a new medical and psychiatric evaluation. These patients were compared with a control sample composed of 80 patients (40 m, 40 f) that underwent the same procedures.

Results In the first observation a significant subgroup of patients had an association with psychiatric comorbidity (PC) (mostly migraine sufferers than tension-type sufferers with the exception of CCQ).

At a distance of 8 years it was noticed that:

- 1) A significant proportion of the subjects were in remission (especially TTH).
- 2) Among the subjects in which the headache (migraine or not) persisted, the association with PC at the first observation was much higher.
- 3) The migraines tended to maintain the diagnosis, with a subgroup that became chronic.

- 4) The TTH partly altered the diagnosis becoming migraines without aura.
- 5) The comparison between the sample and the controls showed a higher frequency of headaches. Migraines became chronic in the sample and no differences were demonstrated with controls for the episodic tension-type headaches.
- 6) Psychiatric comorbidities in second observation were markedly lower than the first, demonstrating how important it is to consider personality and their resilience in the developmental stage.
- 7) Those subjects who maintained PC had more worsening forms.

Sleep habits and subjective daytime somnolence in pediatric migraine

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Introduction The relationship between sleep and headache is meaningful and complex. Children affected by migraines tend to show many sleep disorders. The aim of this study was to assess sleep habits and self-reported sleepiness in a pediatric sample of individuals with migraine without aura (MoA).

Methods The study population consisted of 271 children aged between 6 and 13 years affected by MoA. The control group was composed of 305 typically developing children. To assess the sleep habits of all individuals (MoA and control), parents filled out the Sleep Disturbance Scale for Children, and to check the degree of subjective perceived daytime sleepiness, all subjects were administered the Pediatric Daytime Sleepiness Scale.

Results The two study groups were matched for age ($p=0.124$), gender ($p=0.775$), and z-BMI ($p=0.107$). Parents of children affected by MoA reported a higher total score of sleep disorder symptoms ($p<0.001$), disorders of initiating and maintaining ($p<0.001$), and disorders of arousal ($p<0.001$) than did parents of controls. No significant differences were found in disorders of excessive somnolence. Conversely, in the Pediatric Daytime Sleepiness Scale, migraine children had higher scores ($p<0.001$) and a reduction in referred total sleep time mean duration ($p<0.001$) than typically developing children.

Discussion and conclusions Our study identified differences in sleep habits and found a high prevalence of daytime somnolence in children affected by MoA, suggesting the need for routine sleep screening in the pediatric management of children with migraine.

Motion sickness in childhood migraine: the efficacy and safety of Griffonia simplicifolia/Magnesium complex

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Introduction The purpose of this study was to assess the efficacy and safety of Griffonia simplicifolia/Magnesium complex in a paediatric sample with motion sickness (MS), a very frequent migraine equivalent in childhood.

Methods The study population consisted of 254 children (mean age: 7.56 ± 1.49 years; 141 males and 113 females) with motion sickness, recruit-

ed from the Headache Centre for Developmental Age, Child and Adolescent Neuropsychiatry Clinic, Second University of Naples.

Griffonia/Magnesium complex (50 mg and 200 mg, respectively) was orally administered as prophylactic therapy for MS twice a day for 3 months to one group (Group A; 127 children; mean age: 7.69 ± 2.32 ; 72 males) and no therapy for MS was administered to the second group (Group B; 127 children; mean age: 8.02 ± 1.98 ; 69 males). The signs of motion sickness were identified with an ad hoc questionnaire that was administered to all subjects and parents of both groups.

In order to verify the efficacy on MS of the Griffonia/Magnesium complex treatment, we compared the MS prevalence after 3 months of treatment in Group A with MS prevalence after 3 months of observation in Group B (without MS prophylactic treatment).

Results After 3 months (T1) Group A showed a MS prevalence of 36%, significantly lower than MS prevalence in Group B (73%) ($p<0.001$). No relevant side effects were reported.

Discussion and conclusions The role of Griffonia/Magnesium complex as a potential treatment with mid-term efficacy also for recurrent periodic syndrome as motion sickness.

Attachment style and psychological symptoms in headache children: is there a relationship with maternal attachment and alexithymia?

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Introduction Few studies have investigated the relationship between insecure "attachment style" and somatic symptoms in headache patients and even fewer concerned pediatric patients. In a recent study [1], we found that a low migraine attack frequency was related to separation anxiety in migraine children. Aims of our study were: 1) to compare the psychological profiles according to attachment style in headache children; and 2) to investigate the role of maternal attachment and alexithymia on children's styles.

Materials and methods Thirty-nine children with primary headache were included. They were divided into "secure" and "insecure" ("avoidant", "ambivalent" and "disorganized/confused") attachment patterns. Mothers were grouped according to their children's style. The psychological profile was assessed by SAFA Anxiety, Depression and Somatization scales. Attachment style was measured by the semi-projective test SAT for patients and ASQ questionnaire for mothers. Alexithymia levels were evaluated by TAS-20.

Results Most children (82%) showed an insecure attachment style (43.6% ambivalent, 30.8% avoiding and 17.9% disorganized/confused). When the "ambivalent", "avoidant" and "secure" groups were compared, we found significant differences in all SAFA scales. Ambivalent children showed higher scores. Alexithymia levels were higher in mothers whose children were classified as ambivalent.

Conclusions We can hypothesize that ambivalent children focus on or exaggerate psychological distress in order to be comforted by their mothers, who show high alexithymia levels.

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Clinical features, anger management and anxiety: a possible correlation in migraine children

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Introduction Very few studies have analyzed the role of anger in children with primary headache. Aim of this study was to analyze the possible correlation between pediatric migraine severity and the psychological profile, with particular attention to the anger management style.

Methods Sixty-two migraineurs were studied. Patients were divided into four groups according to the attack frequency (low, intermediate, high frequency, and chronic migraine). Pain intensity was rated on a 3-levels graduate scale (mild, moderate and severe pain). Psychological profile was assessed by Picture Frustration Study test for anger management and SAFA-A scale for anxiety.

Results We found a relationship between IA/OD index (tendency to inhibit anger expression) and both attack frequency ($r=0.328$, $p=0.041$) and intensity ($r=0.413$, $p=0.010$). When we analyzed the relationship between anxiety and the headache features, a negative and significant correlation emerged between separation anxiety and the frequency of attacks ($r=-0.409$, $p=0.006$). In our patients, the tendency to express and emphasize the presence of the frustrating obstacle (EA/OD index) showed a positive correlation with anxiety level ("Total anxiety" scale: ($r=0.345$; $p=0.033$).

Conclusions Our results suggest that children suffering from severe migraine tend to inhibit their angry feelings. On the contrary, children with low migraine attack frequency express their anger and suffer from separation anxiety.

Obesity and headaches in children

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Introduction Primary headaches and obesity are two of the biggest public health issues in adults and children. Both conditions are associated with reduced quality of life and they are a risk factor for cardiovascular events, psychological and social impairments [1]. The aim of this study was to assess this relationship between overweight or obesity and the characteristics of headache pattern. It is hypothesized that higher rates of BMI correspond to a bigger prevalence of primary headaches and greater intensity.

Objective To investigate the interaction between overweight or obesity and primary headaches in children.

Methods Two hundred and twenty children between the ages of 6 to 16 with a BMI >22, were recruited from the Dietologic Pediatric Centre of Policlinico Umberto I and the Pediatric Endocrinologic Centre of Sant'Eugenio Hospital in Rome. The exclusion criteria were: age, BMI < 22, mental retardation and secondary headaches. The non-clinical group was recruited from primary and secondary schools in Rome. Headache Questionnaire, PedMidas and the SAFA (A-D-S-P subscales) tests were administered to all the children.

Expected results Significant correlation between the overweight/obesity condition and primary headaches, specifically migraine with/without aura. Furthermore, we expect to find a positive association between the condition of obesity and headache and psychiatric disorders like anxiety, depression and eating disorders. So, in an organic and psychopathologic perspective, the effect of obesity and weight may change headache outcomes. Indeed, according to some authors, a decrease in BMI causes improvement of headaches.

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Attachment styles and migraine without aura in pediatric age

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Introduction According to the Bowlby's theory attachment can be considered as "lasting psychological connectedness between human beings". Migraine without aura (MoA) in childhood could be accompanied by many comorbidities and peculiar aspects. The aim of study was to evaluate the attachment styles in a sample of children with MoA.

Methods The study population consisted of 47 children (29 M) aged between 6 and 14 years (mean age: 9.43 ± 2.04) with MoA. The control group was composed of 83 (51 M) typically developing children (mean age: 9.71 ± 2.36). To assess the attachment style, all individuals (MoA and control) underwent the Italian modified version of Separation Anxiety Test (SAT).

Results Between the two groups no significant differences were found for age ($p=0.497$) and gender ($p=0.874$). According to the SAT evaluation, the MoA group showed a significantly higher prevalence of Type A (avoidant) of attachment style (44.68%) than control group (14.46%) ($p<0.001$) and a lower prevalence of type B (secure) of attachment style (19.15%) than control group (53.01%) ($p<0.001$). No significant differences were found in type C (ambivalent) (25.53% vs. 21.69%; $p=0.777$) and in type D (at risk) (10.64% vs. 10.84%; $p=0.796$) of attachment style among two groups.

Discussion and conclusions To the best of our knowledge no studies have investigated attachment styles in children affected by MoA. In adults, headache sufferers seem to be characterised by attachment styles of the "insecure" type, that could be considered the evolution of the avoidant styles found in our sample. Further research is needed on this subject, in order to ensure the best psychological treatment in children with MoA.

Chronic headaches in children and in adolescents: cases series of a Juvenile Headache Centre

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Introduction Chronic daily headaches (CDH) in children can be classified as chronic migraine (CM), chronic tension-type headache (CTTH), medication-overuse headache (MOH), new daily persistent headache (NDPH) or, finally, like other chronic headache not elsewhere classified (CHNC) [1]. The definition of chronic headache requires a frequency of at least 15 attacks per month for a minimum of 3 months [1].

Materials and methods Retrospective study of 165 patients with CDH, selected among all the cases ($n=1100$) evaluated at the Juvenile Headache Centre of Padua in the last year (October 2011-September 2012).

Results Patients with CDH represented 15% of cases (165/1100) (70 males, 95 females; mean age: 12 years, range 5-18 years): 58 patients were diagnosed as CM (35%), 42 CTTH (25%), 16 MOH (10%), 33 NDPH (20%), 16 CHNC (10%); other types of childhood CDH (such as hemicrania continua, chronic paroxysmal hemicrania or chronic cluster headache) were not found. In patients with MOH the following drugs were overused: analgesics 50%, NSAIDs 40%, analgesics and NSAIDs 10%; none of our patient overused triptans. The mean duration of drugs overuse, at the time of the evaluation, was 5 months. The detoxification was conducted mainly in outpatient settings (90%), and rarely required a Day Hospital setting (5%) or hospitalization (5%).

Conclusions In our cases, selected in a tertiary Centre, the prevalence of CDH (15%) and MOH (10% of CDH) is similar to other series previously reported; the “transformed” forms by an episodic headache (CM and CTTH) prevail than those with chronicity “*ab initio*” (NDPH). CDH are an emerging and complex problem of pediatric age for the differential diagnostic approach, the comorbidity and the need of multidisciplinary approach.

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Chronic primary headaches in children and adolescents referred to two third level headache centres

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Introduction The prevalence of chronic migraine (CM) and chronic tension-type headache (CTTH) increases with age, as it was especially shown in recent years. As for pediatric age, some points, including the prevalence of medication-overuse headache (MOH) in chronic headache children and the chronification rate in children with episodic primary headache, remain still obscure. The aim of the present study was to investigate the clinical characteristics of children with chronic primary headaches (CPH).

Methods We performed this preliminary retrospective epidemiological study in 2012 and included 5,000 charts of children referring to the Headache Centres of both Ospedale Bambino Gesù and Insubria University Hospital.

Results Among all 5,000 children with diagnosis of primary headache, referred to both Headache Centres, 270 patients (5.4%) received the diagnosis of CPH. This diagnosis was predominant in girls (66.4%). As for headache characteristics, 34.3% of CPH children were classified as CTTH, while 53.7% had a diagnosis of CM. Headache characteristics were undefined in the remaining 12% CPH children. New daily persistent headache (NDPH) and medication-overuse headache accounted for 16.29% and 5.6% of CPH, respectively. Among NDPH patients, most of them (80%) showed migraine characteristics of their headache.

Conclusions Our results showed that CM is the most important cause of CPH in both children and adolescents. Interestingly, we confirm the high prevalence of NDPH patients in pediatric CPH, far higher than that reported in adult CPH (around 6%). On the contrary, as expected, the rate of MOH in our CPH population was low.

Airplane headache: report of two cases in pediatric age

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Introduction Airplane headache (AH) is a rare form of headache disorder associated only with airplane travel. In the literature, AH has been reported in adults and only in three cases in children [1].

Case Report *Case 1:* A 10-year-old girl affected by migraine without aura; she described headache attacks triggered by airplane ascents and lasting about an hour; the pain was mild-moderate, pulsating and with a location in the right fronto-

orbital region. She experienced 3-6 airplane travels/year but, AH were occasional. Her past medical history did not indicate allergic rhinitis or sinusitis.

Case 2: A 13-year-old girl affected by new daily persistent headache for the last 3 months; headache was characterized by pulsating, occipital, intense pain, not responsive to drug therapy. The girl had a past history of only two airplane travels and in both of these she described AH attacks in both airplane ascents and descents. During these flights, she suffered from pressing/tightening, severe headache attacks with a location in the bilateral temporal region and associated with phonophobia. The attacks started when the airplane began ascending and was severe for 10–15 minutes; then it persisted in a mild form for about two hours and it stopped after the descents.

General, otolaryngological and neurological examinations were normal in both cases. Paranasal sinus tomography and cerebral magnetic resonance imaging are in progress (recent cases).

Discussion The aetiology and pathophysiology of this form of headache are unclear; sinonasal barotrauma is found to be responsible for some cases of AH.

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Pharmacological treatment of primary headaches in children: a multicentre Italian study

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Introduction In the literature there are few data about the use of pharmacological treatments (acute and prophylaxis) of primary headaches [migraine (M), tension-type headache (TTH)] in children [1].

Materials and methods Retrospective multicentre study conducted in 13 Juvenile Headache Centres; inclusion criteria: 1) diagnosis of primary headache (ICHD-II 2004); 2) stable headache pattern (>6 months).

Results Seven hundred and thirty-two cases (349 m, 383 f), mean age: 12 years. Headache types: M 68%, TTH 21%, M+TTH 5%, other 4%. The statistical analysis, conducted on patients with M or TTH (n=659), considered: efficacy and safety of several drugs, any differences based on age, diagnosis and geographical distribution.

Symptomatic treatment: 93% of children (M 95%, TTH 88%); type of drug: paracetamol (M 75%, TTH 75%), NSAIDs (M 51%, TTH 27%), triptans (M 6%, TTH 0%); good-excellent efficacy 72%, good-excellent tolerability 92%. **Prophylaxis therapy:** 52% of cases (M 45%, TTH 44%); type of drug: flunarizine (M 18%, TTH 2%), pizotifen (M 6%, TTH 0%), amitriptyline (M 3%, TTH 5%), anticonvulsants (M 7%, TTH 1%), supplements (M 31%, TTH 34%), melatonin (M 10%, TTH 10%); good-excellent efficacy 76%, good-excellent tolerability 85%.

Discussion and conclusions In our study population M prevails (76%). Symptomatic therapy is frequently used (93%), more often in M than TTH, with good efficacy and tolerability for all drugs; it is ineffective only in 10% of cases (range 7-23%). The use of NSAIDs prevail in M than TTH; few M (6%) use triptans.

Prophylaxis therapy, prescribed in about half of cases (both in M and TTH), is ineffective in 12% of cases, but is usually well tolerated; supplements (32%) and flunarizine (14%) prevail.

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Chronic headaches

Cognitive neuropsychological psychotherapeutic treatment in chronic migraine

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Introduction Chronic migraine is a disorder of difficult management in clinical practice. The therapeutic approach could be pharmacological or psychotherapeutic by regulation of emotion.

Materials and methods We proposed a weekly cognitive neuropsychological psychotherapy (PCN) to a group of patients affected by chronic migraine. The patients were asked to fill in a daily diary indicating frequency, intensity of headache, the use of medication and the emotional states correlated to symptom.

A MIDAS (Migraine Disability Assessment Scale) was dispensed at the beginning and the end of the treatment. Four patients were admitted for withdrawal treatment before starting psychotherapy.

The group was composed of 3 males and 5 females mean age 34, range 18-49. Two patients were affected by depression, one by anxiety. The adherence to psychotherapy was good. There were no drop outs.

Results Patients have had three months of therapy until now. The first step was to consider the context of headache attack and put together information regarding onset of pain and the events of daily life. Then, patients had to refer their feelings regarding the migraine. Placing attention on daily life events that facilitate the headache improves the ability of patients to take their feelings into consideration. The event's tale helps them regain control over their headache and feelings offering new possibilities to manage frequency and intensity of pain. A general attention to feelings is required in order to recognize and modulate the emotional states and reduce the impact of symptoms on daily life.

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Chronic migraine: an observational, prospective, multicentre study conducted by the SISC Triveneta Group

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Background Chronic migraine (CM) is a complication of migraine characterized by headache attacks that occur for at least 15 days/month. Although it is much less common than episodic migraine (EM), it is substantially more debilitating. The prevalence of CM worldwide ranges widely, but the majority of studies estimate 1-to-3%.

Materials and Methods We prospectively evaluated 153 patients (123 females and 30 males) with CM for two months, with the aim at gathering the most relevant data on their disorder. A structured questionnaire was delivered at the first visit and was collected at the second evaluation.

Results The patients' mean age was 43.8±7.8 years. The headache had become chronic for 6-to-15 years in about half of the cases. Most patients (64%) over the last year had consulted exclusively the family practitioner, whereas only

17% were seen at the headache centre. Notably, 10% referred to the emergency room, sometimes repeatedly. They underwent several investigations, mainly MRI (45%) and CT-scan (36%), which were normal and could be avoided if they had previously been re-evaluated by a headache specialist. The majority of patients (76%) had taken a variety of preventive treatments, but interestingly 22% were never treated prophylactically. Non-pharmacologic treatments were tried by 32% of cases. Medication overusing patients were 64%, while a detoxification treatment was performed only in 14% of patients.

Discussion CM is associated with greater headache-related disability and impairment of quality of life compared to episodic migraine. Our findings demonstrate that in addition to social and quality of life burden, those with CM also incur greater economic burden.

Conclusions Prophylactic therapies to reduce headache-related disability or therapies that prevent the onset of CM could be important approaches for containing medical costs. The results of this study help to quantify the potential benefit of targeting this highly burdened group of individuals.

Psychological profile in patients with medication-overuse headache and alcohol dependence: are there differences?

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Introduction Personality, as coping strategies and self-efficacy can affect resilience, vulnerability to stress and the choice of behaviours that can help to deal with psychological distress. Different personality profiles have been reported between headache abusers of analgesics and drug addicts. The main objective of the study was to assess psychological addictive aspects in patients with chronic headache plus medication overuse and patients with alcohol dependence referring to our Centre. Moreover, to assess differences with respect to personality, coping strategies and sense of self-efficacy.

Materials and methods We administered psychological tests (IPIP, SF-36, SCL-90, Zung Anxiety and Depression, LDQ) to 112 inward patients. Forty-five patients with medication-overuse headache (mean age 49.5) were compared with 32 alcohol abusers (mean age: 35.5) and 35 healthy controls (mean age: 45.5).

Results Preliminary data suggest that patients with medication-overuse headache have higher scores ($p<.05$) on the scales for anxiety and depression (Zung A 52±3.5; Zung D: 48±2.5) than patients with alcohol dependence (Zung A: 40±4.3; Zung D: 37.3±2.5) (mean±SD).

Patients with MOH and alcohol dependence do not share specific personality characteristics linked to psychological profile, whereas patients with alcohol dependence were characterized by poor impulse control, irritability and low tolerance for frustration (chi-square; $p<.001$); patients with MOH were more concerned about physical symptoms and were inclined to take responsibilities (chi-square; $p<.001$).

Discussion and conclusions The first data confirm the results reported in the literature. MOH patients and alcohol abusers do not share similar personality profile. However, there seems to be a common aspect about self-efficacy to deal with everyday life events.

The impact of chronic migraine on the quality of life and on the National Health System in a population of patients attending a 3rd level headache centre

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Chronic migraine (CM) is a common neurologic condition with a high impact on functional performance and quality of life (QoL). CM also represents a relevant economic burden on the National Health Service (NHS), but precise figures are lacking [1].

Our aim was to evaluate the disability and the impact on QoL of CM, as well as its economic cost on the NHS in a representative cohort. We enrolled 37 subjects with CM and 26 subjects with episodic migraine who attended the Headache Centre of our Institute. Patients were tested with disability scales (MIDAS, HIT-6, SF-36) and with an ad hoc semi-structured questionnaire. CM patients had a MIDAS score of 93.2 ± 55.4 , a HIT-6 score of 67.7 ± 4.4 and an SF-36 score of 40.4 ± 17.6 . In EM group the scores were 16.7 ± 19.7 for MIDAS, 61.4 ± 5.7 for HIT-6 and 66.4 ± 16.6 for SF-36 (CM vs. EM $p=0.001$ for each scale).

The direct mean annual cost (euros) for a single patient with CM was 1976.9 ± 2082.9 (659.9 ± 260.7 for symptomatic drugs, 131.1 ± 484.9 for prophylactic therapy and 1350.91 ± 1337.3 for diagnostic examinations). EM subjects showed a mean annual cost (euros) of 466.9 ± 815.1 (64.6 ± 18.4 for symptomatic drugs, 38.5 ± 61.5 for prophylactic therapy and 380.0 ± 734.8 for diagnostic examinations). The total economic load, as well as the different subitems, were significantly different between groups (CM vs. EM $p=0.001$ for each value).

The present findings, though limited to a relatively small population, confirm that CM is a disabling condition with a huge impact on the QoL of sufferers and a significant economic burden on the NHS. The adequate management of CM, reverting it back to EM, will provide a dual benefit: on the individual and on the society.

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Clinically-oriented stratified approach and patient-preference approach in the management of MOH: a comparison between two strategies

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Introduction The management of medication-overuse headache (MOH) is often difficult and no specific guidelines are available as regards the most practical and effective approaches. The aim of this study was to compare the cost-effectiveness of two different stratified approaches of drug withdrawal in 100 MOH subjects.

Materials and methods In the first approach, called clinically-oriented stratified strategy (COSS), patients were stratified based on the presence/absence of complicated MOH. Complicated MOH was defined by the presence of at least one of the following conditions: a) a diagnosis of co-existent, complicating medical illnesses; b) a current diagnosis of psychiatric disorder; c) a relapse after previous detoxification treatment; d) social and environmental problems; e) daily use of multiple doses of symptomatic medications. Patients with complicated MOH received a standard in-patient withdrawal programme whereas patients with simple MOH received advice to withdraw the offending drug. In the second approach, called patient-preference stratified strategy (PPSS), the patients received information about the effectiveness of the different withdrawal regimens: 1) simple advice, 2) outpatient detoxification, and 3) in-patient detoxification and they were treated according to their preferences.

The primary outcome measures used for comparing COSS and PPSS were: 1) number of responders defined as patients no longer overusing after 2 months; 2) number of dropouts; 3) cost per detoxified patient.

Results The number of responders (80% vs. 70%) and dropouts (16% vs. 18%) did not differ between COSS and PPSS. The cost per detoxified patient was 1.211 € for COSS and 430 € for PPSS.

Discussion A patient preference stratified strategy is as effective as a clinically-oriented stratified strategy, but less cost intense. PPSS should be preferred in MOH management.

Chronic headache: a new therapy

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Introduction This research is based on the experimental thesis: "ATM and plantar support: postural correlations" conducted on 33 patients, 23 female and 10 males, mean age 32 years. The principal aim was to investigate the correlations between mouth and feet and the myofunctional therapy effects on chronic pains, among which headache. All the patients had Angle second class and dysfunctional deglutition.

Methods In order to have the clearest picture of the ex-ante situation, all the patients were evaluated according to the VAS data sheet and showed the following symptoms: 42% suffered from low back pain, 30% from headache, 27% from neck pain, 15% from back pain, and 9% from sciatica.

Sixteen patients were treated with myofunctional therapy, which consisted in several daily exercises (conducted over 2 months and with growing difficulty), with elastics and buttons of different sizes, in order to recover the functional tongue position. This specific therapy was intended to facilitate the functional deglutition and the facial hypo-hypertonic muscles balance. Usually, this treatment is composed of three phases: 1) muscles re-education; 2) functional deglutition education; and 3) new deglutition engram acquisition.

Results In the treated population, the decrease in the total average symptoms was 71%, against 11% observed in the control group. In 11 of 16 treated patients the complete disappearance of chronic symptoms was registered.

The average decrease of symptoms in the treated group, after just 2 month, was: low back pain reduced by -77% (-4% control group), headache by -89% (-0%), neck pain by -36% (-13%), back pain by -100% (-5%), sciatica by -59% (-0%).

Conclusions The myofunctional therapy represents a new possible way to treat chronic headache, considering the remarkable decrease of 89%. Although these results appear very interesting and appealing, they represent just an initial research and need to be replicated with a bigger sample.

Treatment of chronic migraine by means of vagal stimulator

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Introduction Chronic migraine is a highly disabling pathology both for the intensity of the pain and for the associated symptoms, as well as the tendency for the continued use of drugs that can lead to medication-overuse migraine.

Objective To try a new non invasive, vagal nerve stimulator (VNS), the Gammacore.

Methods The study consisted in calling back on a pre-scheduled day a set of chronic migraine patients: 73 showed up (62 f and 11 m). Only 19 (16 f, 3 m) patients on that day were treated since they showed high intensity crisis associated with nausea, phono- and photophobia.

After obtaining informed consent, treatment included two doses of 90 seconds, 15 minutes from one another, from VNS device. In case of low benefits, a second stimulation was performed after two hours using 2 doses.

Results All 19 patients completed two stimulations, only four had another 2 (after 2 hours). The mean of the initial pain of the 19 patients was 6.63, (VAS 1-10) which decreased to 3.95 ($p < .05$) after 2 hours. After two hours: 9 patients no longer had pain, 6 reduced pain and 4 showed no variation. The symptoms associated at two hours, had disappeared in 8 patients, were reduced in 7 and still present in 4. Except for two brief local paresthesia which disappeared after a few minutes, there were no other side effects.

Conclusions This preliminary evaluation of the use of VNS for the treatment of chronic migraine crises, seems well tolerated and effective for reducing or avoiding the crisis. If this data is confirmed by further studies with placebo, then VNS can be considered a new useful instrument for the acute treatment of chronic migraine.

Therapeutic aspects of headache

Monitoring the use of symptomatic drugs in headache: a population study

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Background Headache is an extremely common neurological problem. Italy is the first European country for OTC consumption with related problems of self-medication, inappropriate use and risk of medication overuse.

Aim To collect information about symptomatic assumption behavior to monitor the consumption of symptomatic drugs for headache and to prevent drugs abuse/dependence.

Materials and methods Two hundred and thirteen patients consuming symptomatic drugs for headache were recruited in 34 pharmacies in the Pavia Health District. They first underwent a telephone interview about their headache, then they were programmed for a year follow-up in the headache out-clinic.

Results Pre-clinical interview data showed that 23% had >15 days per month of headache and took >15 doses of drug per month. Fifty-four percent were followed by GP and 30.76% used self-medication. Patients under medication took drugs with medical prescription (52.30%), OTC (33.84%), both (7.69%), and prevention drugs (5.12%).

Comparing these results with those of 100 patients' first visit, it results that patients with >15 days per month of headache were 20%, those who took >15 doses were 18%. Fifty percent took OTC, 46% drugs with medical prescription and 4% no drugs. Seventy-five percent needed a preventive treatment as their headache was at medium/elevated frequency and 10% were programmed for a disintossication treatment.

Conclusions These results highlight how patients often treat headache without medical advice and this condition may lead to abuse of drugs. Periodic monitoring of headache patients may help to control wrong behavior on symptomatic drugs consumption.

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Pilot study on the use of palmitoanilamide (PEA) in a group of patients with migraine without aura

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Introduction In the light of the increasing importance of the mechanisms of central and peripheral sensitization in the pathogenesis of migraine, the mechanisms of activation of the trigeminal sensory afferents assume a central role. These occur as a result of local release of neuropeptides that leads to vasodilatation (mediated by CGRP) and increased vascular permeability (mediated by substance P and neurokinin A), accompanied by mast cells activation.

The proinflammatory neuropeptides released by nociceptors activate mast cells, which in turn react degranulating numerous proinflammatory substances including the Nerve Growth Factor (NGF) responsible for the phenomenon of sensitization of peripheral sensory nerve endings. The NGF is detected by nociceptors inducing increased synthesis of the Transient Receptor Potential Vanilloid 1 receptor (TRPV1). In this triad the mast cell plays a key role.

Materials and methods We selected from the Headache Centre of the "Istituto Clinico Città di Brescia" a population of 20 patients aged between 18 and 65 years, suffering from migraine without aura with a frequency between 3 to 6 crises/month (5 to 15 days with headache/month), not assuming other migraine preventive therapy. They underwent a treatment with palmitoanilamide 600 mg bid for 10 days followed by 600 mg per day for a total of 3 months. Patients were evaluated for frequency, duration, intensity of pain, complexity of the associated symptoms and response to their habitual analgesic drug (data obtained from the diary of headache delivered at first visit).

Results No patient had to discontinue the study due to side effects and no significant side effects were reported. A reduction in frequency of more than 50% in 6 patients and of 30% in 8 patients was registered. Seventeen patients reported a reduction of more than 50% in the duration of pain, and in all the attacks the intensity of the crisis and the complexity of the accompanying symptoms were less severe.

Discussion and conclusions The administration of a molecule able to act in a synergism on both targets, that is, on the sensory termination, desensitizing the TRPV1 receptor and thereby blocking the transmission of pain, and on the mast cell, by reducing the inflammatory processes resulting from its degranulation, was shown to have the conditions to intervene in the complex pathogenic mechanisms that underlay migraine.

Benefits of a preliminary assessment for treatment with topiramate in patients at risk for cognitive disorders: the Frontal Assessment Battery

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The use of topiramate (TPM) in the prevention of migraine can be responsible for cognitive disturbances. Although these disturbances are not frequent (from 10 to 20%), quite mild and always reversible, the occurrence of these adverse events lead the patients to discomfort and worry. Due to the potential side effects, the use of a pre-emptive test could be useful to verify the impact on cognitive functions of patients undergoing this prophylactic treatment.

The Frontal Assessment Battery (FAB) could be the most suitable because of the brevity, the quickness and the diagnostic efficacy.

The scale is composed of 6 steps that assess: language, conceptualization, motility and controlled behaviour. It ranges from 0 (execution impossibility) to 18 (maximum capacity). The average rating for the Italian population is 16.1±1.8; the normalcy range is 9-18. This rating must be adapted for anagraphic and school age. The test should be administered before beginning the therapy and repeated every two months for the complete duration of the therapy.

This brief battery could also be promising to predict the development of cognitive disturbances in migraine patients undergoing TPM therapy.

Warfarin efficacy in migraine without aura but not in exertional headache

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Introduction Controlled studies on the effectiveness of anticoagulant therapy (ACT) are limited in migraine, but single cases have been described in which the administration of ACT in comorbid diseases produced a migraine improvement. We present a case of a patient suffering from both MO and primary exertional headache (PEH, International Headache Classification criteria-II, 2004), in which ACT with warfarin lead to MO remission, whereas PEH remained unchanged.

Case report On February 2013, a 36-year-old woman presented to our out-patient Headache Centre (HC). The patient had a familiar anamnesis positive for migraine; personal anamnesis was negative for oral contraceptive and pathologic remote events. She experienced her first MO episode at the age of 26 years and PEH attacks at 32 years. In May 2012, she presented deep venous leg thrombosis, treated with low molecular weight heparin for three months. Nevertheless, in August, she was diagnosed with pulmonary embolism. Immediately, warfarin therapy was started, attaining a International Normalized Ratio (INR) 2-3, with the resolution of pulmonary disease and with the complete disappearance within one month of MO, whereas PEH attacks remained unchanged. An extensive coagulative screening, neurological and cardiological examinations were normal. A six months follow-up showed a complete remission of MO attacks; instead, PEH attacks recurred with the same frequency.

Discussion Our case seems to confirm the involvement of coagulation mechanisms in migraine, but not in another primary headache, namely PEH. Another consideration is that in our case warfarin showed to be effective in migraine prophylaxis, whereas the previous treatment with low molecular weight heparin for three months was not. These data support the hypothesis of specific mechanisms of action of warfarin on migraine, which could increase our insight on its physiopathology.

TINER in headaches of patients with obstructive sleep night apneas

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Objective To study the benefits of Neuromuscular Emotional Relaxing Treatment Integrated (TINER) in reducing the prevalence of headache in patients suffering from the syndrome of obstructive sleep night apneas and concomitant headache.

Materials and methods We studied 52 subjects, mean age 53.8±2.0. The subjects were recruited within the Department of Psychiatry at the Giulianova Hospital. Headaches were classified according to the criteria of IHS. Thirty-two patients referred with a history of primary headache: 4 affected by migraine and 28 headache. Twenty had tension headache on awakening. Twenty-six subjects were subjected to TINER therapy and interview with a standardised questionnaire on sleep features, on related conditions, on the type of headache, and on risk factors for headache.

Results At the end of the study, after one year, the severity of obstructive night disturbances and headache frequency (frequency greater than patients with insomnia), were reduced, as well as the negative impact, emphasizing the important role of TINER therapy.

Discussion A strength of this study, in addition to the sample size, is the fact that we had collected detailed data on the characteristics of patients regard-

ing sleep disorders and risk factors of headache. The study group seems to have a high reduction in frequency and seriousness of headache.

Conclusions Ultimately, we can say that the headaches of patients with obstructive sleep apnea improve both in frequency and seriousness with TINER therapy. It is very useful to screen sleep disturbances related to respiratory diseases, for a correct diagnostic and preventive therapeutic approach and care in relation to the onset of headaches.

TINER in family members with headaches of patients affected by epilepsy

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Introduction Studies suggest that between epilepsy and headache there could be a possible common pathogenesis of neuronal hyperexcitability caused by dysfunctions present in the central nervous system. Based on this fact, we considered that epilepsy and headache may share a genetic link.

Materials and methods We studied 68 family members each with at least 2 epileptics, checking whether kinship with this latter disorder could increase the odds in their families for complaints of headaches. We studied the prevalence of epilepsy in family members who had experienced episodes of headache. Thirty-four subjects were subjected to TINER therapy.

Results The incidence of headache, in close temporal relation, is greater in patients who have close family members who suffer from epilepsy. At the end of the study, after one year, the headache frequency (frequency greater than patients with epilepsy), is reduced, emphasizing the important role of TINER therapy.

Discussion A strength of this study, in addition to the sample size, is the fact that we had collected detailed data on the characteristics of patients regarding epilepsy genetic susceptibility for headache in the family. All were subjected to an interview with a standardised questionnaire on epilepsy, on related conditions, on the type of headache and on risk factors for headache. The study group, subjected to TINER therapy, seemed to have a high reduction in frequency and seriousness of headache.

Conclusions Our study seems to confirm a shared genetic susceptibility for headache in a large amount of patients with common forms of epilepsy. Ultimately, we could say that the headaches in family members of patients with epilepsy improve both in frequency and seriousness with TINER therapy.

Efficacy of a physical and educational programme on muscle tenderness in a working community with headache and neck pain: a longitudinal, controlled study

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Introduction This study was aimed at examining the effect of a physical and educational programme on pericranial and cervical muscle tenderness in a working community.

Materials and methods Three hundred and eight-four employees of the registry/tax office of the city of Turin, were distributed into a study (group 1; n=192) and a control group (group 2; n=192). Group 1 received a physical/educational intervention with relaxation/posture exercises and a visual feedback. After six months, the intervention was administered to group 2. Both groups were followed for an additional six months until the end of the trial. In all subjects data were taken of headache and neck pain. Palpation of pericranial (masseter, lateral-medial pterygoid, temporal) and cervical (ster-

nucleidomastoid, trapezius, nuke) muscles was carried out in a standardized way. For each patient, a Pericranial Muscle Tenderness (PTS) and a Cervical Muscle Tenderness (CTS) score (0-3) were calculated.

In the two groups the difference between the data at the baseline and those at six months and at the end of the trial was calculated and the data compared (Student's t test).

Results After six months, a significant difference was found between groups in the mean change from baseline in PTS (-0.19; CI: -0.3 to 0.081) and CTS (-0.2; CI: -0.31 to 0.08), which was no longer detectable at the end of the study (PTS: 0.03, CI: -0.07 to 0.141; CTS: -0.2, CI: -0.13 to 0.1).

Conclusions The administration of an instruction programme can significantly decrease pericranial/cervical muscle tenderness in a working community. This finding may be partly due to the beneficial effects of such programme on the headache and neck pain in the study population.

Surgical treatment for headache: personal procedure

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Introduction During the last few years multiple studies have demonstrated the efficacy of surgical treatment in patients who suffer with migraine headaches, based on trigger effect which muscular compression has on peripheral nerves. Guyuron et al. [1] reported the elimination or improvement in forehead migraine headaches through surgical decompression of the peripheral branch of trigeminal nerve (n. supratrochlearis and supraorbitalis) following removal of hyperactive corrugator supercilii muscles, and in occipital migraine headaches through surgical decompression of cervical plexus - C2 (lesser and greater occipital nerves) following removal of hyperactive surrounding muscles. The aim of this study was to demonstrate the efficacy of surgical decompression by means of both endoscopic and open surgery, through innovative and improved technique compared with beforehand evaluated surgical techniques.

Patients and methods Twenty patients who complained of chronic migraine headaches underwent a frontal bilateral selective myotomy procedure of procerus, depressor supercilii and corrugator supercilii muscles by means of video-assisted endoscopic surgery, and an occipital selective myotomy procedure of occipital, trapezius, sternocleidomastoid and semispinalis capitis muscles by means of open surgery.

Results Of the 20 patients included in the study (range: 27 to 72 years), 16 were women and 4 were men. Seventeen of the twenty patients (85%) reported a positive response to the surgery: eight of the twenty patients (40%) observed complete elimination, nine (45%) experienced significant improvement (at least 50% reduction in intensity or frequency), and three (15%) did not notice a change in their migraine headaches.

Conclusions This study goes beyond previous data in the literature, confirming the trigger points theory as a concrete explanation in the onset of migraine headaches. Furthermore, as demonstrated by the results, this kind of surgical procedure obtains as much efficacy as previous surgical procedures and is less invasive and has less adverse effects.

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Neuroscience and Pain

Warmth and nociceptive evoked potentials in Crisponi Syndrome

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Introduction Crisponi Syndrome (CS) is a rare severe infantile autosomal recessive disorder caused by mutations in the cytokine receptor-like factor 1 gene. It is characterized by dysmorphic features, feeding difficulties and hyperthermia. Hyperthermia frequently leads to death within the first months of life, whereas surviving patients develop scoliosis, psychomotor retardation and cold inducing sweating. Cold induced sweating is the most disabling symptom in adulthood. With environmental temperatures of 22°C or less, individuals sweat profusely on their face or upper body, with dermal vasoconstriction. Electromyography, motor and sensory nerve conduction velocities are usually normal, however, up to now, there are no studies evaluating thermal and pain sensations in those patients. The aim of the present study was to assess the function of A-delta and C fibers by means of CO₂ laser-evoked potentials (LEPs) in CS patients.

Materials and methods Four patients were studied, laser pulses were delivered on the skin of the hand and of the perioral region at painful intensity to record LEPs related to A delta-fiber inputs and at non-painful intensity to obtain LEPs related to C-fiber inputs. Results: In all four subjects the latencies of N1/P1 and N2/P2 potentials were normal from both stimulation sites and for both A-delta and C fiber stimulation.

Conclusions This study demonstrates that cutaneous nociceptive and warmth pathways function in CS patients is normal, indicating that cold induced swallowing is not associated with any involvement of warmth and nociceptive fiber inputs.

Cortical changes induced by focal mechanical vibration on nociceptive pathways

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Introduction Focal mechanical vibration (FMV) is able to selectively stimulate the non-nociceptive A β afferents. While FMV has proved useful in modulating motor function, its possible efficacy in pain relief is unknown. Previous studies showed that the electrical A afferent stimulation is able to reduce spontaneous pain and laser evoked potential (LEP) amplitude. The objectives of the current study are to evaluate if FMV may: 1) change the LEP amplitudes and/or latencies and 2) have an analgesic effect.

Materials and methods Ten healthy volunteer have been evaluated in two different sessions in order to test effective and sham FMV. LEPs were recorded from 4 scalp recording electrodes (Cz, Fz, T3, and T4) after stimulation of both the right and left radial and ulnar cutaneous territories. LEPs were recorded in a baseline condition and during either effective or sham FMV delivered over the right radial territory.

Results Neither the amplitudes nor the latencies of both the vertex N2/P2 and the contralateral N1 LEP components were changed by both effective and sham FMV, as compared to the baseline. The psychophysical evaluation of the laser-induced pain did not show any analgesic effect of the FMV.

Conclusions Our results show that FMV is ineffective in modifying the LEP components and in reducing phasic laser pain.

Discussion Further studies are needed to evaluate whether FMV might be useful in reducing a longer lasting pain.

Pain in postsurgical orthopedic rehabilitation: a multicentre study

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Introduction The aim of this study was to quantify and characterize pain in patients undergoing lower limb postsurgical orthopedic rehabilitation and to investigate the impact of pain in slowing or interrupting their rehabilitation.

Materials and methods We studied 139 patients. Pain intensity was measured with a numeric rating scale (NRS); pain characteristics were assessed with the McGill Pain Questionnaire and the ID Pain (able to discriminate nociceptive from neuropathic pain). Quality of life (QoL) was measured with the Short Form 36 Health Status Survey. A semi-structured questionnaire on pain occurrence, impact, and management was administered by the physiotherapist in charge of the patients and by the physician.

Results We found 82% of patients complained of at least moderate pain (NRS ≥ 3). According to ID pain, 45.6% patients complained of probable (33.8%) or highly probable (11.8%) neuropathic pain. A higher pain intensity was significantly related to the probability of having neuropathic pain ($p < 0.001$). Patients with more severe pain reported lower physical and mental QoL scores. In 38.6% of cases, pain interfered with the rehabilitation process, and in 18.5% it was the cause of physical therapy discontinuation. A higher pain intensity was significantly related to the probability of having neuropathic pain ($p < 0.001$). Patients with more severe pain reported lower physical and mental QoL scores. In 38.6% of cases, pain interfered with the rehabilitation process, and in 18.5% was the cause of physical therapy discontinuation.

Discussion The results show the importance of pain in postsurgical orthopedic rehabilitation. A higher pain may be related to lower physical and mental scores. It may limit the rehabilitation process and cause a therapy discontinuation.

Conclusions Clinicians should pay more attention to pain, especially neuropathic pain, in postsurgical patients. Tailored pain pharmacological therapy could possibly improve patient compliance during the rehabilitation process.

Lack of habituation of evoked visual potentials in analytic information processing style: evidence in healthy subjects

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Introduction Analytic information processing style is characterized by the habit of continually evaluating and processing stimuli. A strong correlation between this cognitive style and migraine has been observed, indicating a preference toward a visual sensory approach in migraine without aura [1]. On the other hand, it is known that habituation, an adaptive mechanism of the cerebral cortex when exposed to repetitive stimulation, is modified in migraineurs, suggesting that deficient habituation may represent a trait marker of the migrainous brain.

We investigated a possible correlation between lack of habituation of evoked visual potentials (VEP) and analytic cognitive style in healthy subjects.

Materials and methods According to Sternberg-Wagner Self-Assessment Inventory, AMOS Test and Brain-Dominance questionnaire, 15 HV with high analytic score and 15 HV with high global score (control group) were recruited. Both groups underwent VEP recordings after psychological evaluation for the habituation to be assessed.

Results We observed significant lack of habituation in analytical individuals compared to the whole group.

Discussion and conclusions This finding suggests that analytic cognitive style seems to be associated with the lack of habituation in healthy subjects. This datum might be important in the light of the complex relationship between cognitive style, habituation and migraine.

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A clinical and neurophysiological study of pain in patients with Ehlers Danlos Syndrome

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Although pain is a frequent complaint in patients with Ehlers Danlos Syndrome, its underlying mechanism is still debated, thus limiting the effectiveness of treatment. Although some recent reports suggested that most patients with Ehlers Danlos Syndrome suffered from neuropathic pain, no studies have assessed pain associated to this rare condition with the recently proposed diagnostic criteria for neuropathic pain.

In this prospective study we aimed at assessing prevalence, clinical features and underlying mechanism of pain in twenty patients with Ehlers Danlos Syndrome. All patients underwent a detailed clinical and neurological examination, including the DN4 questionnaires for diagnosing neuropathic pain and the fibromyalgia rapid screening tool. We also recorded the standard nerve conduction study, assessing the non-nociceptive afferent fibres, and laser evoked potentials for assessing nociceptive afferent fibres.

We found that clinical examination, DN4 questionnaire, standard nerve conduction study and laser evoked potentials disclosed no abnormalities consistent with a diagnosis of neuropathic pain. Conversely, clinical examination showed that most patients suffered of widespread pain, with a positive fibromyalgia rapid screening tool.

Our data argue against the view that Ehlers Danlos Syndrome-related pain is a neuropathic pain condition, rather our patients suffered of a widespread, fibromyalgia-like pain.

Pain in a complex case of polyneuropathy and possible schwannomatosis

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Introduction Schwannomatosis is a rare condition presenting with benign tumors along the peripheral nervous system. The most common symptom reported by schwannomatosis patients is chronic pain which is described as local, multifocal or diffuse.

Case report A 41-year-old man was hospitalized for severe pain that started 3 years before. The patient was taking pregabalin 600 mg/d and clonazepam 0.7mg with pain rated as 7/10 at NRS. DN 4:7/10. He described multiple painful areas in the body with painful electrical, pins and needles, stabbing sensations and tingling, sometimes burning. Examination: palpable, soft tissue masses of variable dimensions, in multiple sites of upper and lower limbs with positive Tinel signs on some of them, decreased tendon reflexes in the upper limbs, absent in the lower limbs, slight hyposthenia of lower extremities distal muscles. Hypoesthesia for all modalities in glove and stocking distribution. EMG-ENG study: sensory-motor demyelinating polyneuropathy. LEPs responses were normal, stimulating the radial nerve territory, bilaterally, being painful only on the right side. SNAPs recorded from the same areas were reduced in amplitude only on the right side, with normal conduction velocity bilaterally. NPSI-FW: 31. Cerebrospinal fluid was normal. The family history was negative. Brain and spinal MRI were normal. MRI of brachial and lumbosacral plexuses revealed enlargement of all cervical and lumbar roots and multiple rounded nodules along multiple nerves. A surgically removed tumor from the right thumb proved to be a myxoid schwannomas. Blood sample analysis for NF1, NF2, SMARCB1 mutations were negative.

Adding carbamazepine 400 mg and amitriptyline 50 mg to treatment produced significant pain relief. Pain NRS: 2/10, NPSI-FW: 10.

Clinical, neurophysiological and skin biopsy study of painful neuropathy associated with HCV related-cryoglobulinaemia

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Peripheral neuropathy and neuropathic pain are common and disabling complication of HCV related-cryoglobulinaemia. However little is known about their prevalence, clinical characteristics and risk factors. In this prospective clinical, neurophysiological and morphometric study we collected 65 consecutive patients with HCV related-cryoglobulinaemia. We used DN4 questionnaire to diagnose neuropathic pain, and the Neuropathic Pain Symptom Inventor (NPSI) to rate the intensity of the different qualities of neuropathic pain. All patients underwent standard nerve conduction study to assess Ab-fibre function, laser evoked potentials to assess Ad-fibre function, and skin biopsy to assess C-fibre terminals. Forty-five patients had a peripheral neuropathy and 29 had neuropathic pain as assessed with the DN4 questionnaire. NPSI questionnaire showed that the most frequent types of pain were the superficial burning and the deep pressing pain. While peripheral neuropathy was significantly associated with the duration of HCV infection (time from the diagnosis), it was unrelated to the duration of cryoglobulinaemia. Patients with peripheral neuropathy had an older age than those without ($p<0.05$). In patients with neuropathic pain the amplitude of laser evoked potentials was significantly lower than that of patients without pain; conversely the nerve conduction study and skin biopsy data did not differ. The severity of the superficial burning pain correlated with the amplitude of laser evoked potentials ($p=0.01$), but not with the skin innervation density. Our data showing that peripheral neuropathy is related to age and HCV infection, rather than cryoglobulinaemia, and neuropathic pain is associated with the damage of nociceptive pathways as assessed with laser evoked potentials, might improve the clinical approach to peripheral neuropathy and neuropathic pain due to HCV related-cryoglobulinaemia.

Point prevalence study of multiple myeloma induced-peripheral neuropathy

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Peripheral neuropathy and neuropathic pain are common complications of multiple myeloma (MM) treatment. In this point prevalence study we aimed at assessing prevalence, clinical characteristics and predictive factors of peripheral neuropathy and neuropathic pain in patients with multiple myeloma. We collected 217 consecutive patients with multiple myeloma. All patients underwent clinical examination, DN4 questionnaire for neuropathic pain, the standard nerve conduction study. Patients with sensory disturbances but normal standard nerve conduction study underwent skin biopsy.

Seventy-one percent of patients had a peripheral neuropathy. Sixty-four percent of patients had pain at the time of visit; forty-three percent experienced neuropathic pain according to the DN4 questionnaire. Peripheral neuropathy was significantly associated with the duration of disease and treatment (the longer the disease and the higher the number of treatments during the disease the more frequent the neuropathy; $p<0.05$, Chi-squared test). The different treatments were significantly associated with the development of peripheral neuropathy ($p<0.05$), being the combination bortezomib-thalidomide the most frequently associated with peripheral neuropathy, and the lenalidomide the less frequently associated.

Our data underline the clinical importance of peripheral neuropathy and pain in patients with multiple myeloma and indicate that duration of disease and treatments are associated with a higher risk of developing peripheral neuropathy.

Diabetic small fibre neuropathy diagnosis: a comparison between the diagnostic accuracy of skin biopsy and laser evoked potentials

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Introduction Small fibre neuropathy related to diabetes is a condition characterized by a selective involvement of nociceptive fibres. The currently recommended method for assessing diabetic small neuropathy is the skin biopsy, that assess cutaneous C-fibres. Laser evoked potentials mediated by Aδ-fibres is a widely accepted neurophysiological method for assessing nociceptive pathways.

Objectives We aimed at comparing the diagnostic accuracy of LEPs and skin biopsy in the diagnosis of diabetic small fibre neuropathy.

Methods We screened 100 diabetic patients with distal sensory disturbances that, on the basis of clinical examination and standard nerve conduction study, were divided into three subgroups: pure small fibre neuropathy (16 patients), pure large fibre neuropathy (30 patients) and mixed fibre neuropathy (54 patients). Patients with small-neuropathy and pure large fibre neuropathy underwent LEP recordings and skin biopsy.

Results Using the skin biopsy as the gold standard for assessing the small fibre neuropathy LEPs showed a sensitivity of 91.67% and a specificity of 90%.

Discussion Our data suggest that LEPs have a diagnostic accuracy comparable to that of the skin biopsy in the diagnosis of diabetic small fibre neuropathy.

Paroxysmal pain is mediated by non-nociceptive large myelinated fibres. A neurophysiological study in normal humans

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In this neurophysiological study we aimed at verifying whether high frequency, low intensity electrical stimulation, selectively activating non-nociceptive large myelinated fibres, can produce a painful paroxysmal sensation resembling the electrical shock-like pains typically occurring in neuropathic pain conditions. In 10 healthy subjects high frequency (100 Hz), low intensity (2-5 mA) electrical stimuli producing a painful paroxysmal sensation were delivered to the fifth finger. After lidocaine block of the ulnar nerve at the wrist the painful sensation persisted, while pinprick and thermal threshold significantly increased ($p < 0.05$, paired t -test). Because tactile sensation remained unchanged we conjecture that the painful sensation is mediated by non-nociceptive large myelinated fibres. This finding supports previous data showing that in patients with different neurological diseases paroxysmal pain is associated to large myelinated fibre dysfunction.

Headache in childhood and adolescence

Headache secondary to cardio and cerebrovascular disorders in children and adolescents: our experience

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Introduction Migraine is associated with cardiac and pulmonary right-to-left shunts. Furthermore, its presence elevates the risk of cardiovascular disease and ischemic stroke [1]. We report 3 emergency cases sent to us.

Case 1 A 17-year-old boy was referred to the emergency room for sudden onset of diplopia, vertigo, ataxia and dysarthria; he had a history of several migraine with aura attacks. Neurological examination showed right hemiplegia, so we decided to hospitalize him. The transcranial doppler ultrasound revealed the presence of a right-to-left shunt. The cardiac ultrasound excluded a patent foramen ovale, while the thoracic CT with contrast showed a left lower lobar arteriovenous fistula.

Case 2 A 9-year-old boy came to our attention for the presence, a few days prior, of frontal temporal, drug resistant headache, associated with vomiting, photophobia and phonophobia. The fundus oculi was negative, however because of clinical worsening with drowsiness, confusion and anisocoria, we decided to perform a brain CT, that showed an intracerebral hemorrhage.

Case 3 A 14-year-old girl reported cervical pain secondary to a contracture during sport. Then a severe, frontal headache appeared, accompanied by vertigo, vomiting and weakness. There were no focal neurological signs. A brain CT showed no obvious abnormalities, but since the symptoms persisted, we also performed an MRI, that revealed multiple ischemic cerebellar lesions. The magnetic resonance angiography of the over aortic trunks showed a left vertebral artery dissection.

Discussion The association between migraine and cardio-cerebrovascular diseases, well documented in adults, is not so rare in children and adolescents. Its evaluation requires attention, above all in the paediatric emergency department; clinical reevaluations should be warranted, even if neuroimaging is normal or neurological examination is negative.

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