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SUPPLEMENT

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of Headaches**

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Lifting The Burden

In Official Relations with the World Health Organization
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The Journal of Headache and Pain

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This year the National SISC Congress 2014 anticipates the annual appointment with clinicians, researchers and more generally with health care professionals involved in the fields of headache and neuropathic pain in adults, children and adolescents. The scientific programme intends to conduct the most recent findings in advanced research, the results of innovative interventions and therapeutic procedures, experimental evidence supporting new hypotheses, and clinical and pathophysiological definitions of these disorders, towards a unified interpretation which can be constantly ascribable to the tangible objectives of a Care System - Headache Care - adhering to the foundations of a standard, qualified, validated, safe and inexpensive health care assistance in accordance with what has been accredited at the European level.

The topics proposed will therefore cover specific aspects of pathophysiology with references to basic science (thalamic pain modulation, circuits and mechanisms of drug abuse/addiction, advanced imaging, experimental pain models, and habituation and allodynia) in the prospective of identifying the intermediate phenotypes of disease, on the basis of trait and state markers: biomarkers, neurophysiology parameters of the nociceptive systems, and adaptive responses related to pain and treatments.

Considerable emphasis will be placed on the clinical interpretation, which will focus on the diagnosis of headaches and the appropriateness criteria of the diagnostic and therapeutic pathways under certain conditions and subgroups, in relation to age, gender, history and clinical characteristics of headache: particular forms of migraine aura, cluster headache and other trigeminal - autonomic forms, stages of reproductive life, comorbidities and interactions between treatments, critical review of old and new therapeutic targets (triptans, anti-CGRP, opioids, cannabinoids, botulinum toxin) and the latest neurostimulation/modulation techniques and procedures.

Joint Sessions will also be proposed in this 2014 edition, in collaboration with study groups, scientific societies, associations, institutions and organizations which share the same interests and scientific and clinical objectives of our Society, whose activities are strongly characterized by its multidisciplinary nature and constant commitment towards achieving benefits for patients. This is made possible by SISC's participation in ongoing national initiatives (Italian Migraine Project) and through the activities of the SISC Regional Sections which interact with the local health system.

As usual, a substantial part of the programme will be dedicated to the specific problems of headache in children and adolescents, to thematic symposia and plenary discussion of selected contributions, encouraging the participation of young clinicians and researchers with specific promotional initiatives.

Giorgio Bono
President
Italian Society for the Study of Headaches

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Global Burden of Disease 2010 reported tension-type headache as the 2nd and migraine as the 3rd most prevalent disease worldwide. Migraine alone summarizes over half of YLDs if compared with all other neurological disorders, while migraine is placed as 7th as disease producing ictal disability. Public impact of headache disorders is largely underestimated and the need of health-care resource allocation is completely to be defined.

Lifting the Burden, an international NGO acting for the past 10 years, from 2009 acts in official relations with the WHO. Its main activity is The Global Campaign against Headache that produced special products such as the LTB-EHF-WHO Aids for management of common headache disorders in primary care (2007), the Atlas of Headache Disorders and Resources in the World (2011), and the Handbook of Headache (2012). The Master in Headache Medicine at the Sapienza University continues to be another educational product of LTB since 2006.

Headache Medicine started to represent a challenge at the Sapienza since 2002 and now the Master Degree, which has reached its 11th annual course, produces a virtuous train-the-trainer chain worldwide.

The dissemination of Headache Centres in Italy is optimal and almost completely covered by the two existing Societies, such to represent a healthcare gold standard. The healthcare recognitions of specific PTDA for chronic migraines from pilot regions like Emilia Romagna, Calabria, Lazio etc. is recent history, and it is another piece of evidence on how headache centres integrated with the cultural training of multi-level areas and collaborating with patients' ONG can produce beneficial effects on an endemic pathology such as headache disorders.

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Headache and Sleep Disorders*M.P. Prudenzano**Headache Centre, Neurological Clinic "L. Amaducci",
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Headache and sleep are tightly interwoven and their relationship is very complex. Both lacking sleep and excessive sleep may trigger headache attacks. Frequent nocturnal awakenings for headache occur in about 8% of general population and are associated with several sleep disorders such as restless legs syndrome, sleep-disordered breathing and bruxism.

As a result of HUNT2, a population based study in Norway, insomnia showed to be a significant risk factor for headache (OR: 1.50, 95% CI: 1.16–1.95). Insomnia is also the most frequent sleep disorder among headache patients. A recent study on subjective and objective sleep quality and pain thresholds in migraine and tension-type headache patients showed that specific subgroups of headache sufferers need more sleep than healthy controls and might be relatively sleep deprived supporting the hypothesis that sleep deprivation reduces pain threshold. Unsatisfactory sleep contributes to the worsening of quality of life in headache sufferers. Sleep breathing disorders are considered risk factors for the progression of migraine to chronic daily headache. Obstructive sleep apnea is highly associated with cluster headache and hypnic headache, but can also cause a secondary headache named headache related to obstructive sleep apnea.

Hypnic headache and cluster headache are strictly related to sleep and are both considered chronobiological disorders. In particular cluster headache follows a circadian and circannual rhythmicity and hypnic headache shows an alarm clock pattern. Headache preventive drugs may affect sleep inducing either sleep fragmentation or nightmares (i.e., beta blockers). Other drugs frequently used for headache prevention may cause either nocturnal sleep improvement or sleepiness (i.e., amitriptyline). A common anatomic and physiologic substrate may explain the complex link between sleep and headache, their frequent comorbidity and the effects of therapies. Screening for sleep dis-

orders and taking sleep into account is very helpful for a correct management of headache patients.

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Antidepressants, NSAIDs and chronic pain. The model of fibromyalgia

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Fibromyalgia (FMS) is regarded as a paradigm of chronic pain without any documentable organic cause. It is characterized by diffuse and symmetric musculoskeletal pain and tenderness, with positivity of at least 11 out of 18 Tender Points, non-restorative sleep, frequent headaches and affective disturbance, particularly depression.

Treatment of FMS, directed at reducing the major symptoms of the disorder, includes a number of nonpharmacologic and pharmacologic therapies, often in combination, ideally administered thorough multidisciplinary and individualized treatment programs. Pharmacologic treatment, however, represents the mainstay of the long-term therapeutic plan [1]. Although antiepileptics, especially pregabalin, constitute an important recommended drug class, antidepressants remain the most frequently employed compounds, because they decrease pain and often improve function. Particularly tricyclics, especially amitriptyline, are used, but also selective serotonin re-uptake inhibitors (SSRIs), e.g., fluoxetine, or dual-reuptake inhibitors (serotonin and noradrenalin reuptake inhibitors - SNRIs), e.g., venlafaxine or duloxetine. Being non-inflammatory in nature, fibromyalgia pain is regarded as typically non-responsive to Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) or corticosteroids. However, in many circumstances NSAIDs can indirectly contribute to alleviate FMS pain. Although fibromyalgia is a centrally-based syndrome (enhanced pain transmission, decreased descending pain control), in fact, it most often coexists with peripheral inflammatory conditions, such as myofascial trigger points, inflamed joints or visceral inflammatory pains (e.g., dysmenorrhea, endometriosis). In FMS patients comorbid with any of these conditions, NSAID treatment of the latter (local for myofascial trigger points and painful joints, systemic for visceral pain) significantly improved not only the peripheral pain but also the fibromyalgia pain and tenderness. This allowed a significant reduction of the doses of the specific FMS drugs,

e.g., antidepressants, necessary for the long-term control of the symptomatology. This result is probably due to a reduction – through NSAID treatment – of the sensitizing effect of the peripheral nociceptive input onto sensory neurons in the Central Nervous System. The lesson from fibromyalgia is that chronic pain is a complex condition, most often the result of a combination of multiple factors (peripheral and/or central), all of which need to be taken into account for optimizing its control.

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The work in progress of the Italian Consensus Conference on Chronic Pain in Neurorehabilitation: headaches, cranial neuralgias and facial pain

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The aim of the Italian Consensus Conference on Chronic Pain in Neuro-rehabilitation, promoted by the scientific Italian societies SIRN and SIMFER, is to provide guidelines for any chronic pain condition in diseases undergoing rehabilitation programs. Primary and secondary headaches, cranial neuralgias and facial pain have been included to evaluate the relevance and the occurrence they have in rehabilitation patients and to provide guidelines for their treatment, particularly in their chronic presentation. Therefore, the study group (Authors), by going through scientific literature, tried to find out the incidence and prevalence of those conditions in rehabilitation patients. Regarding primary headaches, this specific query could not be addressed, since there are no reports in the literature that describe how primary headaches may occur in such patients. As for secondary headaches, cranial neuralgias and facial pain are concerned, they are better focused by the other study groups who went through specific diseases causing pain. To answer the queries regarding treatment (pharmacological and non-pharmacological), the available scientific literature was evaluated and level of evidence for final recommendation was given. Substantially, no further or different recommendation can be given for primary headaches, after the SISC guidelines (2011). In fact, clinical trials or meta-analyses did not add further information that could change what SISC guidelines had stated for both pharmacological and non-pharmacological treatments, the latter including manual therapy, acupuncture, psychotherapy, herbal extracts. Secondary pain syndromes should at first be treated

by removing/treating the cause of pain, when possible. Besides, not always treatment of the cause adequately controls pain (see for example trigeminal neuralgia in multiple sclerosis patients). In such condition, pharmacological and non-pharmacological options have to be adopted, alone or in combination. Among facial secondary pain, temporomandibular joint disorder is the most common; robust evidences for recommending any treatment option are scant, even though manual therapy seems better than occlusal splint in reducing pain. Untreatable cranial neuralgias deserve invasive procedure, either with local injection of substances or ablation techniques. Despite of the evolution of neuro-surgical techniques, aiming to reduce side effects and complications, ablation techniques should be reserved to otherwise untreatable pain syndromes. Interestingly, there is robust evidence that onabotulinumtoxin-A might be a useful tool for management of trigeminal neuralgia and should be considered as an alternative aid to pharmacological treatment before any invasive/ablative procedure.

“Cervical pain” study in a tertiary referral headache center

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Introduction The majority of migraine patients remain undiagnosed or misdiagnosed in Italy [1]. In our experience, many patients affected by migraine self-diagnose it as “cervical pain syndrome” (CP) assuming cervical spine pathology as the cause.

Aim To phenotype and classify, in a tertiary referral headache center, the headache types of patients with self-diagnosed CP, and to describe this sample of patients.

Methods All patients aged 18 to 75 years, referred to the Mondino Headache Center for a first visit for headache, completed a questionnaire about CP. A detailed history was taken and a neurological exam was performed in each patient. Brain and cervical imaging were performed when deemed necessary. All patients finally received a diagnosis based on ICHD-III β criteria.

Results Of 110 consecutive patients, 25 did not meet the inclusion criteria, 47 were suffering from self-diagnosed CP, 3 had suffered from self-diagnosed CP, 35 never had self-diagnosed CP. In all of 50 CP descriptions, the pain involved the head. ICHD-III β diagnoses included migraine without aura (n=29), migraine with aura (n=1), probable migraine without aura (n=4), chronic migraine (n=7), medication-overuse headache/chronic migraine (n=5), tension-type headache (n=2), hemicrania continua (n=1); no patient presented with a phenotype suggestive

of cervicogenic headache. Twenty-four out of 50 patients with CP answered the question “who told you that these attacks were CP?” with: general practitioner/medical specialist. The majority of these patients underwent exams without a clear indication and ineffective treatment.

Conclusions To the best of our knowledge, this is the first study that systemically assessed the headache phenotype of patients with self-diagnosed CP. The results suggest that the phenomenon of self-diagnosing CP is very common in Italy, even in patients referred to a tertiary headache center. The majority of these patients suffer from typical migraine attacks, without any evidence of pathological conditions of the cervical spine.

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Individual migraine aura symptoms may, not infrequently, last for more than 60 minutes: preliminary results of a prospective diary study

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Objective To evaluate the duration and variability of individual symptoms of non-hemiplegic migraine aura (NHMA) in a clinically-based population.

Background In ICHD-III β , NHMA duration is considered normal when each symptom is no longer than one hour. A recent systematic review of the topic [1] did not find any article exclusively focusing on the duration of the aura. The pooled analysis of data from the literature on aura duration showed that visual symptoms lasting for more than one hour occurred in 6%–10% of patients, sensory symptoms in 14%–27% and dysphasic aura in 17%–60%.

Methods We recruited 136 consecutive patients affected by NHMA at the Headache Centers of Pavia and Trondheim. The study received the approval by the local Ethics Committees. All patients signed an informed consent form. All the patients prospectively recorded 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 136 patients recruited so far, 44 completed the diaries during three consecutive auras for a cumulative number of 132 auras recorded. Of the remaining 92 patients, 21 dropped-out and 71 have not completed three aura attacks. Visual symptoms lasted for more than one hour in 21 out of 129 auras (16%), somatosensory symptoms in 9 out of 47 auras (19%), dysphasic symptoms in 3 out of 15 auras (20%). Six patients out of 44 experienced the same aura symptoms lasting for more than one hour in one attack and for less than one hour in another attack out the three.

Conclusions Our preliminary data suggest the duration of single symptoms of NHMA may be longer than one hour in a significant proportion of migraineurs, and that the one-hour limit needs review.

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Tension-type headache and tongue habits

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Introduction This research is based on clinical observation of the lingual habits in people with tension-type headache (TTH). This was conducted in 159 patients, 55 healthy and 104 with TTH, diagnosed according to the ICHDIII- β criteria. The principal aim of this research was to investigate a correlation between TTH and swallowing dysfunction, highlighting the potential of perform the myofunctional therapy on tongue for those who suffer from this disease.

Methods The sample had been selected at the Headache Center of Policlinico Umberto I of Rome. Criterion of eligibility for the group of cases was to suffer from TTH, on the other hand the control group had to have less than one attack per month, with Visual Analogue Scale (VAS) value never greater than 5 and have never asked for help to a Headache Center or to a family physician for problems related to headaches. For both groups, the age was between 16 and 65 years. To evaluate the deglutition we examined rest tongue position, crenated tongue, test of swallowing, gritted teeth and open lips, test with fluorescein performed with Payne's technique.

Results With the Wilcoxon-Mann-Whitney test we showed that there is a difference between the healthy and TTH's group, given by the presence of swallowing dysfunction. The Pearson's Chi-square confirmed the relationship between headache and swallowing. The Probit model was then used to estimate the probability of finding swallowing dysfunction in the general

population of patients with TTH. The results showed that there is a significant difference between the two groups for the parameter of swallowing and swallowing dysfunction positively correlated with the presence of TTH, with p-value <0.001. It also had a predictive value of finding such a relationship in the general population of TTH, with a predictive accuracy of 88%.

Conclusions The dysfunctional deglutition may represent a new area to be explored to study the underlying mechanisms of TTH. The myofunctional therapy of the tongue could represent a new way of intervention. In fact, the presence of deglutition dysfunction in patients with tension-type headache is significant compared with the percentage observed in healthy subjects (99% vs 34%). These results appear very interesting and appealing. The dysfunction of deglutition appears from our study closely related with tension-type headache.

Evaluation of proteomic profile in menstrually-related migraine

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Introduction Approximately 50% of women suffering from migraine have attacks in at least 2/3 of the menstrual cycles. These attacks are of longer duration, more severe and resistant to treatment and tend to recur more than non-menstrual attacks. The mechanisms underlying this disorder, classified as "menstrually related migraine" (ICHD-3beta, Appendix, A1.1.2), have not been completely elucidated. In some women, menstrual migraine attack appears to be associated with estrogen withdrawal. However, for this disorder, so frequent and disabling, there are no specific therapies of high effectiveness. Therefore, further studies are needed to identify potential biomarkers and therapeutic targets. The aim of this pilot study was to evaluate/characterize blood and urine proteomic profile of female suffering from menstrually related migraine.

Materials and methods Up to now, twenty women (mean age 35 ± 5 years) with menstrually related migraine and ten men, as controls (mean age 29 ± 2 years), were recruited. Serum and urine samples were collected for proteomic analysis. Morning midstream urine samples were centrifuged, to remove cell debris, and then concentrated and desalted using 5kDa filter devices. Venous blood samples were centrifuged after clotting to obtain serum samples that underwent fractioning by SDS-PAGE gel electrophoresis. Colloidal Coomassie staining was perfor-

med to reveal protein bands that were imaged by PDQuest software. Protein bands were excised from the gel and digested by trypsin. After digestion, peptides were analysed by LC-MS/MS on a Q-TOF mass spectrometer and protein identified using MASCOT software.

Results and discussion The serum and urine proteomic profiles of menstrual migraine patients and control subjects, obtained by mono-dimensional gel electrophoresis, were compared and protein identified. The most relevant differences in the intensity of the protein bands were observed in the middle-low molecular weight (range 40-10 kDa) both for urine and serum samples. In particular, in urine samples all patients showed more intense protein bands (at 25 and 35 kDa respectively) than controls.

Conclusions The proteomic analysis performed in this pilot study might be useful to reveal differences in proteomic profile of menstrually related migraine women and discover proteins related to the disorder. However, due to the great number of protein identified, further analyses are needed to better understand the protein expression differences.

Development of an optimization model to plan and manage a Headache Day Service

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Introduction Inpatient admission for primary headache is inappropriate in the Italian National Health System and therefore not reimbursed by the National Health Fund; however, especially in comorbid and chronic cases, headache assessment and therapy require a multidisciplinary team and many clinical and instrumental interventions rarely available outside a hospital setting. Day Service is, alongside full inpatient and day hospital admission, a relatively recent possibility of supplying a complex set of healthcare interventions for a specific pathology, using a co-paid package of scheduled and time limited hospital accesses thus avoiding admission costs and reducing the time patients spend at the hospital. A 30 days Headache Day Service is used in our Headache Centre. Provided interventions include: neurological and pharmacological assessment, disability assessment, psychological testing and evaluation, pain screening tools, electrophysiological examinations, radiological examinations and prescriptions. Organising the Day Service requires high level clinical and management coordination. Purpose of this study is

to develop an optimisation method for planning and managing the Headache Day Service to improve access, patients flow, and carrying out of diagnostic and therapeutic procedures.

Materials and methods Outpatient clinical records of headache patients referred to the Headache Day Service were reviewed and data about number of patients, headache severity, prescribed interventions, hospital accesses and time needed to complete each patient's diagnostic and therapeutic path were retrieved; prevalent patterns of patients access to the Day Service in terms of monthly schedule and waiting list were identified and they were optimised through a computational model aimed at maximising the amount of patients accessing the day service and minimising each patient's accesses to only needed interventions.

Results The output of the computational model shows a decreased number of hospital accesses for each patient and an increased number of patients accessing the headache day service in a monthly time span.

Discussion and conclusions Optimising the scheduling of a Headache Day Service through a computational model can provide an improvement in terms of accessibility to care in a limited period, shortening of day service waiting lists and reduction of hospital accesses for headache patients, benefitting patients' quality of life and health care costs and organization.

Patient features in chronic migraine with medication overuse

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Introduction Medication-overuse headache (MOH) patients are often treated in tertiary level headache clinics where multidisciplinary assessment and care are provided; while treatment is usually outpatient, inpatient admission may be required to control withdrawal symptoms. The cause of medication abuse is unknown: serotonin uptake and concentration, central sensitisation by repetitive antinociceptive activation, lack of impulse control by orbital-frontal cortex hypoactivation and psychological aspects such as psychopathological and abuse comorbidity, cognitive features and personality traits are believed to play a role in MOH onset; purposes of this study are obtaining preliminary data to evaluate MOH prevalence among patients accessing to our headache centre, identifying MOH patients features in terms of medication usage, comorbidity, psychological aspects and level of disability.

Materials and methods Outpatient clinical records of 68 patients accessing from January 2014 to March 2014 to our headache centre were reviewed and 18 MOH patients (2 males; 16 females) from 30 to 66 years of age ($M=41.71$; $DS=10.27$) clinical records were selected; information about age, gender, occupation, headache familiarity, comorbidity, primary headache, headache frequency, disability, anxiety, depression, self-efficacy, alcohol, smoking, drug and medication usage were retrieved. Frequencies and covariance analyses were performed using GNU/PSPP 0.8.2.

Results MOH prevalence in our centre accounts for 26.47% of the accesses; migraine monthly frequency was high ($M=17.37$; $DS=7.10$); autonomic signs were common (88.89%); migraine familiarity rate was 50.00%; comorbidity rate was 77.78%; most prevalent comorbidities were psychopathological (50.00%) and metabolic (33.33%); Mood disorders rate was 33.33% and anxiety disorders rate was 16.77%; MIDAS average score was 46.62; Zung-A mean score was 47.39; Zung-D mean score was 47.44. Prevalent personality traits were: evitating (27.78%), obsessive-compulsive (27.78%) and cyclothimic (16.67%); Self efficacy was predominantly low (mode: never); Overused medication was prevalently NSAID analgesics (55.56%) and combination analgesics (27.78%) with an average medication usage of 6292.78 mg/month and a mean overuse duration of 56 months; Anxiety level correlated with headache chronicity ($p<0.05$); Depression level correlated with degree of disability ($p<0.05$).

Discussion and conclusions Medication-overuse headache patients present with complex cases in comorbidity and psychosocial terms. The study suggests a relationship between medication overuse, health problems comorbidity and psychological aspects such as personality traits, self efficacy cognitions, psychopathological syndromes and disability.

Rare Headaches in the Emergency Department

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Background Headache is one of the most common symptoms that lead patients to the Emergency Department (ED). Rare headaches are often underdiagnosed in the ED setting, not specifically treated, and rarely referred to a Headache Center.

Objective To evaluate the efficacy of a dedicated Acute Headache Centre (AHC) in identifying and managing rare headaches in ED.

Methods We performed a four-year prospective study of all consecutive patients referring to ED for non-traumatic headache and afterwards evaluated in the AHC of the University of Trieste. Patients with a diagnosis of rare headache (ICHD-3

beta criteria) were enrolled. Demographic and clinical characteristics, causes of presentation to the ED, diagnostic tests, consulting visits, ED diagnosis, therapies administered, diagnosis and therapies administered in the AHC were analysed using SPSS 14.0.

Results Out of 3.427 patients totally admitted in ED for non-traumatic headache, 392 subjects were referred to the AHC, and 27 (6.9%; 74.1% M and 25.9% F; mean age 50 ± 15 years) were enrolled as rare headaches. The most frequent cause of presentation to the ED was “first episode of headache” (44.4%). ED diagnoses were not-otherwise specified headache (55.6%), primary headache (37%), secondary headache (7.4%). Fourteen patients (51.1%) underwent a cerebral CT. Neurological evaluations were required in 20 patients (74.1%). Twenty-one patients (77.8%) received symptomatic therapy within ED, most being NSAIDs. No prophylactic treatment was initiated in ED. In 15 patients (55.6%), headache was still present at ED discharge. The diagnoses after AHC evaluation were trigeminal autonomic cephalalgias (51.8%), other primary headache disorders (25.9%), trigeminal neuralgia (14.8%), other rare headaches (7.5%). In the AHC, the most administered attack therapy were triptans (40.7%) and NSAIDs (37%), while Ca^{++} -antagonists (40.7%) and anticonvulsant drugs (33.3%) were mainly used as prophylaxis.

Conclusions Our data demonstrate that rare headaches are often underdiagnosed, although they are not so infrequent in the ED setting. AHC is effective in identifying and specifically treating rare headaches in ED. A proper diagnosis and therapy started in the AHC soon after ED evaluation, represent an efficient approach for management rare headaches.

Orthostatic headache without spontaneous intracranial hypotension: a novel headache attributed to psychiatric disorder?

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Introduction SIH is characterized by orthostatic headaches, low CSF pressure, distinct abnormalities on MRI. It generally results from spontaneous spinal CSF leakage.

Material and methods From among 214 patients referred to one of us (E.F.) over a 21-year period for evaluation of orthostatic headache (OH) and suspected SIH, those patients with negative head and spinal MRI and normal CSF opening pressure (CSF-OP) were identified and their medical records reviewed.

Results Ten patients satisfied the above criteria for absence of CSF leak. Nine patients were women. Mean age at the time of evaluation was 37 years (range 16-65). All patients also had anxiety-depressive disorder (mild grade in seven pts and moderate grade in three pts), one of them was also suffering from conversion disorder, another from pseudoseizures and one from mild hyperlaxity joints. Median duration of orthostatic headache prior to evaluation at our institution was 9.5 months (range 3-36). Cochleovestibular symptoms were present in four patients. Eight patients performed the lumbar puncture in lateral position [mean CSF-OP was 140.2 mmH₂O (range 80-240)], while two in a sitting position [mean CSF-OP was 490 mmH₂O (range 440-540)]. On the top of best psychiatric treatment nine patients performed epidural blood patch (EBP) in Trendelenburg position ex juvenibus criterium. One patient was treated with bed rest and overhydration for a short time. After mean follow-up of 21.6 months (range 6-74), three patients experienced a complete recovery and three improved after EBP, the one treated with only conservative therapy improved with a low dose of aripiprazole (1mg/day). Three patients with moderate psychiatric disorder had persistent OH.

Discussion and conclusions OH can occur without evidence of intracranial hypotension or detectable CSF leak despite extensive diagnostic testing. Clinical features alone are unlikely to differentiate between orthostatic headache with and without identifiable CSF leak. Potential mechanisms include 1) very slow or intermittent CSF leak that cannot be detected at the time of evaluation or by current diagnostic tools or 2) increased compliance of the lower spinal CSF space without actual leak or 3) underlying psychiatric disorder.

We think that in our series the underlying psychiatric disorder was the major cause of orthostatic headache which might be considered as a new type of headache attributed to psychiatric disorders. Further studies are needed to confirm these data.

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Pain in stroke patients: characteristics and impact on the rehabilitation treatment

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Introduction The aim of this study was to quantify and characterize pain (nociceptive/neuropathic) in a sample of post-stroke patients undergoing rehabilitation and to investigate the impact of pain in slowing down or discontinuing the rehabilitation program.

Materials and methods Pain intensity was measured with a numeric rating scale (NRS); pain characteristics were assessed with the Douleur Neuropathique in 4 Questions (DN4), able to discriminate nociceptive from neuropathic pain, and the Neuropathic Pain Symptom Inventory questionnaire (NPSI), focused on neuropathic pain. Quality of life (QoL) was measured with the Short Form 36 Health Status Survey (SF-36). 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 studied 106 post-stroke patients. About 1/3 of the patients (32.9%) with normal cognitive/language reported pain occurrence after stroke; 81.8% of them had NRS \geq 3 and 31.8% DN4 \geq 4. In about 20% of the patients the Pain Assessment in Advanced Dementia (PAINAD) was used to measure pain (for cognitive/language impairment); 17.4% of them presented a score \geq 3. Patients with hypoesthesia presented neuropathic pain scores significantly higher than patients with normal sensibility. In 24.5% of our sample, pain influenced rehabilitation treatment (namely, 11.3% modified, 12.3% slowed down, and 0.9% stopped rehabilitation program). Finally, according to the physical therapist, in 16% of the whole sample, pain influenced patients' attention during rehabilitation sessions.

Discussion Pain may significantly affect functionality and negatively influences physical activity of post-stroke patients but very few data on this topic are available.

This is the first study in which the impact of pain on the rehabilitation treatment was evaluated. In this study we analyzed, through validated and commonly used outcome measures focused mainly to assess disability and pain, a heterogeneous sample of stroke patients who are representative of the rehabilitative stroke population. The results from this multicentric study in Don Gnocchi rehabilitation centres showed that pain has a relevant role in the rehabilitation treatment of stroke patients.

Conclusions In light of the common occurrence and relevant impact of pain on the rehabilitation program, clinicians should pay more attention to pain, especially neuropathic pain, in post-stroke patients. Tailored pharmacological therapy, to treat and prevent pain, might improve patients' compliance during the rehabilitation process.

Alexithymia in medication-overuse headache: a controlled study

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Background Alexithymia (Ax) is a term used to describe a disorder where patients have difficulty in expressing their feelings in words. The presence of Ax had been related to the occurrence of chronic pain, but poorly studied in headache disorders, even though alexithymic traits have been evidenced both in migraine and Medication Overuse Headache (MOH). Alexithymia has been stated as both a primary and stable personality construct and a secondary state that is created as a reaction to medical illnesses. Noteworthy, the presence of Ax has been linked to specific correlates at level of posterior cingulate cortex [1].

Objective The aim of this study was to analyze the construct of Ax in MOH patients.

Methods A clinical sample of 105 MOH patients (27 M, 78 F, mean age 47.49±10.03) and 78 control subjects (28 M, 50 F, mean age 41.51±11.03) were enrolled for the administration of the Toronto A Scale (TAS-20).

Results Compared to controls, MOH patients showed significant values in the total score ($t(181) = -4.706, p < .001$), in Factor 1 (Difficulties in identifying feelings) ($t(181) = -5.296, p < .001$), Factor 2 (Difficulties in describing feelings) of TAS-20 ($t(181) = -1.999, p < .05$) and a trend for Factor 3 (Outside oriented thought) ($t(181) = -1.799, p = .099$), without differences for gender. In the MOH group, a pathological level of Ax was shown by 47% of patients (vs 15.4% of controls), a borderline level by 28.1% (vs 23.6%), and no-Ax by 24.9% (vs 61%).

Discussion and conclusions Alexithymia seems to be an important psychological factor involved in MOH, even if the link with headache (a primary or a secondary state?) is unclear, but pathophysiological and therapeutic meanings should be considered in further studies.

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Gender differences in the clinical presentation of cluster headache

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Introduction Cluster Headache (CH) is a rare primary headache disorder classified with similar conditions under the group of trigeminal autonomic cephalalgias (TACs). CH mostly affects men, but a large percentage of women also suffer this headache disorder. Very little is known about the gender-related differences from studies where the diagnosis of CH was validated. In this study, we evaluated the differences in the clinical presentation of 198 CH patients diagnosed and followed at the Pavia Headache Centre.

Material and methods We carried out a retrospective analysis on the clinical database of our CH patients with specific focus on demographics, clinical characteristics of the headache, concomitant diseases and treatment response.

Results Data from a total of 198 CH patients were collected: 134 male (mean age 40.95±10.49) and 64 female (mean age 41.7y±10.7). The mean age at CH onset was lower in women than in men (24.8±10.78 years vs 28.03±10.24 years, $p < 0.43$). CH presented with an episodic pattern in more than 91% of subjects, without gender difference. No differences were detected as regards the mean number of CH periods per year and their mean duration (1.17 vs 1.03 and 49.57 vs 50.40 days, respectively); during the cluster period, the average frequency of attacks per day was similar and without significant difference between the genders. Attack duration, without therapy, was longer in men (107.37 minutes vs 89.7 minutes, $p < 0.02$). CH women (71.4%) tended to have more frequently a family history of headache, usually migraine, as compared with men (59.1%) ($p = 0.065$). Nausea, vomiting, photo- and osmophobia were reported more frequently by women than men. Local autonomic associated symptoms were almost equally prevalent in women and men. No difference was found in treatment response between genders. As regards concomitant conditions, female CH sufferers presented more frequently thyroid disorders (21.3 vs 1%, $p < 0.00$) and psychiatric illness (18% vs 6.8%) than men. On the contrary, snoring in sleep occurred statistically more frequently in men (56.2% vs 25.4%, $p < 0.00$). No gender differences emerged as regards other medical concomitant conditions (namely, kidney stones, cardiovascular diseases, insomnia, diabetes).

Conclusions This retrospective survey shows some specific features for CH in women: earlier onset of disease, more frequent association with “migrainous” symptoms during the attacks and a shorter duration of untreated attacks. Concomitant thyroid and psychiatric diseases mostly occur in women than men, as in the general population.

Plasmatic markers of oxidative stress in chronic migraine patients with medication overuse headache: report of a series of cases

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Introduction Migraine is a complex multifactorial neurobiological disorder, whose pathogenesis remains not fully understood as well as the mechanisms associated with migraine transformation from episodic to chronic pattern. A possible role of impaired oxidative mitochondrial metabolism in migraine pathogenesis was hypothesised and increased levels of peripheral markers of oxidative stress were reported in migraine patients, although literature data are limited and heterogeneous.

Objectives The aim of the present study was to determine plasmatic levels of advanced oxidation protein products (AOPP), ferric reducing antioxidant power (FRAP) and total plasmatic thiol groups, i.e. plasmatic markers related to oxidative stress, in a sample of chronic migraine patients, with overuse of symptomatic drugs.

Methods Twelve consecutive patients with a diagnosis of chronic migraine and medication-overuse headache (ICHD-3 beta) were enrolled. Patients with comorbid/coexisting conditions were excluded as well as patients in treatment with migraine preventive drugs. Plasmatic levels of AOPP, FRAP and thiol groups were determined in each patient. Data are reported as mean \pm standard deviation.

Results Concerning demographic data, twelve females were included; mean age was 50.42 \pm 13.38 years (range 30-67 years). Four patients showed high AOPP levels (range values 124.5-190.5 nmol/ml), whereas eleven patients presented reduced FRAP levels (normal values >0.7 mmol/l) and all patients had low plasmatic total thiol groups (normal range 0.4-0.6 μ mol/l). Furthermore, mean AOPP levels were 166.2 \pm 69.07 nmol/ml, mean FRAP levels were 0.55 \pm 0.11 mmol/l and mean plasmatic total thiol groups were 0.26 \pm 0.04 μ mol/l.

Conclusions Data from the present report, evidencing reduced plasmatic FRAP levels and total thiol groups in a sample of chronic migraine patients with symptomatic drug overuse, although preliminary, seem to show that antioxidant capacity is reduced in these patients; further evaluation is certainly necessary in order to assess the causal or consequential role of an imbalance between pro-oxidants and antioxidant defenses, i.e. oxidative stress, in migraine pathogenesis and chronification and its potential role in therapeutic approach.

Collaboration between general practitioners and neurologists in the headache centre

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Introduction Traditional barriers to optimal headache management are misdiagnosis and undertreatment at primary care level, especially by general practitioners (GPs). Therefore, integration between a GP, particularly expert in the headache management, and neurologists in the conduction of a headache centre was experimented for the first time in Italy, with the aim to create a strict collaboration between GPs and the headache centre.

Materials and methods The headache centre conducted by a GP and neurologists in the Empoli Health Authority 11, covering 241,165 residents in 2013, was created in November 2010. The principal objectives were: 1) to increase the registration of headache diagnosis (based on IHS classification) in the GPs database, 2) to optimize and to increase the utilization of triptans in migraine patients (evaluated through claims data available from pharmaceutical department), 3) to reduce the unnecessary and overutilized neuroimaging.

Results After three years the following results appear:

1. The number of migraine diagnosis coded in the database of a group of GPs increased from 1.6% (data of 2006) to 2.1%, with a high inter-individual variability.
2. The number of triptan users in the general population did not increase in the years 2011-2013 in comparison with the 2008-2010 (0.5% of the general population).
3. The CT or MRI scans were requested by the GP of the headache centre in 10.9% of 1,078 (85% of migraine patients) new patients (802 F, 276 M, mean age 41.0 \pm 15 S.D., range 7-90). Considering only the 676 subjects which had never received a neuroimaging the percentage was 14.6. MRI was requested in 107 patients and CT in 11 patients.

Conclusions The increase of migraine diagnosis coded in GP databases is partial but encouraging. The non-increase of triptan users in the general population may be due to the high turnover in the triptan utilization reported in previous studies. The number of headache patients investigated through neuroimaging was much lower than that previously reported by GPs with a special interest in headache (30%) [1] or by neurologists. These results show that a strict collaboration between GPs and headache specialists may improve the quality of headache care.

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Functional reorganization of brain networks in patients with painful chronic pancreatitis

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Objective To investigate the organization of brain networks involved in nociceptive processing in patients with painful CP.

Methods Contact heat-evoked potentials (CHEPs) were recorded in 15 CP patients and in 15 healthy volunteers. The upper abdominal area (sharing spinal innervation with the pancreatic gland) was used as a proxy of 'pancreatic stimulation', while stimulation of the right forearm was used as a control. The brain source organization of CHEP components was analysed.

Results After abdominal stimulation, brain source analysis revealed abnormalities in the cingulate/operculo-insular network. A posterior shift of the operculo-insular source ($p=0.004$) and an anterior shift of the cingulate source ($p<0.001$) were seen in CP patients, along with a decreased strength of the cingulate source ($p=0.01$). The operculo-insular shift was positively correlated with the severity of pain ($r=0.61$; $p=0.03$).

Conclusions CP patients showed abnormal cerebral processing after stimulation of the upper abdominal area. These changes correlated with the severity of pain, probably reflecting maladaptive neuroplastic changes.

Differences in total cholesterol according to severity of migraine in female patients

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Introduction In recent years, migraine has been increasingly recognized as an independent risk factor for ischemic stroke; furthermore, a higher association with cardiovascular risk factors, such as hypercholesterolemia, has been documented in migraineurs with respect to healthy controls [1]. However, no

research has investigated the possible correlation between lipid values and severity of crises. The aim of this study was thus to evaluate the relationship between frequency and intensity of headache crises and levels of total cholesterol (TC) in female migraine patients.

Methods Forty-four women (aged 37.02 ± 11.51 years) affected by migraine (with and without aura) were evaluated for TC and parameters of migraine severity. The study was conducted retrospectively on medical records of patients examined at the Headache Center of the Chieti University. Four categories of parameters were established: high frequency (HF, number of monthly crises ≥ 8), low frequency (LF, number of monthly crises < 8), high intensity (HI, pain intensity ≥ 5) (Numeric Rating Scale), and low intensity (LI, pain intensity < 5).

H and L categories were compared by means of Student's t-test for unpaired samples. The linear regression analysis was applied to evaluate the possible correlation between migraine parameters and cholesterol levels. Statistical significance was set at $p<0.05$.

Results TC was significantly higher in 21 patients with HF than in 23 patients with LF (mean TC, 228.14 vs 168.39 mg/dL, respectively; $p<0.0001$). Furthermore, TC was significantly higher in 26 patients with HI than in 18 patients with LI (mean TC, 216.77 vs 165.67 mg/dL, respectively; $p<0.0001$). There was a significant direct linear correlation between frequency and intensity of crises and levels of cholesterol ($p<0.0002$).

Conclusions The results of this retrospective study indicate an impact of headache severity on cholesterol levels in female migraineurs. Though needing confirmation in future prospective controlled studies, these findings suggest that migraine severity can influence the cardiovascular risk in the affected patients.

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Impaired pain processing in patients with silent myocardial ischemia

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Introduction Silent myocardial ischemia (silent MI) can be defined as objective evidence of myocardial ischemia in patients without symptoms related to ischemia, in particular without chest pain. The relationship between pain and ischemia is complex and asymptomatic myocardial ischemia has been shown to occur more often than symptomatic ischemia in patients with stable coronary artery disease (CAD). The aim of the study was to investigate the nociceptive system in patients with silent Myocardial Ischemia (MI) by CO₂ laser evoked potential (LEP) recording.

Methods We studied 3 groups: 1) 11 asymptomatic, non-diabetic patients with documented obstructive CAD (silent-MI group); 2) 10 patients with obstructive CAD showing the clinical pattern of chronic stable angina (symptomatic-MI group); 3) 14 healthy subjects matched for age and gender to patients (control group). LEPs were recorded from 3 electrodes, placed at Cz, Fz, and T3 according to 10-20 International System, in response to chest as well as right hand skin stimulation. Three sequences of stimuli were applied, separated by 5-minute intervals.

Results Basal N2-P2 LEP component amplitude after chest skin stimulation was lower in silent-MI group compared to other groups ($p=0.03$). Nevertheless, the amplitude of the N2-P2 component decreased across the 3 sequences of stimuli in symptomatic-MI group and control group, but not in silent-MI group (comparison among groups, $p=0.015$).

Discussion CAD patients with silent-MI show a reduced amplitude of N2-P2 component and inadequate habituation to painful stimuli.

Conclusions These findings are consistent with an abnormal central pain processing in patients with silent-MI that might, at least in part, explain their typical misperception.

Headache in advancing age: primary and secondary forms

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Introduction Prevalence of headaches certainly declines with advancing age, especially over 60 years, but it is not uncommon for elderly patients to present with this complaint. Indeed, 10% of women and 5% of men still report severe headaches at the age of 70 years. Also etiology and presentation of headache vary with age, which explains the need for particular vigilance for secondary or unusual headaches in elderly that are prognostically worse. In addition the frequent presence of chronic comorbid illnesses and excessive analgesic use may aggravate a

pre-existing headache. Finally there are headaches that occur exclusively after the age of 60, which are mistakenly diagnosed as migraine or tension-type headache.

Objectives The objectives of this study is to describe the prevalence of the different types of headache in elderly patients.

Results Among the elderly aged 75 years or more, the prevalence of headache was found to be 55% in females compared to 22% in males; all the subtypes of headache are observed, but migraine occurs less frequently (4,6%). There are different factors that can explain the age-related decline in prevalence: delayed reporting of headache, biochemical changes. In particular, attacks of migraine without aura progressively decrease and eventually disappear or become even more reminiscent of tension-type headache. Migraine with aura is rare (1-2%), and can appear like aura without headache (especially visual aura). Tension-type headache is the most important primary form; there is an increase in frequency and duration, variability in headache location, occurrence of nausea and analgesic intake. Cluster headache is rare in elderly, but may start at this age. Hypnic headache is a rare form of primary headache, affecting elderly women more than men (0.1%). In about 1.5% of elderly with daily intake of analgesics we have to consider also “medication overuse headache”. In this contest broad differential diagnosis must be made, in particular when there is a new onset headache, which can reflect underlying organic diseases such as giant cell arteritis, intracranial mass lesion, cerebrovascular diseases or metabolic abnormalities. Finally we have to consider the unusual forms such as trigeminal autonomic neuralgias (for example SUNCT) and primary cough headache.

Conclusions While headache declines with age, certain primary headaches are more common in elderly adults and secondary forms become of greater concern. Therefore the approach should be individualized, not only for the presence of comorbid disorders, but also because of the physiological changes due to the aging, that can reduce drug tolerance and increase the likelihood of side effects.

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Primary headaches and work: health oversight and criteria to make the judgement of suitability

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Introduction Primary headaches account for 90% of all the forms of headache. This disease occurs mostly in the working-age population, having a significant impact in countries with high economic and social development. These aspects carry important economic costs calculated as loss of working days due to illness and loss of labour productivity. In the occupational setting, several circumstances are known to be able to cause cephalalgic attacks in workers who already suffer from primary headache, for example the interruption of the circadian sleep-wake rhythm, physical/mental distress, not ergonomic postures, prolonged use of display screens, acoustic discomfort and among chemicals, the olfactory characteristics.

Objectives The aims of this study are: to provide useful information to occupational physicians on the management of workers suffering from primary headaches, to the formulation of the judgement of suitability and to the planning of the work; to identify the preventive measures in order to reduce the probability of recurrence of headache attacks and to ensure workers efficiency.

Material and methods We identified three critical factors: the form of primary headache, the characteristics of the work and the effects due to pharmacological therapy. On the basis of these considerations we suggest guidelines for a flow chart aimed to understand worker's suitability and to guarantee safety and health of workers.

Results A decision process for judgement formulation articulated in different steps (history, neurological examination and the periodic verification of the adherence to treatment prescribed) can guide the physician to identify the characteristics of the headache and the appropriate measures to make this disease less invalidating.

Conclusions Primary headaches are "social" diseases; the physicians have to consider their impact on work, and can formulate a true judgement of suitability only after a right evaluation of their characteristics, that can be made with simple but basic steps.

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Prevalence of medication-overuse headache in adolescents seen in a third level Headache Centre

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Introduction Epidemiological studies indicate a sparse prevalence of MOH in children and adolescents. In a recent study [1] we reported a prevalence of 9.3% of MOH in a group of children and adolescents first seen for headache in a third level centre in Italy, increasing to 20.8% in patients with chronic headache. The present study intended to investigate the prevalence of medication-overuse headache (MOH) in a group of adolescents seen for headache in a third level center in Italy from January 2011 to January 2014, in comparison with findings from other studies.

Materials and methods The study sample was represented by 180 patients aged between 11.0 and 17.11 years (mean age: 14 years), 43.3% male and 56.7% female. A detailed history was taken to assess the presence of MOH, using criteria defined by ICDH-III beta; moreover sex, headache type, age of onset, age at the first visit and use of drugs were collected for each patient.

Results Nineteen (10%) of our patients presented MOH (14 F and 5 M); in the group with chronic daily headache, the prevalence raised to 30%. Most of them (85%) had a simple analgesic overuse, two patients (10%) had a multiple drug classes overuse and one (5%) had a combination analgesic-overuse headache. Two out of three patients with MOH were abusing of self-prescribed medications, while the remaining one-third received a physician's prescription (16% by a paediatrician, 11% by a general practitioner and 5% by a neurologist).

Discussion and conclusions This study confirmed that medication overuse for headache was a real problem in teens and that self-medication was very common. This confirmed the importance to consider the risk for paediatricians and general practitioners prescribing treatments for headache in these patients, to provide limitation on drug's use and to try to prevent or at least control medication overuse.

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The impact of chronic daily headache 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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Introduction Chronic daily headache (CDH) is a common neurologic condition with a high impact on functional performance and quality of life (QoL). CDH also represents a relevant economic burden on the National Health Service (NHS), but precise figures are lacking.

Our aim was to evaluate the disability and the impact on QoL of CDH, as well as its economic cost to the NHS in a representative cohort.

Materials and methods We enrolled 92 patients, 51 subjects with CDH and 41 subjects with episodic headache (EH) who attended the Headache Center of our institute. Patients were tested with disability scales (MIDAS, HIT-6, SF-36) and with an ad hoc semi-structured questionnaire.

Results The mean score for MIDAS is 98.38 ± 72.32 for CDH and 15.5 ± 17.7 for EH (CDH vs. EH $p = 0.001$). The mean HIT-6 score is 66.1 ± 8.36 for CDH and 58.68 ± 10.1 for EH (CDH vs. EH $p = 0.001$). The mean score in the General Health SF-36 questionnaire was 39.93 ± 14.74 for CDH and 66.18 ± 18.21 for EH (CDH vs. EH $p = 0.001$).

The direct mean annual cost (euro) for a single patient with CDH amounts to 2250 ± 1796.1 (624.3 ± 980.0 for symptomatic drugs, 137.6 ± 452.3 for prophylactic therapy and 1242.9 ± 1251.2 for hospitalizations). The cost to NHS is 2110.4 ± 1756.9 , while 139.6 ± 181.1 euros are spent by the patient.

An EH subject costs annually 523.6 ± 825.8 euros (55.3 ± 78.2 for symptomatic drugs, 60.6 ± 121.9 for prophylactic therapy and 242.6 ± 753.5 for diagnostic examinations). Of these, 468.3 ± 801.8 are incurred by the NHS, whilst the patient contributes directly with 55.3 ± 83.2 .

The total economic burden, as well as cost-drivers, were significantly different between groups (CDH vs. EH $p = 0.001$ for each value).

Discussion and conclusions The present findings confirm that CDH 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 CDH, reverting it back to EH, will provide a dual benefit: on the individual and on the society.

The pharmacist as the first reference for the headache patient: a pilot study in the Province of Perugia

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Introduction About 6 million Italians suffer from headache. In 2-3% of cases it is a severe form that significantly affects quality of life. It is estimated that only a minority of headache patients contact their family doctor, while only 16% consult a specialist. Pharmacies provide an excellent network to help improve headache outcome. The aim of the present pilot study is to provide assistance to patients who turn to pharmacies in Perugia to optimize the diagnosis and treatment of headache.

Materials and methods In November 2013 a training course on headache took place for pharmacists of the Province of Perugia, organized by the Headache Centre, Neurological Clinic, "Santa Maria della Misericordia" Hospital of Perugia. The key topics included: *i*) recognition of primary headaches, "red flags" suggestive of secondary headaches and triggers/aggravating factors using a specific flow chart; *ii*) development of an ad hoc questionnaire to be used by the pharmacist in evaluating headache patients; *iii*) setting up of a follow-up chart to collect information on headache changes after adequate advice; *iv*) development of tables to identify available over-the-counter (OTC) medications comparing them with medication dosages recommended by SISC treatment guidelines and supplements. In addition, Info Points will be set up in the pharmacies, and pharmacists will be in touch with Neurologists of the Headache Centre, through a dedicated e-mail address. All patients who will turn to an Info Point for their headache in the 6 months following the beginning of the study, will be included in the study.

Expected results The proposed research will review the characteristics of patients seeking pharmacist recommendations and the use of the questionnaire will allow us to verify the type of drugs used. Other expected results include the improvement of symptomatic medication usage and of lifestyle habits and the reaffirmation of the role of the pharmacist as a vital first contact point for headache sufferers.

Discussion and conclusions The role of the pharmacist is essential in providing information on the proper use of medications, educating the patient to a healthy lifestyle, and to monitor use of medication and patient adherence therapies. The pharmacy is thus a unique counseling 'door' because painkillers are among the best selling OTC drugs for headache. The pharmacy is an integrated network of health facilities and, as such, may, if necessary, refer patients to specialist centres.

ICHD-3 beta: lost track of osmophobia

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Introduction Osmophobia (Os), an unbearable perception of odors that are non-aversive outside the headache attacks, has been described since the 2nd century a.D. as an accompanying symptom of migraine (M). It has been demonstrated to be much more relevant in M, both with (MA) and without aura (MO), than in other primary headaches (PH) and authors demonstrated its high specificity in the differential diagnosis between M and tension-type headache (TTH).

In 2004 Os was included in the appendix (A1.1) ICHD-2 among the proposed diagnostic criteria of MO. In 2013, a provisional revised version (ICHD-3 beta) of the previously released classification was offered to the approval of the scientific community. In this version Os disappeared from the appendix, without explanations.

Aim and methods To try to understand this choice and to investigate the available scientific data of Os in differential diagnosis of PH and its specificity in diagnosis of M, we extensively reviewed the literature on the subject. An open search on MedLine using the term “*osmophobia*” yielded 37 articles. We focused especially on papers published after the release of ICHD-2. Among 29 articles issued between 2005 and 2014, 19 were eligible. Of these, 9 investigated Os only as an accompanying symptom in M and other PHs, 10 focused on Os also as a diagnostic criteria.

Results and conclusions All the reviewed articles confirm a much higher prevalence of Os in M (up to 86%) than in other PHs, particularly TTH. Even if there are some differences in the calculated sensitivity and specificity among papers, published data support the usefulness of Os in the differential diagnosis between M and TTH in adults. As far as Os in children is concerned, it appears to have even a more important role since the presence of OS in a child presenting as suffering of TTH is a prognostic marker of the future clinical development of M [2]. In conclusion, published papers consistently suggest the inclusion of Os among the M diagnostic criteria. On this ground, the unexplained decision to remove Os from ICHD-3 appears unjustified and we firmly suggest a revision of this choice.

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Cluster headache benefits from treating its co-morbidities

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Introduction Cluster headache is a rare type of primary headache, affecting mainly men and a dysfunction of hypothalamus is suspected. The most common therapies are steroids and triptans to treat the acute attack and vasoactive or antiepileptic drugs for headache prevention.

Patients and methods This is an observational study carried out examining the computerized database of the Headache Centre in Alba, from 2004 to 2013. All files were recorded using MedOffice database, and a search by keyword “Cluster headache” was performed.

Results In the years 2004-2013 more than 4000 patients have been visited in our headache centre, mainly suffering from primary headache. Among these, 19 patients were suffering from cluster headache. They were 17 men and 2 women, whose mean age was 46 years. Their mean BMI was 24, and all the patients were smokers. Mean age of onset of their headache was 33 years. In 3 cases the cluster headache was chronic, in all the others it was episodic. All patients underwent an MRI of brain, hypophysis and ANGIO MRI. In 4 cases an anterior anatomical variant of circle of Willis was detected, 3 patients had gliotic subcortical lesions, 2 a pituitary microadenoma. Routinely all our patients are studied for metabolic disorders, iron and thrombophilic disorders. Surprisingly, 18 patients out of all showed an hyperinsulinism with normal or high glycaemia. Seven men had hyperhomocysteinemia and 2 S protein deficit or aPL positivity, and 3 patients carried high levels of ferritin. Hypertension was found in 4 cases. All patients were treated for their headache treating their associated diseases, both with diet or drugs, as appropriate. All of them benefit from these treatments and only 2 patients needed a standard prophylaxis therapy.

Conclusions Searching for co-morbid diseases is usually easy and at low cost. This type of working seems to be useful to better care patients suffering from cluster headache, mainly using specific diet or drugs as appropriate. Treating co-morbidities seems also to reduce the need of prophylaxis therapy.

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

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Objectives Cluster headache (CH) is considered a disorder of young men, which predominantly begins at age 20-to-40 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 the patients with CH aged 65 years and older. For the last 15 years we have observed 261 patients suffering from CH. Out of these cases, 43 patients (16.5% of the whole population) were over 65 years.

Results In this group of elderly patients, 24 were females (55.8%) and 19 were males (44.2%). We diagnosed 4 patients with CH (only one bout, according to the International Classification of Headache Disorder), 25 with episodic CH, and 14 with chronic CH. The onset occurred at 35–44 years of age for 21.4% of cases, 45–54 years for 16.7%, 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. Out of the patients aged over 65 years the prevalence of chronic CH was remarkably higher than in previous ages, resulting 25.6%. In patients under 65 years, chronic CH was found in 9.5% of cases.

Discussion The onset of CH seems to be independent of the life period of the patients. This study, confirming our previous results, demonstrates that CH can begin in geriatric age [1]. The increasing number of elderly patients with CH could be related to an inadequate recognition of this headache disorder, which has been believed for a long time to affect mainly young and middle-aged subjects.

Conclusions In CH patients over the age of 65 years, females represented the majority of cases, in contrast with the evident male preponderance in the previous ages. Apparently peculiar to 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.

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How migraine is affected by therapies for Multiple Sclerosis

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Introduction There are an increasing number of available disease-modifying therapies for Multiple Sclerosis (MS). Since the prevalence of migraine, already remarkable in the general population, is even higher in MS patients, possible effects of these preventive treatments on migraine should be monitored. A review of the literature on the subject is presented.

Materials and methods PubMed, Ovid and Google Scholar

searches were conducted looking for Migraine combined with Beta-Interferon (β IFN), Glatiramer Acetate (GA), Natalizumab, Fingolimod, Laquinimod, Teriflunomide, Azathioprine, Methotrexate, Mitoxantrone and Cyclophosphamide.

Results Use of β IFN was related to worsening of previously diagnosed migraine (37.5–41% according to different sources, $p < 0.05$) and to high percentage (41–44%, $p = 0.05$) of de novo headache presentation, with migraine features in approximately one fourth of cases. β IFN 1a seemed more associated with worse outcome on migraine than β IFN 1b.

GA was associated with only 11% of worsening of migraine, and a direct comparison with β IFN showed the latter as much more migraine-inducing.

Effects of Natalizumab on migraine were evaluated in a small sample, but a significant reduction in migraine frequency and MIDAS scores was detected.

Only spurious cases of worsening of migraine were reported with use of Fingolimod.

Effect of immunosuppressive medications used in MS on migraine are not available in the literature, nor are data on high doses of steroids, used for the acute relapse of MS.

Discussion Among all disease-modifying therapies used in MS, β IFN is the only one which showed a clear association with worsening of previous migraine. About increased incidence of migraine after starting a disease-modifying treatment, interpretation of data is difficult, due to uneasy distinction between facilitation of a true migraine and secondary headache, attributable to medications.

Moreover, another issue that limits investigation is the poor report of many patients about worsening or new appearance of migraine-like headache, sometimes interpreted as part of the flu-like syndrome typically associated with β IFN therapy.

Conclusions Migraine should always be carefully assessed in all patients affected by MS, and in particular in all subjects who are to be treated with disease-modifying medications, in order to evaluate possible modifications of migraine itself. In known migrainous patients, worsening of migraine can more easily occur with β IFN treatment.

Are migraine without aura and migraine with aura two distinct entities?

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Objectives The different headache Classifications of the International Headache Society (IHS) have defined, since the first

edition published in 1988, migraine without aura (MO) and migraine with aura (MA) by separate diagnostic criteria. The distinction over the years has caused controversies whether MO and MA are separate entities or subtypes of the same disorder [1]. The two forms are distinguishable by several aspects, both clinical and pathophysiological, in particular by the presence of aura, which underlies spreading depression.

Materials and methods We retrospectively evaluated the clinical records of 4,126 headache patients referred to our Headache Centre from 2005 to 2013.

Results In this large case series we could diagnose 3,234 subjects with migraine, accounting for 78.4% of the total population. Of these individuals, 2,273 had migraine without aura (MO), 240 migraine with aura (MA), and 207 MO + MA. Moreover, 142 subjects had chronic migraine and 372 had MO + tension-type headache. The distribution by gender showed a clear female preponderance, 79.4% in MO, 86.0% in MO + MA and, less prominent, 67.1% in MA. The mean age at onset was 21.1 ± 11.6 years in MO and 25.9 ± 11.3 years in MA, respectively. The MO:MA ratio was 9.5:1, whereas the female:male ratio was 3.8:1 in MO and 2.0:1 in MA.

Discussion MO attacks are significantly more frequent, last longer than MA attacks, and have more readily identifiable triggers. Mean age at onset was lower in MO compared to MA. The gender distribution of MO and MA was different, indicating that hormone-related factors may be of greater importance in MO. The earlier onset of MO could be a function of the menarche. Overall, the relationship between female hormones and MO was clearly stronger than with MA. On the other hand, the coexistence of MO and MA in the same patient is not infrequent, and both migraines respond to the same specific medications (i.e. triptans).

Conclusions The clinical characteristics indicate that MO and MA are distinct, although closely related, entities, fitting with the model of migraine as a spectrum disorder.

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2003-2013: trends in clinical characteristics and health care use of MOH patients attending a headache centre in Italy

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Background Over the past 15 years clinical experience and scientific evidence about MOH has accumulated providing the basis for new simplified diagnostic criteria, treatment guidelines and possibly an increased awareness about this disorder. It may

be hypothesized that due to these initiatives the clinical profile and the pattern of health care use of MOH patients could have been changed over time. The aim of this study was to analyze the trends in prevalence, clinical severity and health care utilization in MOH patients attending a specialty headache centre.

Methods Data regarding the prevalence of MOH, the socio-demographic status (SES), the clinical characteristics and the health care use measures were extracted from the Headache Clinic database (year 2003 and 2013). The following variables were considered; a) prevalence of MOH; b) SES variables (gender, age, education, occupational status); c) clinical characteristics (headache frequency, headache severity and related-disability, type of medication overuse, duration of MOH, frequency of drug intake, complicated vs. simple form); d) health care use (self-reported MOH diagnosis, source of referral, medication used, headache-related visits).

Results The prevalence of MOH patients visited at the INI Headache Centre decreased over time (17.3%-5.7%, $p < 0.0001$) due to a significant reduction in the proportion of MOH females (18%-6%, $p < 0.01$), whereas no difference was observed in males (10%, 8.2%). When compared with the 2013 MOH cohort, MOH patients visited in 2003 were significantly more disabled (MIDAS IV, 66 vs 32%, $p < 0.001$), had a higher frequency of headache (28.2 vs 24.3 days/month, $p = 0.03$), had a higher drug intake (42 vs 26 drugs/month, $p < 0.01$), had a longer duration of chronification (48 vs 24 months), had a higher rate of complicated forms (73 vs 48%) and had used more frequently a preventive treatment (54% vs 32%, $p = 0.03$). No difference was found for the other SES variables, the source of referral, the type of overused drugs, the number and type of headache-related visits and the rate of patients already diagnosed and treated as MOH.

Discussion Over a ten-year period, MOH has become less prevalent and the clinical profile of MOH patients visited at a specialty headache centre in Italy has improved over time. These data suggest an earlier recognition of MOH and an improved access of these patients to specialists' service.

Frontal thermography in healthy individuals: reliability of the method

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Introduction Infrared Thermography (TH) detects infrared light emitted by the body to visualize changes in body heat due to abnormalities in the surface blood flow of diseased areas. It is useful in making diagnoses and doing evaluations in the field of pain medicine where a diagnosis is based on subjective complaints of symptoms.

Material and method 26 volunteers (20 females and 6 males) with a mean age of 32±10 years (range 23-55 years) were examined. All the subjects were right handed, and none was medicated at the time of testing. Seven of the 26 volunteers had a history of low frequency migraine.

TH has been assessed with an infrared thermal camera (model LT3, Zhejiang Dali Technology Co. Ltd) measuring the spatial distribution of the heat over the face. The image analysis evaluated the temperature in two target points (left [L] and right [R] side) in the frontal polar sites. The measurements were taken in one session (N=26), 19 subjects underwent a second session at least one day apart. The Asymmetry Index (AI) ($100 \times (L_{\text{side}}/L_{\text{side}} + R_{\text{side}})$) was also calculated in order to assess side difference. Concerning the first test session analysis of variance (ANOVA 1 way), intra-class correlation coefficient (ICC) and Pearson's correlation coefficient were calculated. Measurements between two different days (T1 and T2 sessions) were evaluated with the ANOVA 2 ways with replication.

Results The analysis of variance showed no significant difference between three consecutive measurements during the first session both on the R side ($p=0.30$) and the L side ($p=0.32$). Considering 0.75 excellent score of reliability (Fleiss) both R and L ICC measurements showed a good reliability (respectively 0.55 and 0.66). TH values of healthy subjects showed no large asymmetry (49.98 ± 0.22). ANOVA 2 ways did not reveal intraindividual variations between the first and second testing session on separate days. TH measurements were not influenced by external factors (sex or age of subjects and room temperature).

Conclusions These results demonstrate that frontal TH in humans can be an effective method for temperature evaluation. In our experience, TH measurements were rather symmetrical and reproducible on both sides. TH could be a reliable method for the evaluation of localized/lateralized pain syndrome.

Trigger factors of migraine: the role of food intolerance. An open study

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Introduction Several factors can trigger migraine; among them, dietary factors play a very important role in the onset of migraine attacks.

Objective The aim of our study was to evaluate the incidence of food intolerance in a group of migraineurs, by using the Cytotoxic test: it is able to identify the presence of specific food intolerances by observing the appearance, the size, the shape or the integrity of leukocytes exposed to extracted food antigens or other materials derived from specific foods.

Materials and methods 100 consecutive patients suffering from migraine and coming to three Headache Centres in the province of Salerno were examined according to the Cytotoxic test. The sample characteristics were: 66 women, mean age 36.2 years, range 18-48 years; 34 were men, mean age 45.8 years, range 22-58 years.

Results We found that: 37 women (56%) and 15 men (44.1%) were intolerant to tyramine; 13 women (19.7%) and 5 men (14.7%) were intolerant to milk; 13 women (19.7%) and 5 men (14.7%) were intolerant to yeast; 15 women (22.7%) and 3 men (8.8%) were intolerant to Solanaceae; 14 women (21.2%) and 1 man (2.9%) were intolerant to coffee; 18 women (27.3%) and 2 men (5.9%) were intolerant to cocoa; 6 women (9.1%) and 1 man (2.9%) were intolerant to tea; 5 women (7.6%) and 3 men (8.8%) were intolerant to eggs; 3 women (4.5%) and 1 man (2.9%) were intolerant to pork; 4 women (6.1%) and 2 men (5.8%) were intolerant to sugar.

Conclusions Our study showed a high incidence of food intolerance in migraineurs (in women more than in men). The dietary factors which gave more significant results were tyramine, yeast, Solanaceae, coffee and cocoa. These results are consistent with those of other studies found in literature, proposing tyramine, coffee and cocoa as very important migraine-precipitating factors. Few are, on the contrary, the evidences of a comorbidity between migraine and intolerance to Solanaceae. For this reason, further studies are requested to confirm this hypothesis.

Headaches in the Emergency Department: features, management and integrated territorial network

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Introduction Headaches in the Emergency Department (ED) show specific epidemiological and clinical features compared to those observed in the general population; furthermore their management is different from management in the physician's office.

Objective The aim of this study was: 1) to investigate some features of acute headaches afferent to EDs of three Hospitals in the province of Salerno (Sarno, Eboli, Vallo della Lucania); 2) to establish a shared clinical management with direct admission for primary headache patients to the local Headache Centre.

Patients and methods 517 subjects with acute headache, referred to the three above mentioned EDs from 2012 until today, were evaluated following a diagnostic algorithm (Valade et al 2008) and diagnosed according to ICHD-2 criteria. All the primary headache patients non hospitalized were directly sent to the local Headache centre with first visit within 48 hours and a follow up visit within 7 days.

Results The sample characteristics were: 335 F (64.8% F), 182 M (35.2 %), mean age 38 years (19% over 50 years); 10% of patients were Repeaters (patients with 3 or more accesses to the ED/month, six months along). The ICHD-2 diagnoses were: 1) Primary headaches 74.6%: Migraine 43.8% (Chronic migraine 31.4%); Tension type headache 20.6%; Cluster headache and other TACs 10.2%; Probable primary headache 17.8%; 2) Other primary headaches 3.2%; 3) Secondary headaches 19%; 4) Cranial neuralgias and other essential facial pains 2%; 5) Unclassified 1.2%. Repeaters were represented by Chronic migraineurs (6.5%) and Cluster headache patients (3.5%).

Discussion Headaches in the ED present different features, particularly about prevalence and clinical presentation, compared to those observed in the general population: higher prevalence for Migraine – in particular Chronic Migraine – and Cluster headache; high percentage of Probable primary headaches, sometimes with non specific clinical features. It's very important to know these peculiarities to establish the specific next step (hospital admittance or not, which investigation or therapy).

Conclusions The main aims to optimize the management of headaches in ED are represented by: 1) presence of a headache-specialist neurologist; 2) shared diagnostic algorithms; 3) for primary headaches, a ICHD-2 First Level Diagnosis and effective symptomatic therapy (why not triptans?); 4) institution of an integrated territorial network: the direct and rapid admission to the Headache Centre - within 48 h - and a follow up within 7 days – can allow to reduce the percentage of Repeaters and the occurrence of medication overuse.

Oxidative balance evaluation by d-ROMs test and BAP test in migraine patients

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Introduction Migraine is the most common neurological disorder, but the molecular basis is still not completely understood. An impairment of mitochondrial oxidative metabolism might play a role in the pathophysiology. Moreover there is strong evidence associating migraine with a variety of comorbid disorders, including cardiovascular disease and stroke, in which oxidative stress seems to be an important underlying mechanism. However, data are in part controversial and the possible underlying mechanism remains elusive to date and data regarding the interictal state in migraineurs are limited.

Aim To evaluate the oxidative balance in a sample of patients with migraine by means of routine specific serum tests, such as d-ROMs test and BAP test.

Methods 70 outpatients (46 F, 24 M), mean age 35 years (SD 11.2), range 18-58 years, suffering from migraine without aura (ICHD-II 2004 criteria) were enrolled. The mean duration of disease was 1.75 (SD 1.4) years, range 1-6 years. Serum total oxidant capacity was determined by performing the d-ROMs test (2), whose chemical principle is based on the ability of a biological sample to oxidize N,N-diethyl-paraphenylenediamine (normal range 250-300 CARR U, where 1 CARR U is equivalent to 0.8 mg/L H₂O₂), while serum total antioxidant capacity was assessed by means of the BAP test, which measures the ability of a serum sample to reduce iron from the ferric to the ferrous ionic form (optimal value >2200 micromol/L reduced iron).

Results Mean values of d-ROMs tests were 371 CARR U (SD 120.2) while mean values of BAP test were 1779.3 micromol/L reduced iron (SD 443.7).

Discussion and conclusions According to herein reported data, enrolled patients were found to be in a classical condition of oxidative stress. In fact, compared to the normal range, oxidant capacity, as measured by means of d-ROMs test, was increased (>300 CARR U) and biological antioxidant potential (as measured by means of BAP test) was decreased (<2200 micromol/L reduced iron). Although preliminary, our study confirms that migraine without aura is associated to oxidative stress and suggests that d-ROMs test and BAP test can be useful to identify an oxidative unbalance in the clinical routine of patients suffering from this frequent disease. Our data suggest that oxidative stress may represent a key event in the pathophysiology of migraine and a suitable therapeutic target. Further knowledge about this issue may contribute to elucidate the cause and complications of migraine and may be essential for the the development of treatment approaches.

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Cortical spreading depression and migraine: new experimental evidence

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Cortical spreading depression (CSD) is believed to play a crucial role in migraine with aura. A number of mechanisms have been shown to have a role in fostering CSD wave initiation and propagation including: ion diffusion, membrane ionic currents, osmotic effects, spatial buffering, neurotransmitter substances, gap junctions, metabolic pumps, and synaptic connections [1, 2]. Notably, it has been shown that spreading depression (SD) changed neuronal activity and consequently modulated extracellular dopamine in the terminal fields during stimulation of the prefrontal cortex. Moreover, in SD, the sharp increase of potassium concentration is accompanied by the release of dopamine in *in vivo* experiments. Cortical stimulation increases basal levels of dopamine in the caudate and in the nucleus accumbens. The mechanisms by which SD can modulate the dopaminergic presynaptic terminals in striatum are unknown. There is evidence that cortex can enhance dopamine release in striatum via activation of glutamatergic neurotransmission. Another study indicates elevation of evoked dopamine release in the nucleus accumbens and a decrease in the nucleus caudatus resulting from depression of the cortical activity induced by SD. Therefore, SD in the cortex may modulate neurotransmitter release in subcortical structures and may have a general impact on the redistribution of the oxygen supply in these subcortical areas. In spite of these studies, the role of dopamine in initiation and propagation of cortical SD still needed to be clarified. However, in clinical trials, several dopaminergic candidate genes have been investigated in different migraine case-control cohorts with varying results [3]. In a large subgroup of migraineurs, dopamine acts as an endogenous protagonist in the pathophysiology of the disorder. Therefore, modulation of dopaminergic neurotransmission should be considered in the therapeutic management of migraine.

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Mechanisms and circuits underlying drug addiction

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Three features characterize drug addiction as a chronically relapsing disorder: (i) compulsion to intake the overused drug, (ii) inability to control drug intake, and (iii) appearance of a behavioral disorder (depression, anxiety, irritability) reflecting a motivational withdrawal syndrome when access to the drug is prevented.

Both impulsivity and compulsivity characterize the drug addiction cycle. This cycle includes three stages: intoxication, withdrawal, and craving. Animal and human imaging studies have revealed discrete circuits that mediate the three stages of the addiction cycle with key elements of the ventral tegmental area and ventral striatum as a focal point for the intoxication stage, a key role for the extended amygdala in the withdrawal, and a key role of orbitofrontal cortex-dorsal striatum in craving.

The transition to addiction involves neuroplasticity in all of these structures that may begin with changes in the mesolimbic dopamine system and it includes a cascade of synaptic events from the ventral to dorsal striatum and orbitofrontal cortex. A synaptic dysregulation also of additional structures of the prefrontal cortex, cingulate gyrus, and extended amygdala has been postulated in drug addiction.

These synaptic mechanisms might operate not only in classical forms of drug addiction but also in medication overuse headache (MOH) [1, 2]. Moreover, MOH might be prompted and sustained in some patients by psychological states, psychiatric comorbidities and substance abuse disorders. MOH seemingly shares with other kinds of drug dependence, some

common neurobiological pathways, including those that modulate motivation, reward, novelty seeking, behavioural control, response to stress and relapse. The significantly increased familial risk for chronic headache, drug overuse, and substance abuse suggests that a genetic factor might be involved in the process of headache chronification.

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The putative role of genetic factors in medication-overuse headache

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Medication-overuse headache (MOH) is a common and debilitating disorder, with a prevalence of 1-2% in the general population. Despite a growing interest, the pathophysiological mechanisms of MOH are not entirely clear. A hereditary susceptibility to MOH has been proposed on the basis of epidemiological evidence. The risk of MOH is increased threefold if there is a family history of MOH or other substance abuse such as drug or alcohol abuse. The risk of developing drug overuse or substance abuse is increased fourfold if another family member has had MOH. Recently, molecular genetic factors have also become a focus in research on MOH pathophysiology. The Val66Met polymorphism in brain-derived neurotrophic factor, which is related to behavioural disorders and substance abuse, is associated with increased analgesic drug consumption in patients with MOH. This finding suggests that MOH is, at least in part, a substance abuse disorder rather than just a complication of the underlying idiopathic headache disorder. In another study, allele 10 of the dopamine transporter gene (SLC6A3; also known as DAT1) was significantly under-represented in patients with MOH compared with patients with episodic migraine [1]. Similarly, the presence of polymorphisms at the catechol-O-methyltransferase (COMT) locus are associated to a fourfold decrease in enzyme activity, which in turn leads to higher dopamine levels in the synaptic cleft, and to inter-individual differences in pain sensitivity. Given the occurrence of dysfunctions in the mesocorticolimbic dopamine circuit and in other pain-processing-related areas of MOH patients, it was hypothesized that an alteration of COMT activity may have an impact on the prognosis of MOH

patients. The different genotypic and allelic distributions of the known polymorphisms of several serotonin (5-HT) receptor genes do not seem to have a role in the genetic susceptibility to MOH. Recent evidence suggests that genomic patterns could identify patients at high risk to develop MOH and to respond to medication cessation, as glutamate transporter protein EAAT2 and dopamine D2 receptor. In particular, results from the SAMOHA study suggest that HDAC3 gene could be implicated in excessive medication consumption in MOH patients, independently of the need of acute medication for pain relief. Since all studies on molecular genetics in MOH were done with small sample sizes, the results must be regarded as preliminary at this stage.

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Cortical excitability in episodic cluster headache

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Background Cluster headache (CH) is a severe primary headache disorder characterized by strictly unilateral pain attacks accompanied by ipsilateral autonomic symptoms. The pathophysiological processes underlying CH remain largely unknown. Evidence of central disinhibition of the trigeminal nociceptive system and hypothalamic impairment has been provided. Although a cortical involvement has also been supposed, very few studies have explored this issue. Therefore, aim of this study was to evaluate cortical excitability in episodic CH patients by using different paradigms of transcranial magnetic stimulation (TMS).

Subjects and methods Twenty-five patients with episodic CH and thirteen healthy subjects underwent an experimental session where we evaluated, in both hemispheres, motor cortical response to: **1.** single-pulse TMS: i.e., motor threshold (MT); input-output (IO) curves and cortical silent period (CSP) and **2.** paired-pulse TMS: i.e., intracortical facilitation (ICF) and short intracortical inhibition (SICI). Thirteen patients were evaluated outside bout, while the remaining twelve patients were inside bout at the time of recording.

Results We showed increased ICF values in the hemisphere ipsilateral to the side of pain in patients evaluated both outside and inside bout. Differently, IO curves showed increased slope in both hemispheres in patients examined outside bout, but only

on the hemisphere contralateral to the affected side in those evaluated during bout. No significant changes in the other electrophysiological parameters were observed.

Discussion Our results show a condition of increased cortical excitability in episodic CH both outside and inside bout. Interestingly, cortical excitability was greater in the hemisphere ipsilateral to the side of pain in patients outside bout, but decreased in patients inside bout possibly due to activation of compensatory inhibitory mechanisms of cortical excitability.

Conclusions Along with subcortical and peripheral mechanisms, changes in cortical excitability could also play an important role in the pathophysiology of CH.

Nitroglycerin-induced enhancement of orofacial formalin pain: a model of trigeminal hyperalgesia relevant for migraine

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Systemic nitroglycerin (NTG) administration in the rat activates cerebral nuclei involved in nociception, as well as in neuroendocrine and autonomic functions. These changes are likely relevant for migraine pain, since NTG consistently provokes spontaneous-like migraine attacks in migraineurs. The underlying mechanisms are unknown, but it is likely that NTG-induced vasodilation and the increased availability of nitric oxide at the trigeminovascular level, and possibly also at central sites, may induce a condition of sensitization. This hypothesis is partly confirmed by the demonstration that NTG indeed induces hyperalgesia at the formalin test induced by plantar formalin injection. In this study we investigated the effect of NTG administration in the orofacial formalin test in order to investigate more specifically the effect of NTG on the trigeminal system.

The subcutaneous injection of formalin (1.5%) was performed in male Sprague-Dawley rats pre-treated with NTG or vehicle, 2 and 4 hours before the experimental test. The pain-related behavior was quantified by counting the number of seconds that the animals spent grooming the injected area with the ipsilateral fore- or hindpaw in both Phase I and Phase II of the test. Data showed that NTG injected before the formalin injection significantly increases behavioral responses in Phase II of the test, when compared to the vehicle group. The study showed for the first time that systemic administration of NTG does enhance pain in the trigeminal area. This model seems to be specific for migraine, a disabling primary headache characterized by pain in the trigeminal distribution area.

The thalamo-cortical dysrhythmia in migraine

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The thalamus seems to be profoundly involved in the expression of migraine clinical and neurophysiological correlates. From animal models, some hypothesized that a temporary sensitization of third-order thalamic neurons receiving convergent input from the dura, periorbital skin, and skin areas at different body sites explains the spread of cutaneous hypersensitivity, i.e. allodynia, beyond the referred pain area on the ipsilateral side of the head during an attack. Abnormal modulatory activity of the thalamic lateral geniculate complex might be involved in the process leading to photophobia that is present during and, sometimes, even outside an attack. From experimental model, it appears that the thalamic nuclei can mediate the antinociceptive response to common acute and preventive migraine medications. Thalamic and thalamocortical activity involvement in migraine was even seen outside an attack through the application of more sophisticated techniques of clinical neurophysiology. Studies of spontaneous EEG and visual or somatosensory evoked high frequency oscillations indicate that the cortical functional activity in migraine could be set by abnormal thalamic rhythmic activity, namely to “thalamo-cortical dysrhythmia”. The thalamo-cortical dysrhythmia fluctuates with the migraine cycle (ictal vs. interictal) and with the attacks frequency (episodic vs. chronic). The anatomical correlates of these fluctuations are only recently beginning to be understood.

Reduced visual cortical reactivity in migraineurs with a positive family history of migraine

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Background In migraine, the genetic load can be seen as determining, on the one hand, a critical threshold for the disease development, and on the other hand, it may be responsible for interictal nervous system dysfunction. Here, we aimed to verify whether having a positive family history of migraine might influence cortical abnormal information processing in migraine patients.

Methods We retrospectively collected 109 migraine patients from those reviewed who had visual evoked potentials (VEPs) recordings (6 blocks of 100 sweeps, 15 min of arc cheques, 3.1 repetition rate) and information about parental history of migraine. Neurophysiological recording data were compared with those of 42 healthy volunteers (HV) without a personal or family history of migraine.

Results We recruited 109 migraineurs, 85 with and 24 without a positive family history of migraine. Patients who had one parent affected (mother or father) had significantly lower N75-P100 VEP amplitude blocks overall than those who had no parents affected, the latter resulting not different from HV. Lack of VEP N75-P100 amplitude habituation was found in overall migraineurs compared with HV, irrespective of whether they had a parent affected or not.

Conclusions These findings suggest that familial occurrence of migraine may predispose to a general reduced cortical reactivity to visual stimulation.

Impaired VEP after photostress in migraine patients between attacks

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Background Subtle impaired macular vision was observed among different psychophysical experimental tasks in migraine patients. Here we studied visual evoked potential (VEP) after photostress (PS) representing an objective index of the dynamic properties of macular performance after exposure to intense light stimulation.

Methods We recorded VEPs in basal condition and after PS in 43 migraineurs patients (19 with and 24 without aura) and 14 healthy volunteers (HV). We compared P100 implicit time and N75-P100 amplitude of baseline VEP with those collected every 20 s up to 200 s after PS.

Results VEP parameters did not differ between groups at baseline. In all groups, the VEPs recorded after PS showed a significant increase in latency at 20s. In HV, N75-P100 amplitude significantly decreased 20s after PS, and recovered subsequently. There was no effect in the migraine groups. In fact, the percentage reduction in N75-P100 amplitude observed at 20s after photostress in MO and MA patients was lower than in HV (MO vs HV $P < 0.05$, MA vs HV $P < 0.05$). When data of migraine patients were combined, the percentage of amplitude changes at 20s was negatively correlated with the number of days since the last migraine attack ($r = -0.525$, $p = 0.02$).

Conclusions We documented altered recovery after PS under the influence of imminent attack. Whether or not the present VEP findings are related to the ictal/interictal migraineur susceptibility to abnormal sensory perception, such as visual discomfort, remains to be determined.

Does the epidermal nerve fibre density measured by skin biopsy in patients with peripheral neuropathies correlate with neuropathic pain?

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The different neuropathic pain types (e.g. ongoing burning pain and allodynia) are frequent and disabling complaints in patients with peripheral neuropathies. Although the reference standard technique for diagnosing painful small fibre neuropathies is nerve fibre density assessment by skin biopsy, the relationship between the epidermal nerve fibre (ENF) density and neuropathic pain is still unclear. In a clinical and skin biopsy study designed to investigate whether changes in ENF density are directly related to pain, we enrolled 139 consecutive patients with distal symmetric peripheral neuropathy.

All patients underwent clinical examination. The Neuropathic Pain Symptom Inventory was used to distinguish the different neuropathic pain types. A skin biopsy was conducted and ENFs were immunostained with the antiprotein gene product 9.5 and their linear density was quantified with bright-field microscopy. No difference was found in ENF density between patients with and without neuropathic pain, nor between patients with and without ongoing burning pain. Conversely, ENF density was

higher in patients with provoked pain (including mechanical dynamic allodynia) than in those without.

The variable association between ENF density and symptoms of neuropathic pain supports the idea that neuropathic pain symptoms arise through distinct underlying mechanisms. The lack of relationship between ongoing burning pain and ENF density suggests that this type of pain reflects factors other than loss of nociceptive afferents. The association between ENF density and provoked pain (including mechanical dynamic allodynia) suggests that this type of pain might be mediated by spared and sensitised nociceptive afferents.

Changes in nociceptive withdrawal reflex thresholds in women affected by menstrual migraine related to estro-progestinic therapy

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Migraine is a common and disabling neurological disorder that affects women three times more than men. Migraine is deeply influenced by menstrual cycle and by estro-progestinic therapies. The aim of this study is to investigate pain modulation effect of estro-progestinic therapy in women affected by menstrual migraine. According to a validated method for the investigation of pain pathways, we analyzed the nociceptive withdrawal reflex (NWR), recorded from femoral bicep, obtained following the electrical stimulation of the homolateral sural nerve. Reflex threshold of NWR, considered as the lower current intensity needed to evoke a stable EMG response, was obtained with a single stimulus (RT-SS) of increasing intensity and for temporal summation, elicited with a train of 5 consecutive stimuli (RT-TST).

We enrolled 10 women (age 32.4 ± 8.6 years) affected by migraine without aura, with headache attacks restricted to the suspension week of hormonal therapy. Patients underwent two tests: the first (T1) during the week before suspension of the estro-progestinic therapy and the second (T2) during the suspension week. At each visit, patients were also asked to graduate their psychophysical pain sensation using a 1 to 10 VAS scale. At T1, under estro-progestinic conditioning, RT-SS was 15.5 ± 6.8 mA (VAS 5.2 ± 2.1) with an average area under the EMG track of 1416.1 ± 711.1 mV/mS, while RT-TST was 10.1 ± 3.1 mA.

At T2, during the suspension phase of the estro-progestinic drug,

RT-SS was 13.0 ± 5.6 mA (VAS 5.1 ± 1.9) with an EMG area of 1978.8 ± 1194.3 mV/mS, while RT-TST was 10.0 ± 2.8 mA. Statistical analysis showed that RT-SS was significantly lower at T1 when compared with T2 values ($p < 0.005$). A tendency toward an increase in the EMG area, although not significant, and an unchanged psychophysical pain sensation, suggest that suspension of the estro-progestinic therapy is associated with a drop in pain threshold. This phenomenon may play a role in triggering or facilitating the occurrence of the migraine attack.

Pain stimuli processing in pre-symptomatic and early Huntington's disease

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Introduction Huntington's disease (HD) is a neurodegenerative genetic autosomal dominant disorder, caused by an abnormal expansion of CAG on the IT-15 gene which results in movement, cognitive and psychiatric disorders. Data suggest that the basal ganglia may be involved in the sensory-discriminative, affective and cognitive dimension of pain, as well as modulation of nociceptive information and sensory gating of nociceptive information to higher motor area. A delay in nociceptive input processing emerged in HD patients, concurring with the main features of the disease, in absence of clinical evidence of abnormalities in pain perception [1]. Recent theories about Laser Evoked Potentials (LEPs) outlined that they reflect cortical-not pain specific activation through salient stimuli, probably preparing to motor action. In this sense HD patients seem to be affected by a slowing in detecting salient stimuli, potentially related to a motor activation. This may be relevant for sensory-motor integration. The aim of the present study was to evaluate evoked responses by laser stimuli (LEPs) and auditory event related potentials (Auditory ERPs) in pre-symptomatic and early HD patients.

Methods Ten HD patients, 10 pre-symptomatic subjects (pre-HDs) and 20 controls subjects were selected. LEPs were obtained by 62 scalp electrodes, stimulating the dorsum of right hand. All patients were also evaluated by Auditory ERPs.

Results Preliminary results confirm LEPs N2 latency increase in HD patients compared to controls, while no difference was detected compared to pre-HDs. An amplitude decrease of LEPs late P2 component emerged, concurring with Auditory ERP reduction in both HD patients and pre-HDs compared to controls.

Discussion HD patients and pre-HDs may be characterized by a disturbance in salient stimuli processing, with a reduced activation of cortical zones devoted to stimuli processing and motor response planning (cingulate). This may explain a normal pain perception, with a probable deterioration of voluntary and involuntary motor reaction and pain symptoms expression.

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CO₂ versus Nd-YAP lasers: are they really the same?

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Objective To compare amplitudes and latencies of the laser evoked potentials (LEPs) to CO₂ and Nd:YAP laser stimuli.

Methods In 6 healthy subjects, A-delta LEPs were acquired using a 32 channel system. CO₂ and Nd-YAP laser pulses were delivered on the dorsum of both hands and feet in two sessions.

Results After stimulation of both hand and foot, the N2 latency was shorter to CO₂ than to Nd:YAP pulses. Only after foot stimulation, the P2 latency was significantly shorter with CO₂ than Nd-YAP laser. Both the N2 and P2 amplitudes to hand and foot stimulation were significantly enhanced in YAP-LEPs, compared to CO₂ LEPs. In both CO₂ and Nd-YAP LEPs, the N1 amplitude to hand stimulation was higher in the contralateral temporal than in the contralateral central trace, even if the difference was not significant. After foot stimulation, the N1 amplitudes in the contralateral temporal and central traces were similar.

Conclusions LEP latencies were shorter to CO₂ than to Nd-YAP laser stimulation. With both techniques, hand stimulation produced a higher N1 amplitude in the contralateral temporal trace, while after foot stimulation a N1 component was observed in both the contralateral temporal and central traces with the same amplitude. These results confirm the N1 origin in the opercular region.

Modulation of nociceptive pathway during an application of noxious cooling pain: a study with Nd:Yap Laser Evoked Potentials

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Introduction The negative interaction between pain sensations elicited simultaneously by two remote sources of noxious stimuli is a classical clinical observation. Such a 'pain inhibits pain' effect, depends on specific neurophysiological mechanisms involving endogenous modulatory systems which have been termed 'diffuse noxious inhibitory controls' (DNIC). However, only a few neurophysiological studies have investigated the possible functional modifications caused by pain within the nociceptive pathways. The Laser Evoked Potentials (LEPs) can explore the nociceptive pathway and the brain areas responding to nociceptive inputs. The present study aimed to investigate the effect of noxious cooling stimulation on the cortical processing of nociceptive stimuli by laser stimulation.

Subjects and methods We studied thirteen healthy right-handed subjects (five male, eight female, mean age 30 years, range 26 - 35), who gave their informed consent. As noxious cooling stimulation, subjects were required to dip their right foot into ice water at the temperature around 0°C. Scalp Nd:Yap LEPs were recorded by stimulation of the right hand under the following session: before, during, and immediately after 10 minutes of a noxious cooling stimulation. LEP components were identified on the basis of their latency and polarity. Latency and amplitude were measured for the N1 wave and N2/P2 complex.

Results During noxious cooling stimuli, both N1 and N2/P2 amplitudes were significantly decreased compared with the baseline values. No amplitude change was observed ten minutes after noxious cooling stimulation.

Discussion The amplitude reduction of both the middle-latency (N1) and the vertex (N2/P2) LEP amplitudes could be an effect of DNIC. N1 and the N2/P2 components are generated by different dipolar source: the N1 potential is generated in Secondary Somatosensory Cortex and is correlated with tactile-discriminative pain perception, whilst N2/P2 component is generated in the Anterior Cingulate Cortex and it is linked with emotional component of pain sensation. These results suggest that noxious cooling pain may lead to rapid changes probably mediated by DNIC in cortical representation of nociceptive inputs which are thought to encode different aspects of pain sensation.

Balance control impairment induced after OKS in patients with vestibular migraine

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Objective To assess the effects of optokinetic stimulation (OKS) on postural control in migraine patients with recurrent vertigo.

Material and methods Fifteen patients with vestibular migraine (VM) were enrolled in a posturographic study in eyes open (EO) and eyes closed (EC) conditions. The tests were performed between headache and vertigo attacks at three different times: before, during, and 60 minutes after OKS. Data of patients with VM were compared with those obtained from two control groups matched for sex and age (15 for each group): a) normal subjects not suffering from migraine with no history of recurrent vertigo (N group); b) subjects suffering from migraine with no history of recurrent vertigo (M group). Mean sway velocity and sway area were analysed.

Results OKS increased instability in all groups during the stimulus, and both velocity and area values were higher in M and VM group. However, there was no significant difference between these two groups when stability was examined in EO condition before, during and after OKS. Conversely, in EC condition a significant greater instability was induced after OKS only in VM. In particular, post-stimulus values were significantly higher than the pre-stimulus ones only in this group, while no significant difference was observed in the other groups. A spatial analysis of the sway area evidenced that the instability induced by OKS in VM group occurred along the direction of OKS.

Discussion A continuous unidirectional optokinetic input is an unusual stimulus that is counteracted by the visuo-vestibular system, as shown by the building up of an opposite directed after-nystagmus [1]. It is like that during the development of this after-effect the fine balance function in the horizontal visuo-vestibular circuitry is disrupted. However, normal subjects are able to quickly recover through central adaptive mechanisms, such as the visuo-vestibular calibration system. In presence of a deficit in this adaptive central process, the unbalance in the visuo-vestibular circuit would be maintained. This may be the case for the VM patients in which the balance appeared impaired after prolonged optokinetic stimulation.

Conclusions Our study showed persistent effects induced by optic flow stimulation on postural control that relate only to migraine patients with a history of recurrent vertigo.

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Fluorodeoxyglucose positron emission tomography/computed tomography findings in migraine sufferers and control subjects: preliminary note

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Aim This was a serendipity observation the aim of which was to observe possible abnormalities of regional glucose metabolism in migraine patients and headache exempt, pain-free subjects who had to undergo SPECT/TC (SPECT/TC Symbia™) for diagnostic purpose. The basis of the observation was represented by different studies indicating, with conflicting data, changes in the frontal cortex of migraine sufferers. Thus, the aim was to evaluate the hypothesis of peculiar functional abnormalities in discrete brain areas of migraine sufferers versus controls, as well as differences between attack phase and pain-free period.

Patients and methods The functional imaging was carried out on subjects with migraine either during the attack (5 subjects) or in the pain-free period (4 subjects), as well as in 5 normal controls using fluorodeoxyglucose positron emission tomography/computed tomography. Statistical Parametric Mapping (SPM) software was used to evaluate outcomes.

Results and conclusions Results obtained by means of SPM software ($p=0.0001$) were not discussed due to the low number of observed subjects and because of the great homogeneity of results regarding abnormal character of cerebral glucose metabolism. We would like to emphasise that we only observed an abnormal glucose metabolism in the frontal lobe of all the migraine sufferers who underwent examination during a migraine attack. This feature was not present in the pain-free period as well as in controls.

Evidence for rapid brain morphometric changes during the migraine cycle

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Background Neurophysiological investigations have demonstrated that there are unique fluctuations in the brain’s electric signals between the ictal and interictal periods of recurrent migraine. Whether structural plasticity of the brain is also an important feature of episodic migraine remains unresolved. We therefore investigated the possibility that there are fluctuations over time in whole brain morphometry of patients affected by episodic migraine without aura.

Methods Twenty-four patients with untreated migraine without aura (MO) underwent MRI scans (3-Tesla Siemens Verio) during ($n=10$) or between attacks ($n=14$) and were compared to a group of 15 healthy volunteers (HV). We then performed voxel-based-morphometry (VBM) analysis of structural T1-weighted MRI scans to determine if changes in brain structure were observed over the course of the migraine cycle.

Results During the interictal phase, MO patients had a significantly lower grey matter (GM) density within the right inferior parietal lobule, right temporal inferior gyrus, right superior temporal gyrus, and left temporal pole compared with HV. During attacks, GM density increased within the left temporal pole, bilateral insula, and right lenticular nuclei, but no areas exhibited decreased GM density.

Conclusions The morphometric GM changes between ictal and interictal phases reported in our study suggest that aberrant structural plasticity may be an important mechanism of migraine pathology. Given the functional neuroanatomy of these areas, our findings suggest that migraine is a condition associated with global dysfunction of multisensory integration and memory processing.

Periaqueductal gray connectivity in patients with Fibromyalgia. Preliminary results

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Fibromyalgia is a chronic pain condition characterized by widespread pain and muscles tenderness, often associated with fatigue, sleep disorders and depression. Although pathophysiological mechanisms underlying this condition are still unclear, abnormalities of the descending pain modulatory system, such as the periaqueductal gray (PAG), might play an important role. In this functional neuroimaging study we aimed at verifying differences in PAG connectivity between healthy subjects and patients with fibromyalgia. We enrolled 15 patients and 15 healthy subjects; all of them underwent functional connectivity MRI study. Anatomical and functional scans were performed with a 3 Tesla Verio (Siemens-Erlangen). In the healthy subjects, we found positive correlations

between PAG and nearby structures, including the brainstem, thalamus, putamen, hippocampus, amygdala, and cerebellum, and with distant regions, including the anterior and posterior cingulate, frontal and temporal cortex, cuneus and precuneus and insula. In patients with fibromyalgia PAG connectivity significantly correlated with nearby brainstem structures, anterior cingulate cortex, insula and cerebellum. The PAG connectivity in patients with fibromyalgia was significantly lower than that of healthy subjects. Our findings showed that in patients with fibromyalgia the PAG connectivity is reduced in specific areas compared to the healthy subjects. These findings suggest a descending pain modulatory system dysfunction in patients with fibromyalgia.

Supplement versus amitriptyline in the prophylaxis of primary headaches: comparative data

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Introduction Study on patients with CTE, CTC and ESA.

Objective To compare the efficacy of a product based on Magnesium bisglycinate, L-tryptophan, niacin, Vitamin B2 and Vitamin D (Pineal Tens sachets, Laborest Italia Spa = PT) and amitriptyline (AMT) in the prophylaxis of these primary headaches [1].

Materials and methods We evaluated a total of 140 patients. All had a history of primary headache and had never undergone prophylactic therapy. The observation covered a period of 7 months (T0, T1 = 90, T2 = 180, T3 = 210 days).

Eighty-one patients were operated for a period of three months monotherapy prophylaxis with PT two sachets in a day. During a second period of three months, the patients received 1 sachet of PT in a day. In a third phase the patients discontinued treatment for 30 days and were reassessed at control.

Another 59 patients were subjected to daily prophylactic drug therapy with AMT 10 drops daily for 180 days, then suspended for 30 days and later they were re-evaluated.

Primary data outcome constituents, also headache diary, and the VAS have been used as assessment tools.

Results At T0 patients treated with PT had a higher VAS, a lower frequency of attacks and analgesic consumption slightly higher than patients treated with AMT.

At T1, the reduction of the VAS was higher in the PT group vs AMT, but was inferior to T2 and T3. The higher frequency of headache days in a month with the group PT at T0 has turned into a reduction in T3 compared to the group with the AMT. The higher consumption of analgesics in the PT group at T0 has turned into a similar consumption in the AMT group at the subsequent checks (T1, T2, T3).

Discussion and conclusions The study was developed based on our experience in the outpatient clinic. The overall data confirm that in the prophylaxis of patients with primary headache the use of a supplement containing Magnesium bisglycinate, L-tryptophan, niacin, Vitamin B2 and Vitamin D produces an effective result compared to the reduction of days in a month with headache, both with respect to the analogue scale of pain and analgesic

consumption. Moreover, in comparison with patients undergoing prophylactic therapy with amitriptyline, the effectiveness of the pineal TENS was found to be almost superimposable.

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Cannabinoids versus conventional drugs in the acute treatment of severe migraine attacks

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Background In a previous epidemiologic observation we suggested that headache could follow a chronic abuse of dependence substances. Nonetheless, marijuana is historically known as a therapy for migraine attacks.

Aim 1. To investigate about the possible pain induction after marijuana abuse withdrawal; 2. To highlight the possible therapeutic effect and side-effects of cannabis sativa (Bedrocan, BV) in very severe migraine attacks compared to sumatriptan 100 mg or indomethacin 100 mg.

Observation 1 - Start date: March 1994.

Methods and results N=605 marijuana abusers were consecutively admitted. All patients filled out a headache questionnaire and 315 patients were included. Over 50% (n=178) of the subjects developed headache after withdrawal. Persistent migraine was observed in those patients who showed a family history clearly positive for primary headache, in spite of the history of their headache some patients (n=101) used marijuana to control the severest attacks.

Observation 2 - Start date: January 2014.

Methods Twenty-four patients suffering from 14 to 18 very severe attacks/month were recruited. In a randomized multiple-attack experience eight migraine attacks were treated by using 50 mg, cannabis sativa 300 mg m infusion or current abortive anti-migraine treatments: indomethacin 100 mg muscularly or subcutaneous sumatriptan 6 mg. Subjects were asked to treat severe-very severe pain (VAS 6-9). Measures regard pain-free at 2 hours. De-

crease was esteemed versus baseline rated on a 0-10 VAS. Side-effects were monitored by a trained general medicine operator.

Results The mean VAS (0-10) of migraine attacks decreased significantly during the 2 hrs following cannabis, sumatriptan and indomethacin (Cannabis sativa 7.4 ± 1.4 SD baseline vs 3.0 ± 3.3 SD 2 hrs post-treatment $p=0.0005$; Sumatriptan 5.7 ± 1.6 SD baseline vs 2.9 ± 1.9 SD 2 hrs post-treatment $p=0.005$; Indomethacin 6.5 ± 1.8 SD vs 1.9 ± 3.0 SD 2 hrs post-treatment $p=0.001$). None gave response to 50 mg cannabis. Subjects refractory (benefit less than 20%) to sumatriptan or indomethacin gave positive response to 300 mg cannabis, except 1 female who gave response 0 to cannabis and reported relief following indomethacin. Side-effects of cannabis (Bedrocan) were mydriasis and drowsiness (all treated subjects), impulsivity and frontal lobe activity depression in the youngest 4 patients aged 24-35. Motor incoordination was particularly evident in 35-50 year old subjects.

Conclusions Cannabis can induce benefit on the painful attack in chronic migraine but is not devoid of side-effects.

Efficacy of frovatriptan vs. other triptans in the treatment of patients with moderate-to-severe attacks of migraine with or without aura

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Introduction Triptans are recommended for treating moderate-to-severe migraine attacks or when NSAIDs are ineffective. In this post-hoc analysis of individual data of three double-blind, randomized, controlled, cross-over trials with an identical design we compared the efficacy of frovatriptan with those of rizatriptan, zolmitriptan, and almotriptan in patients who treated only moderate or severe attacks of migraine with or without aura.

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 6 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 or almotriptan 12.5 mg).

Results Three hundred and forty-six patients were included in the intention-to-treat analysis: of these 334 had suffered from at least one moderate or severe migraine attack. Patients treated 793 mod-

erate-severe attacks with frovatriptan and 773 with another triptan. Pain-free at 2-hours did not differ between frovatriptan (25.3%) and the other triptans (28.1%, odds ratio and 95% confidence interval: 1.15, 0.92-1.44; $p=0.220$). The rate of 24-hour relapse was significantly ($p<0.01$) lower under frovatriptan than under the other triptans: 15.4% vs. 25.8% (odds ratio: 0.52, 0.32-0.85). This was the case also for 48-hour relapse rate, which was 25.4% under frovatriptan and 40.1% under comparators (odds ratio: 0.51, 0.33-0.77; $p<0.01$).

Conclusions In patients with moderate-to-severe migraine attacks frovatriptan is equally effective at 2-hours but has a significantly lower recurrence rate than other triptans, this difference being clinically relevant.

Efficacy of frovatriptan vs. other triptans in the treatment of patients with migraine with or without aura and a MIDAS score of III/IV

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Introduction Migraine Disability Assessment (MIDAS) questionnaire is used in clinical trials to determine how severely migraine affects a patient's life [1]. Once scored, the test provides clinical information on how debilitating migraine is, based on a four grade scale, ranging between I (little or no disability) and IV (severe disability). In this post-hoc analysis of individual data from three double-blind, randomized, controlled, crossover trials, with an identical design, we compared the efficacy of frovatriptan vs. rizatriptan, zolmitriptan, and almotriptan in the subgroup of patients with the highest MIDAS scores (III or IV).

Materials and methods Patients aged 18-65 years with migraine with or without aura (following IHS criteria) and having experienced one to six migraine attacks per month for 6 months prior to entering 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 The intention-to-treat analysis included 346 patients, of which 264 had a MIDAS score of III or IV. A total of 746 attacks were treated with frovatriptan and 754 with another comparative triptan. Pain-free at 2-hours did not differ between frovatriptan (29.2%) and the other triptans (32.0%, odds ratio

and 95% confidence interval: 0.87, 0.70-1.09; $p=0.228$), this being the case also for pain relief at 2-hours (45.0% frovatriptan vs. 46.2% comparators; odds ratio: 0.96, 0.78-1.17; $p=0.665$). The rate of migraine relapse over 48 hours was significantly lower ($p<0.05$) with frovatriptan (27.2%) than with the comparators (37.5%, odds ratio: 0.62; 0.42-0.93).

Conclusions In patients with a severe form of migraine at baseline as assessed by MIDAS questionnaire, frovatriptan demonstrated to be equally fast when compared to other triptans, in terms of pain-free and pain relief, but differs for a significantly lower risk of relapse. This action of frovatriptan is most likely associated with its specific pharmacological properties characterized by a prolonged elimination half-life.

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Use of oxycodone/naloxone extended release for menstrual migraine

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Menstrual migraine is a big challenge for the migraine expert. Severity and duration of hormonal stimulation determines that menstrual attack often appears to be the most painful and prolonged of the month, often exceeding the conventional 72 hours of the typical migraine attack.

Various schemes of prevention try to alleviate these attacks, usually long half-life triptans and/or anti-inflammatory drugs, combined with caffeine, magnesium etc.

Sometimes it is very difficult to find the right drug to control menstrual attacks, which particularly occur in women with uterine fibroids or endometriosis. In these cases the use of NSAIDs may worsen the bleeding and triptans with long half-life may be too weak.

To support this limited class of patients and because of the increasing improper use of opioid combinations for pain control in menstrual migraineurs, we considered to use the Oxycodone/Naloxone Extended Release (O/N-ER) because of its favourable mechanism of action on neuropathic pain, half-life (over 12 hours) and well documented gastrointestinal safety. Although the drug has an indication for chronic pain, many reports are appearing in literature for its use in acute pain, with good results. Recruitment included only patients who were non-responders to classical preventive therapy. In addition to the in-

formed consent of the patient, our protocol provided the clear explanation of the use of opioids, the use of O/N-ER therapy exclusively for menstrual attacks and for three consecutive periods, together with the possibility of using a triptan of medium-short half-life at the beginning of the attack followed by O/N-ER bid for 3-5 days. Patients filled in a headache diary where they reported intensity and duration of headache and side effects; at the end of the 3 months every patient had to fill in a satisfaction questionnaire on this therapy. These data were compared with the data recorded in the previous quarter of year and a pharmacoeconomic analysis was also carried out. At the moment 5 patients have completed the study and 12 are continuing the trial. About 70% of the patients who completed the study showed a mean reduction in intensity of attacks from 8 to 4 on a scale of 10, and a grade of satisfaction of 8/10, without significant side effects. More data will come from the analysis of the entire group of the enrolled patients.

Pilot study on the use of palmitoylethanolamide (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 NGF (Nerve Growth Factor) responsible for the phenomenon of sensitization of peripheral sensory nerve endings. The NGF is detected by nociceptors inducing increased synthesis of the TRPV1 receptor (Transient Receptor Potential Vanilloid 1).

In this triad the mast cell plays a key role.

Materials and methods We selected from the Headache Center of "Istituto Clinico Città di Brescia" a population of 50 patients aged between 18 and 65 years, suffering from migraine without aura with a frequency between 3 to 6 crises/month (4 to 12 days with headache/month), not assuming other migraine preventive therapy. They underwent a treatment with palmitoylethanolamide 600 mg bid for 3 months. Patients were evaluated for frequency, duration, intensity of pain, response to trigger factors and re-

sponse to their habitual analgesic drug (data obtained from the diary of headache delivered at first visit). It was also evaluated the improvement of the thermographic pattern.

Results Two patients had to discontinue the study due to worsening of headache (disappeared after discontinuation of treatment). A reduction in frequency and intensity of more than 50% in 35 patients, 10 patients reported reduction of more than 50% in the intensity but not in frequency (<50%), 5 patients had no improvement of symptoms. In 45 patients the complexity of the accompanying symptoms was less severe and they noted a reduction of the response to trigger factors.

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.

What is the mechanism of the antinociceptive effect of botulinum toxin type A? Cues for a better use in the treatment of chronic migraine

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Introduction In the last decade the efficacy of botulinum toxin type A (BT-A) against pain has been proved, particularly for chronic migraine (CM). However the mechanism of the antinociceptive action of BT-A is not fully understood. We aimed to better understand the mechanism, particularly in relation to migraine, examining the effects of BT-A on the pain induced by capsaicin (agonist of TRPV1 receptors) and by allyl isothiocyanate (AITC, agonist of TRPA1) in mice.

Methods BT-A (15 µg) was subcutaneously injected in mice in the inner side of the medial part of the hindlimb thigh, near the vasculo-neural femoral main trunk. After an interval ranging from 7 to 30 days, capsaicin (2 µg in 10 µl) or AITC (10 µl of 1%) were subcutaneously injected on the same hindlimb region. Licking, lifting, biting, and/or shaking of the injected hindlimb were recorded as nocifensive response. Moreover, the motor efficiency (rotarod test) and the effect on the territory of innervation of the femoral nerve were evaluated (capsaicin or AITC injection in the dorsal surface of the hindpaw).

Results In absence of BT-A, both capsaicin- and AITC-injections induced an extensive nocifensive response. The maximal pain induction appeared by capsaicin during the first 5 min, rap-

idly declining and disappearing in 25 min; by AITC, instead, it appeared between 15 and 30 min, lasting largely beyond the time of desensitization of TRPV1 receptors. Pre-treatment with BT-A markedly reduced both the capsaicin- and AITC-induced pain for at least 21 days, during which pain perception in peripheral territory of innervation of the femoral nerve remained normal.

Conclusions Our data are coherent with the inhibition of the expression of TRPV1 and of TRPA1 as antinociceptive mechanisms of BT-A. Several data support the role of such receptors in migraine, therefore suggesting this being a mechanism of the beneficial effect of BT-A in CM. In our experimental model, BT-A acts on perivascular and connective nociceptive afferents, without involving the muscles and main neural structures. Given a role of perivascular neural afferent in migraine, our data suggest the possibility of a better efficacy in CM of BT-A injected near perivascular structures of the scalp, instead of in pericranial muscles.

Natural history and outcome of 200 outpatients with classical trigeminal neuralgia treated with carbamazepine or oxcarbazepine in a tertiary centre for neuropathic pain

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Carbamazepine (CBZ) and oxcarbazepine (OXC) are the first-choice medical treatments in patients with trigeminal neuralgia (TN). The aim of this retrospective study was to analyze the natural history of classical TN in a large cohort of patients, focusing on drug responsiveness, side effects related to CBZ and OXC, and changes in pain characteristics during the course of disease. We selected the last 100 consecutive patients with typical TN who began treatment with CBZ and the last 100 with OXC. All had MRI scans and a complete neurophysiological study of trigeminal reflexes. Among them, 12 were excluded on the basis of neuroradiological or neurophysiological tests, to avoid the inclusion of patients with an even possible symptomatic TN. The initial number of responders was 98% with CBZ with a median dose of 600 mg and of 94% with OXC, with a median dose of 1200 mg. In a mean period of 8.6 months, 26% of responders to CBZ incurred in undesired effects to a level that caused interruption of treatment or a dosage reduction to an unsatisfactory level. In a mean period of 13 months, the same occurred to 18% of responders to OXC. The worsening of pain with time and the development of late resistance only occurred in a small minority of patients. We did not observe the onset of a clinically manifest sensory deficit at any time in any patient. CBZ and OXC were confirmed to be efficacious in a large ma-

jority of patients, but the side effects caused withdrawal from treatment in an important percentage of patients. These results suggest the opportunity to develop a better tolerated drug.

N-acetyl-cysteine inhibits nociceptive pathway function. A combined animal and human study

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Despite concerted efforts from pharmacologic research into pain, many patients fail to achieve sufficient pain relief with the currently available drug. N-acetyl-cysteine (NAC), an old and safe drug used as a mucolytic agent, enhances the endogenous activation of presynaptic metabotropic glutamate receptors type 2 and inhibits neurotransmitter release, thus possibly negatively modulating nociceptive pathway function. In this study we verified whether 1200 mg of oral NAC inhibits nociceptive pathway function by investigating how this drug modulates pain related responses in animals and humans.

We have investigated the NAC-induced changes in tail flick evoked by heat stimulation in 6 mice; then in 10 healthy subjects we measured changes induced by NAC on thermal-pain perceptible thresholds as assessed by quantitative sensory testing and laser evoked potentials, according to a cross over, double-blind placebo-controlled design.

In mice, NAC caused a tail flick delay, reverted by a single injection of the mGlu2/3 receptor antagonist (LY341495). In humans, NAC did not change the thermal-pain perceptible thresholds as assessed by quantitative sensory testing ($P > 0.08$), but reduced the laser pain ratings and the amplitude of laser evoked potentials ($P < 0.05$).

Our data, showing that NAC delays the tail flick response and reduces the laser pain ratings and the amplitude of laser-evoked potentials, indicate that NAC inhibits nociceptive pathway function. These findings suggest that this drug is worthy of being tested in a clinical trial in patients with pain.

Chronic migraine and botulinum toxin: one-year case series and clinical experience

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Background In meta-analytical studies, the use of botulinum toxin type A (BoNT-A) has been shown to be effective in reducing, significantly, the headache frequency compared to placebo in patients with chronic migraine (CM) [1]. In some patients, the benefits may become evident after 10-14 days from the first session, while others, who do not experience any improvement after the first session, need additional sessions to achieve results. We report data about the clinical experience of our Headache Center on onabotulinumtoxin A use for prophylactic treatment of CM patients, since it was approved for this use in our country (February 2013).

Patients and methods From March 2013 to February 2014, our Center proposed the treatment with onabotulinumtoxin A to all CM patients who had shown an inadequate response or were intolerant to medications for migraine prophylaxis. During an outpatient session, the patient was injected, in 31-39 sites, 155-195 onabotulinumtoxin A UI diluted with 2 mL of saline, every 3 months.

Results Twenty-eight patients were eligible for this treatment, 2 of these refused to undergo the procedure. Of the 26 patients who accepted the treatment, 3 did not want to continue beyond the first session due to lack of efficacy or because they deemed the procedure too uncomfortable, whereas 8 have undergone at least 3 treatments. Of these, 4 patients have reported a reduction of at least 50% in terms of headache days per month, intensity and intake of symptomatic drugs. Another patient reported only a reduction in intensity. The side effects that have been reported are cervical muscular contracture and asthenia.

Conclusions In our Headache Centre, the use of onabotulinumtoxin A shows an excellent safety and efficacy profile in patients with refractory chronic migraine.

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Use of illicit drugs as self medication in cluster headache

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Introduction Cluster headache (CH) is characterized by recurrence of very severe facial pain. Although some drugs are effective as symptomatic or prophylactic therapy, several patients are drug-resistant or unable to tolerate side-effects. In lack of satisfactory therapies, some patients try as therapeutic strategies some illicit substances, anecdotally reported as effective in CH treatment [1]. With the intent to know the impressions of patients about the

effectiveness of these substances in CH, we asked them about their experiences regarding their use.

Methods We left a questionnaire inquiring the recreational and the therapeutic use of illicit substances to our CH patients. The same questions were also given to a self-aid group of patients active on Internet.

Results We received positive response about the use of at least one illicit drug during CH attacks by 44 patients.

Thirty of them assumed Tetrahydrocannabinol (THC); 12 cocaine; 12 psilocybin; 10 ergine, also known as Lysergic acid amide (LSA); 8 heroin i.v.; 4 Lysergic acid diethylamide (LSD). Eighteen of patients that assumed THC during attacks reported no benefits, in 8 cases pain reduction or disappearance was reported and in 4 cases worsening of pain. Seven patients that assumed cocaine during the bouts reported no efficacy, in 4 cases pain disappeared and in one case pain worsened. Seven patients that assumed heroin during the attacks reported pain reduction, only one patient experienced a sudden disappearance of pain after the drug infusion.

Psilocybin, LSA and LSD were not assumed during the active phase of pain, but as preventive treatments. Patients that observed a positive effect (the stop of cluster) were 8 with psilocybin, 7 with LSA and 3 with LSD. In the case of psilocybin and LSA they were assumed in a sub-hallucinogen dose.

Discussion Patients reported ineffectiveness of illicit drugs as abortive therapies in CH. On the contrary, they reported a prophylactic effect of hallucinogen agents. Far from considering these data as significant of a real effectiveness of these substances in CH, it is certain that the use of illicit drugs by our patients is substantially unknown to us.

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Low-dose methadone in chronic headache patients: preliminary data of a prospective cohort study (METACEF Study)

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Introduction Satisfactory treatment of chronic headaches remains an unmet medical need. The utilization of chronic opioids in headaches remains controversial. In order to select patients suitable for daily opioid treatment, Saper et al. [1] have devised

a set of guidelines, which apply to patients refractory to properly executed prophylaxis treatments, or who cannot tolerate any alternative. Patients should be over 30 years of age, have frequent and disabling pain, and be well known to the skilled prescriber (for adherence and abuse risk). In observational reports, a controlled regimen of methadone has been shown to be efficacious in chronic headache patients.

Methods and materials In 2013 we started a prospective cohort study which includes chronic headache patients, selected in accordance to Saper criteria [1], treated with a low-dose methadone. The methadone daily dose ranged from 4 mg to a maximum of 60 mg.

Results Up to March 29, 2014, 12 patients were enrolled. Three patients dropped out because of early adverse reactions, including nausea, emesis and stipsis. One patient withdrew because he moved to another city. The median follow-up time of the 8 patients still on treatment is 7.5 months (range 2-22 months). In 6 patients, methadone reduced the number of headache days per month (HDM) and/or of analgesics and/or triptans per month (AM). Two patients experienced a remarkable amelioration (from 30 HDM each other, to 5 and 7 HDM, respectively, and from 240 and 60 AM, to 3 and 5 AM, respectively), while 3 patients experienced moderate amelioration (no reduction of HDM, i.e. 30 HDM, with a mean 76% reduction in AM). Two patients did not show any benefit from methadone treatment.

Discussion These preliminary data suggest that chronic methadone therapy, similar to other migraine prophylaxis treatments, may be efficacious in a limited proportion of treated patients, which is not, however, far from the efficacy of other treatments in this particularly severe subgroup of patients.

Conclusions Methadone therapy seems to bring benefits to some patients affected by refractory chronic migraines. However, the conclusion of the present investigation clearly requires further proof in a larger population and prolonged follow-up.

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Effects of prolonged topical treatment with Diclofenac Epolamine (DHEP) Plaster of cervical myofascial trigger points on migraine pain: pilot study

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Introduction Previous studies in migraine patients have shown that repeated anesthetic injections of cervical myofascial trigger points (TrPs, targets coinciding with migraine sites), reduce migraine symptoms during the treatment period [1]. This study aimed at verifying if a prolonged, less traumatic TrP treatment procedure (diclofenac plaster) in these patients produces similar effects and if these effects persist beyond the treatment period.

Methods Fifty-nine migraineurs were subdivided into two groups: 35 patients (30F, 5M, mean age 31.4 yrs) were treated with DHEP plaster at TrP level, 24 patients (19F, 5M, 33.3 yrs), were not treated. Twenty healthy subjects (15F, 5M, 29.3 yrs) served as controls. All patients: -had shown at least 6 migraine crises/month over the 2 months preceding the evaluation, -presented cervical TrPs (in sternocleidomastoid, semispinalis cervicis and splenius capitis) whose targets coincided with the migraine sites (frontal/temporal), and -had intolerance or scarce responsiveness to classic migraine treatments. All patients underwent evaluation of: -electrical pain thresholds in skin, subcutis and muscle at TrP and target level before treatment and after 60, 120 and 180 days, and of -number and maximal intensity (VAS scale) of migraine crises for 60 days before and 180 days after the start of treatment. Treatment consisted of application of $\frac{1}{4}$ of a DHEP plaster [8x6 cm] over the most active TrP, twice/daily, every 3 days for 60 days. Normal subjects underwent threshold evaluation in the same areas as patients, on a single occasion. Written, informed consent was obtained from all subjects.

Results Before treatment, skin, subcutis and muscle thresholds at trigger and target level were significantly lower in patients than in controls ($p < 0.001$). Treated, but not untreated patients, showed a significant: -raise in all thresholds after 60 days, persisting until the 180th day [$0.01 < p < 0.001$]; -reduction of number and intensity of crises during treatment (60 days), persisting after treatment (180th day) ($p < 0.0001$); -direct linear correlation between reduction of crisis number and muscle threshold increase at target level ($p < 0.01$). No side-effects or discomfort due to treatment were reported.

Conclusions In migraine patients, extinction of cervical TrPs (whose targets coincide with migraine sites) with application of DHEP plaster produces tissue desensitization and net improvement of spontaneous pain, both persisting far beyond the treatment period. Being atraumatic, this procedure could represent a useful complementary therapy for migraine control in selected cases.

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Association of coenzyme Q10, riboflavin, magnesium, dry extracts of *Tanacetum parthenium* and *Andrographis paniculata* (Partena®) in the prophylactic treatment of episodic migraine: a case series

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Introduction The efficacy and safety of complementary medicines, such as herbal preparations, vitamins, and minerals, for migraine prophylaxis in adults have been assessed through clinical trials. According to the American Headache Society guidelines, the utilization of magnesium, riboflavin and stable extract (feverfew) of *Tanacetum parthenium* (Level B), and coenzyme Q10 (Level C) for episodic migraine prevention is evidence-based. Extracts from the leaves of *Andrographis paniculata* showed antinociceptive and antiedematogenic activities in animal models. In Italy in 2013, a nutraceutical product containing coenzyme Q10 (20 mg), riboflavin (4.8 mg), magnesium (281.25 mg), dry extracts of *Tanacetum parthenium* (150 mg) and *Andrographis paniculata* (100 mg), Partena®, has been licensed for migraine prophylaxis, nociceptive modulation, and treatment of muscular tension. In October 2013, we started to prescribe Partena® to episodic migraine patients.

Materials and methods We retrospectively reviewed clinical charts of patients affected by episodic migraine, who were prescribed Partena® for the prophylaxis of headache by physicians working in the Careggi University Hospital Headache Centre.

Results Patients (n=15) were prescribed Partena®, one tablet once a day, as monotherapy for migraine prophylaxis: 12 were female (80%), and the median age was 31 years (17-58). Twelve patients had migraine without aura, 3 migraine with and without aura. In 7 patients (47%), Partena® was the first headache preventive therapy ever prescribed. After 2 months of treatment, 10 patients (67%) experienced an amelioration of migraine (decrease - at least 30% - of both intensity and frequency of attacks, n=7; decrease - at least 55% - of attack frequency, n=2; 25% decrease of attack intensity, n=1), while 5 patients (33%) reported no modification in headache frequency or severity. Treatment with Partena® was highly tolerated, and no side effects were reported.

Discussion This case series suggests that Partena® can effectively prevent migraine in a relevant proportion of treated subjects, while being extremely safe. However, methodological issues due to the retrospective nature of our observation limit the validity of its results.

Conclusions Partena® seems to represent an effective therapeutic option for episodic migraine prevention, and it could be considered as a first-line therapy.

Monitoring the use of symptomatic drugs in headache patients: a 6 month follow-up

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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 headache (MOH).

Aim To collect information about symptomatic assumption behavior, to monitor the consumption of symptomatic drugs for headache and to prevent drug abuse/dependence.

Materials and methods 274 patients using symptomatic drugs for headache were recruited in 32 pharmacies of Pavia Health District. A telephone interview to collect clinical general information on headache was first carried out in 199 patients; 179 entered the study at baseline (T0) and 112 (22 M and 90 F, mean age 45.0±11.5 yrs.) were followed-up at six months (T6).

Results The number of patients with chronic migraine or MOH decreased from 39 (T0) to 7 (T6). The mean number of days/month with headache significantly decreased when comparing T6 vs T0 (4.3±0.6 vs 9.7±0.8 p<0.0001). The mean number of headache attacks/month when comparing T6 vs T0 was slightly reduced (1.9±0.2 vs 7.6±0.8 p=0.09). Besides, the mean headache intensity/attack was found to be increased at T6 vs T0 (3.7±0.3 vs 2.0±0.1, p=0.03). Patients showed a significant decrease of the mean number of analgesic doses per month (T6=13.2±1.2 vs T0=17.0±2.2, p=0.013). In parallel to clinical data, a significant increase in quality of life was found on MIDAS scores at T6 vs T0 (respectively: 13.4±1.8 vs 23.7±2.5; p=0.00) and in the quality of treatment received (HURT) (respectively: 5.6±0.4 vs 9.9±0.5; p=0.00).

Conclusions Our results highlight that the change from self medication to medical care may reduce the number of symptomatic treatments, the headache days per month and ameliorate the quality of life in patients suffering from headache. A longer follow-up (i.e., 12 months) may provide further evidence on improvement of clinical features of headache patients and prevention of medication-overuse headache.

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High dose intravenous methylprednisolone in cluster headache patients non responders to oral therapy

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Introduction High dose verapamil is the recommended first choice drug in the prophylaxis of episodic and chronic cluster headache. Oral corticosteroids are often concurrently prescribed with the initiation of verapamil prophylaxis in order to quickly obtain a reduction in cluster headache (CH) attacks. To date, literature is scarce regarding the efficacy of intravenous methylprednisolone in CH patients non responders to oral preventive therapy.

The aim of the study was to assess the efficacy and safety of high dose intravenous methylprednisolone in a cohort of cluster headache (CH) patients not responders to oral preventive therapy.

Methods We screened all CH patients referring to Headache Center of the University of Turin (Italy) between 2006 and 2013. A standardized combined therapy of verapamil 320 mg daily and oral prednisone 50 mg daily was prescribed at the beginning of each cluster active period (CAP). After 3 weeks of oral therapy, patients not responders (attacks with a frequency more than one every other day) were hospitalized in Day Hospital regimen and treated with intravenous methylprednisolone (500 mg/day iv for 5 days), in association with verapamil. Twenty nine CH patients (26 males, 3 females, 42.8± 29.8 years) were treated with this protocol, during 42 CAPs. Data on headache characteristics were collected using headache diaries.

Results Minor adverse events were reported by 11.9% of CH patients (skin flushes during infusion, mild increase in blood pressure, gastric symptoms, hyperglycemia, insomnia, and agitation). After 5 days of iv therapy, in 35 CAPs out of 42 (83.3%) the patients were headache-free, whilst in 3 CAPs (7.1%) a reduction (> 50%) in the number of daily attacks was observed. No clinical benefit was reported in the remaining CAPs. In 85.6% of CAPs, no recurrence of cluster headache was observed at 6-months follow-up visits.

Discussion and conclusions Intravenous methylprednisolone is an efficacious and reproducible treatment in CH patients non responders to oral therapy. Given the acceptable tolerability profile, this approach can play a useful role in the management of cluster headache, allowing a rapid pain relief in an otherwise highly disabling disease. Confirmatory RCTs and large prospec-

tive cohort studies are needed to fully assess the efficacy and safety of this treatment in CH patients.

Further data on the use of high doses of corticosteroids and verapamil in cluster headache

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Introduction A short course of corticosteroids is considered the most fast-acting prophylactic therapy of cluster headache (CH), rapidly suppressing attacks during the time required for verapamil (V) to have effect. It is common experience that the current use of both drugs is unsatisfactory. We report our results of an open clinical study on an enlarged series of patients (P) affected by Cluster Headache (CH) treated with high doses of iv methylprednisolone (MP) and verapamil (V) per os.

Materials and methods A consecutive series of 26 P (7 females, 19 males, 40.4 ± 10.5 years), affected by Episodic Cluster Headache (ECH, ICHD-3 beta 2013) was followed during 38 active cluster periods (CP). Most P were recruited within 2 weeks from the beginning and more than 1 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 per os tapered in the following 8 days. Concomitantly, oral V was started or incremented up to 320-400 mg/day; and later, on the base of clinical results, up to 640 mg/day in selected cases.

Results The 38 CP considered were stopped within the third day from the start of MP/V administration. In 28/38 (74.6%) CP, no recurrence was observed during a 6 month follow up. In 7/38 (18.4%) CP a recurrence, but presenting only with mild attacks, was observed within the first month. In this group, an increase of V from 400 mg/day up to 640 mg/day blocked the attacks within a week, with no further recurrence during a 6 month follow up.

In 3/38 (7%) remaining CP, a reduction of > 50% in frequency and intensity and of > 75% in the length of active phase was observed: however, 2 patients had not constantly adhered to the prescribed therapeutic protocol.

In all our P, V was gradually tapered in not less than 1 month, and at least 30 days after the last attack.

Conclusions These results confirm the data we previously reported about the efficacy of high doses of iv MP and V per os in ECH. The combination of the two drugs, along with their doses and timing of starting/tapering therapy, appear to be crucial and deserve further clinical trials.

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Efficacy of a long-term acting triptan for headache attributed to aeroplane travel

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Headache attributed to aeroplane travel, also named “Airplane headache” (AH) is a disorder that appears exclusively in relation to airplane flights. Its diagnostic criteria have been published in the International Classification of Headache Disorders [1]. The attacks are characterized by the sudden onset of a severe head pain, more often during the landing phase. Secondary causes must be ruled out. With more than 3.3 billion seats offered annually on commercial flights with an occupancy of 70% [2], in keeping with our preliminary epidemiological data, AH is not a rare condition. Despite the severe intensity of pain, less than half of the reported AH cases use medications for preventing the attack, most frequently simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and nasal decongestants [3]. A complete or partial benefit is achieved in about 50% of patients. A complete response of AH to fast-acting triptans has been previously reported in three cases [4].

Case report A 37 year-old migrainous (MO) woman suffers of AH during landing in about 75% of her flights. As prophylactic treatment, in her recent long-lasting (about 9 hrs) air travel, she took a long-acting triptan (frovatriptan) before take-off and a NSAID (dexketoprofen 25 mg) 60 min before landing. As a result, AH did not appear. Instead, she complained of an AH attack in her last flight, when she took only dexketoprofen before landing, but not frovatriptan before take-off. This case report, to be verified in a large series of patients, would indicate the efficacy of the long-term triptan frovatriptan as an appropriate therapeutic approach for preventing AH attacks, particularly when occurring during long lasting flights.

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Tiner (Integrated treatment neuromuscular emotional relaxing) in the elderly with headache associated with depressive mood disorder

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Objective We studied twenty-five subjects, aged between 65 and 75 years, suffering from headache associated with depressive mood disorder and early cognitive decline, to assess the clinical utility of Tiner (although this method falls under the disciplines that are characterized as “manual arts”, it also favors an approach based on theoretical knowledge and a function of “counseling”). Tiner treats both emotional areas which the trigger points identify as decisive elements in the treatment of resistance, which is precisely the principle of minimal stimulation plays an essential role.

Materials and methods The subjects underwent an initial psychological evaluation with Test D. Hamilton. The criterion for inclusion in the study was a Ham-D score between 10 and 20. Thus, the entire sample underwent Tiner sessions specifically, on a weekly basis, for the duration of 3 months, with subsequent maintenance sessions, for further 3 months.

Results At the end of the 6 months, all subjects underwent a psychological evaluation. The scores obtained in the comparison between the HAM-D and the initial testing, showed a decrease of 35% in 8 points, 6 points in 25%, 3 points in 25%, with the situation unchanged in 15% of cases. Subsequently, the objective of the majority of subjects undergoing Tiner was to reduce the frequency and intensity of the headache episodes and to improve the emotional state.

TINER ADD-ON GROUP	HAM-D	HAM-D
Patient Groups	Baseline	9 Months
35%	10-20	8 points
25%	10-20	6 points
25%	10-20	3 points
15%	10-20	Unmodified

Conclusions Based on the results obtained, the Tiner method seems to play a useful role in decreasing headache and in im-

proving the emotional state in the elderly suffering from headache associated with depressive mood disorder. The therapeutic approach inherent in the Tiner method, is an amazing placebo, as compared with an expected minimum, the positive results are surprising, with the unique advantage of the absolute absence of negative side effects (nocebo effect).

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“Reading” migraine with the instruments of psychoanalysis

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There is no evidence for use of psychoanalysis in migraine therapy because it is not classified according to EBM.

For medicine the symptom is something that must be relieved, but many times migraineurs live their condition as a life mark, because of this we have headache sufferers associations!

An analytical cure is not just one kind of psycho-knowledge that oscillates between the patient’s well-being and an adaptive socio-educative solution. It is, rather, a new social bond, not informed by previous subjective experiences – philosophical, religious or scientific – because it sets up a different structure of discourse and thus permits the subject to define and describe his own mode of *enjoyment* and migraine may be just a form of *enjoyment*!

Jacques Alain Miller said: “We qualify a body phenomenon as «sinthomes» when they settle permanently and order the life of the subject” and who better than the migraineur represents the sinthome! Then the symptom takes on a new definition, it becomes “body-event” since it is tied just to the enjoyment “is a logical definition of the symptom”, from which there is no escape from the moment that you grab the symptom as enjoyment, since you grab in terms proposed by Freud in inhibitions, symptoms and anxiety as a fulfilment of the drive. If the symptom is a satisfaction of the drive, if enjoyment is influenced by life under the body shape, this implies that the living body is prevalent in every symptom. Here is the horizon of what I call the Lacanian biology: the recovery of symptoms starting

body events “Many times migraine can be a source of satisfaction, it can have the function of permitting the subject to stop thinking, of putting his body in motion, etc.”.

Lacan said: “What is unexpected is that the subject himself confesses his truth and confesses without knowing it”.

Migraine can be considered “a disorder caused at the most by personal juncture between the subject and his sense of being alive.” When psychoanalysis analyzes a choice of lifestyle, as to be migraineur for example, it is on the condition that the process be applied “in a literal sense as treatment to a speaking, hearing subject”. Lacan presents “psychoanalysis as the last flower of medicine, the tail of medicine, that is exactly the place where medicine can find refuge.” The taking-charge of the medicine operating with the transference by psychoanalysis, supposes the reintroduction of the dimension of the subject in that field, *not the migraine but the migraineur!*

Osteopathic treatment of migraine without aura

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Background Migraine without aura is the most known and widespread primary headache (IHS:1.1-ICD10:G43.0), with more than one person out of 10 suffering from it, in 1/3 of cases from childhood. It leads to a marked decrease in quality of life and health status of the patient. The management of the patient with migraine is complex and can not be separated from a pharmacological approach, considering that alternative and complementary therapies are increasingly present in patient management [1]. This study aims to verify the efficacy of osteopathic manipulative treatment (OMT) in patients with migraine without aura undergoing drug treatment as needed.

Methods Twenty-two (22) patients from the Headache Surgery of San Giovanni Battista Hospital in Rome, of whom three (3) males and nineteen (19) females, were included in a single treatment group. Five treatments were carried out in a period of 8 weeks. All patients completed the headache diary for a total period of 6 months and the MIDAS questionnaire before the first treatment (t_0) and 1 month after the last treatment (t_1). Patients needed to take the medication recommended by the doctor. The MIDAS questionnaire and headache diary were used to assess the frequency and intensity of the attacks and the frequency of intake of drug therapy. Data on the frequency, intensity and drug therapy were evaluated by comparing the average of the diary data for 3 months before and 3 months after t_0 and the values of the scale MIDAS

at t_0 and t_1 . The OMT was applied to each subject individually and different techniques were used depending on the dysfunction that was found.

Results The outcomes observed in the study, analyzed (t-test) at 3 months, showed a general improvement after OMT: the average of the frequency of migraine attacks was reduced by 5.36 days ($p=0.018$), the average rate in drug taking was reduced by 6.14 days ($p=0.001$), the average intensity of the pain was reduced by 1.41 points ($p=0.0005$). Anatomic segments were also evaluated since they are more frequent in dysfunction, getting the results of 5.7% for the sigmoid colon and the synchondrosis sphenobasilar joint.

Conclusions This study suggests that osteopathic manipulative treatment has a positive effect on migraine without aura, so it can be inserted in the patient’s migraine management. Future studies with a control group and with a follow-up in the long term are needed to collect more data regarding the effectiveness of osteopathy in the treatment of patients suffering from migraine without aura.

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Spirit healing: significant results in migraine

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Introduction Spirit Healing (Italian: Pranoterapia) is a complementary therapy not always recognized, exercised by subjects having a particular electromagnetic field, defined “bioenergy”, supposed but not yet proved. Although the action mechanism is only presumed, many patients declare to have benefited from it. This work does not discuss the existence, source, forming, property, variability and functioning of this phenomenon. All these factors can not be proved, since they have not been investigated enough [1], but after a thorough analysis of registered results emphasis will be placed on the surprising efficacy of Spirit Healing in keeping primary headaches and trigeminal neuralgias under control.

Methods Research is based on observational data, about treatment results on fortuitous patients suffering from different types of primary headache, lasting from 5 to 20 years, usually treated in major Ligurian and Piedmont headache institutes with pharmacological therapies without result. Moreover, results achieved in patients suffering from trigeminal neuralgia are presented.

Results Sixty-eight patients presenting with migraine were treated with periodical sessions of Spirit Healing from 3 treatments a week to 1 every 3 weeks according to personal requirements.

Fifty-one (75%) achieved excellent results and suspended pharmacological therapy, 10 (15%) obtained good results using analgesics rarely, 3 (4%) had mediocre results but with a considerable reduction of usual drug consumption. Moreover, 15 medical cases with trigeminal neuralgia highlighted 9 (60%) excellent results, 4 (27%) good and 2 (3%) mediocre.

Discussion Patients came from headache institutes and were undergoing pharmacological therapy for many years without lasting benefits. Notwithstanding uncertainty of the mechanism of action, observational data provided efficacy evidence of analgesic treatment with natural electromagnetic fields. Spirit healing efficacy (90%) ruled out an action comparable with placebo. Absence of pain for a long time and recurring relapses (especially before atmospheric disturbances) suggest the chance of a function-

nal re-balance of neuroreceptorial functions susceptible to electromagnetic fluctuations.

Conclusions Positive results, with a therapy without side effects, should place Spirit Healing as the first-line treatment in primary headache, reserving pharmacological therapy or neurosurgery only for cases of non-responders. These simple observational data should lead to further research in a field which has for a long time been neglected, since efficacy demonstration of electromagnetic fields in migraine could open new perspectives to improve electronic equipments in NMR to spread an innocuous, reliable therapy.

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Techniques, targets and applications of the neurostimulation procedures

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Introduction Neurostimulation procedures were recently introduced for the management of chronic drug-resistant headache patients with promising results. We review indications, improvements, complications of the more frequently used techniques.

Materials and methods We carried out the review of the literature on two main procedures of neurostimulation for headaches: deep brain stimulation (DBS) and the greater occipital nerve stimulation (ONS). In the revision other techniques of neurostimulation such as the stimulation of the sphenopalatine ganglion, the transcranial magnetic stimulation (TMS) and the stimulation by transcranial direct current (TCDS) are reported.

Results The subcutaneous implants improve the pain suffered by patients with chronic cluster headache as well as the DBS procedures; yet the DBS shows more surgical complications. The ONS has also shown promising results in the treatment of chronic migraine, with an improvement in 50% of the implanted patients.

Conclusions The peripheral neurostimulation techniques for primary headache appear to be safe and with good results. The DBS implants have shown severe complications. The subcutaneous implants should be used as a first step in the neurostimulation procedures. Sham controlled and large trials must be performed to clarify the benefits of these therapies and the pharmaco-economic aspects of the neurostimulation.

Transcutaneous supraorbital neurostimulation (tSNS) versus Transcutaneous vagal nerve stimulation (nVNS) in migraine attacks: Active versus sham devices application

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Aim To assess efficacy and side-effects either of trigeminal neurostimulation with a supraorbital transcutaneous stimulator (tSNS, Cefaly, Belgium) or portable vagal nerve stimulator (nVNS, Gammacore, Germany) for acute treatment of attacks in chronic migraine sufferers and overuse headache.

Methods This was a randomized, sham-controlled, single blind, multiple-attack experience. Four migraine attacks were treated after a 6-day de-chronification therapy with specific NMDA-antagonist, patients were randomized to verum or sham stimulation. Subjects were asked to self-treat at moderate or severe pain no later than 20 min. after the beginning of the single migraine attack. Rescue treatment (indomethacin 50 mg or imigran 50 mg) were allowed. Measures regard pain-free, from complete to 50% pain decrease, at 2 hours. Decrease was estimated versus baseline rated on a 0-10 VAS. Side-effects induced by both devices, verum and sham, were listed.

Results Forty patients were randomized and included in the intention-to-treat analysis. The mean VAS (0-10) of migraine attacks decreased significantly in the verum of tSNS and nVNS, but no more than 10% in the sham group (tSNS 3.6 ± 0.7 SD baseline vs 1.9 ± 0.2 SD post-treatment $p = 0.0001$ and 3.5 ± 0.8 vs 3.3 ± 0.1 sham; nVNS 3.6 ± 0.69 SD baseline vs 2.7 ± 1.3 SD treatment; $p = 0.02$ and 3.45 ± 0.6 SD vs 3.35 ± 0.13 SD sham). The 50% responder rate was greater for tSNS $p=0.0003$ vs nVNS, $p=0.04$. Rescue drug intake was also significantly reduced in the verum ($p=0.0001$) but not in the sham group. Rescue treatment intake was lower following tSNS than after nVNS ($p=0.03$). There were no adverse events in all the four groups. Side-effects were relatively long-lasting relaxation (range 120 min-12 hrs) in 10 patients reporting benefit from tSNS and transitory (range 40-180 min) mental and productive motor activation in asthenia suffering patients who did not significantly benefit from nVNS stimulation

Conclusions Supraorbital transcutaneous and vagus nerve stimulation with the devices used in this experience are effective and safe as a therapy for migraine attacks. In this experience the therapeutic gain is higher for tSNS ($p=0.0001$) than for nVNS. Nevertheless, both the devices can induce partial benefit on the painful attack of chronic migraine and medication-overuse headache sufferers.

Management of refractory chronic migraine: review of type A botulinum toxin and occipital nerve stimulation

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Introduction At the Headache Centre at the Pugliese-Ciaccio Hospital in Catanzaro, sequential treatments with increasing degree of invasiveness are performed with chronic headache patients. Diagnosis is defined by frequency, type, and intensity of pain, presence of aura and drugs abused; then a symptomatic drug therapy is first established. In case of high headache frequency a prophylactic treatment is prescribed. If prophylactic and symptomatic therapy is not effective, then additional approaches are available such as Type A Botulinum Toxin and Occipital Nerve Stimulation (ONS). The ideal candidate for ONS is an adult with chronic headache (migraine for >15 days/month) without medication overuse, involving the occipital or suboccipital region and refractory to preventive, abortive and behavioral therapies. Purpose of this study is to report the effectiveness of these procedures reviewing the existing literature.

Materials and methods Botulinum-A: We reviewed the PRE-EMPT study, two phases 3 studies: 24 weeks double-blind, placebo-controlled, parallel group phase followed by the 32 weeks open label phase. ONS: we reviewed 9 prospective observational open label studies on 137 headache patients and one multicentre, randomized, single blind, controlled study (ONSTIM) on 66 migraine patients.

Results Botulinum-A: PREEMPT study showed statistically significant differences between the two groups with regard to headache days, moderate-to-severe headache days, and also showed the cumulative effect of the treatment on the clinical benefit. ONS: Open label studies were very encouraging with 61% patients reporting at least 50% improvement on VAS scale. ONSTIM: The responder rate was defined as a 50% reduction in headache days/month or at least a three point decrease (on VRS 0–10) in pain intensity at 3 months. The responder rate was 39% in the adjustable stimulation group compared with 6% in the preset stimulation group and none in the medical management group.

Discussion and conclusions Besides the validated type A Botulinum toxin procedure, Occipital Nerve Stimulation is emerging as a promising treatment for intractable primary headache syndromes. However, the ultimate confirmation of the usefulness of this therapeutic modality should come from randomized, double-blind, placebo-controlled trials that need to be performed.

Continuous transcranial magnetic stimulation in treating chronic migraine and medication-overuse headache

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Introduction There is evidence that repetitive Transcranial Magnetic Stimulation is effective in Chronic Migraine prophylaxis [1], however, the efficacy of continuous TMS in treating CM is unknown. Purpose of this study is to obtain data about the effectiveness of cTMS in CM and MOH.

Materials and methods A randomized, placebo-controlled trial on 15 CM and MOH patients (2 males, 13 females, 20–61 years old) accessing to the Headache Centre at the Pugliese-Ciaccio Hospital in Catanzaro was performed. Patients underwent medical, psychological and disability assessment, radiological and electrophysiological examinations and completed a headache diary, MIDAS questionnaire, Zung Self Rating Anxiety and Depression Scale (T0). Patients were randomized to the cTMS or the sham-cTMS group. Treatment consisted of 4 cycles of cTMS or sham-cTMS; stimulation intensity was 2mA; stimulation duration was 20 minutes and was delivered on left prefrontal cortex. The first cycle consisted of 5 days/week of stimulation for 2 consecutive weeks; the next 3 cycles consisted of 5 consecutive days every month for 3 consecutive months. Two successive controls were carried out: 30 days after the first stimulation cycle (T1) and 30 days after the last stimulation cycle (T2). Repeated measures ANOVA was used for comparisons between the two groups and within each group for the variations at the observation times of headache days/month and questionnaires scores. Post-hoc test was employed for the analysis of differences between individual variables.

Results The ANOVA for headache days showed significant effect of treatment ($p=0.000001$) and treatment-observation time interaction ($p=0.000001$). At T2 a significant reduction was appreciated only in the cTMS patients ($p<0.05$). The ANOVAs for the MIDAS score, Zung anxiety and Zung depression scores showed a significant effect on time and on the treatment-observation time interaction; post-hoc analysis showed significant scores reduction in the cTMS group.

Discussion and conclusions cTMS might be effective in treating CM and MOH, reducing headache days and improving psychopathological and disability correlates of migraine.

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Benefits of vagal stimulation for the treatment of migraine crises

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The vagal stimulation is a new tool to treat migraine crisis that was being tested by our center [1]. In the present study we evaluate the effects, the reaction times and side effects on patients.

The protocol used to treat acute migraine crises was to perform two vagal stimulator applications on the right side of the neck, each of 90 seconds, in the first 15/30 minutes from the beginning of the crisis; in case of failure, treatment was repeated after 2 hours.

Evaluation was carried out with the VAS scale at: t.0 (beginning of the crisis), t.1 (2 hours from onset), t.2 (4 hours from onset). Chronic migraine patients with 4 crises in a 2 month period were included in the study. Twenty-four patients entered the study, but only 13 had 4 attacks (2m, 11f). Overall 52 attacks were studied. After 4 hours the pain (VAS 6.3 ± 1.6 ; $3.59 \pm .86$; $3.16 \pm .85$; .001 alpha level) had ceased in 29 attacks, improved in 14, and stayed at the same level in 9 cases. Associated symptoms improved in different ways: nausea (36-20-11), vomiting (2-13-9), phonophobia (35-17-11), and photophobia (36-18-12).

The second stimulation was performed in 5 patients, without any effect.

Studying the 9 cases of non-responders, in 6 instances the stimulation was performed after 30 minutes from the crisis onset, and under this circumstance there was no improvement in pain and the associated symptoms. For the other 3, only the associated symptoms were partly improved. Side effects reported include paresthesias in 4, muscle contractures in 2, this phenomena being resolved spontaneously within the first hour. We believe that the stimulator is another effective tool as a treatment for the migraine attack, but it must be used in the first minutes from onset of the attack, to achieve its full effect.

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Selection of migraine patients eligible for occipital nerve stimulation: a questionnaire and a checklist by the University of Florence and University of Chieti

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Introduction Satisfactory treatment of chronic migraine still remains an unmet medical need. In 2011, in Italy, a medical device system (Genesis™ and EON™ system, Saint Jude Medical, Inc.) for occipital nerve stimulation (ONS) was granted marketing authorization for chronic migraine refractory to other treatments. This innovative approach represents a novel opportunity which requires careful patient selection. Patients included in the trial, which has proven the efficacy of the medical device, had to be: diagnosed with chronic migraine according to 2004 IHS criteria and refractory to at least two different classes of prophylactic medications and two specific antimigraine medications [1]. However, in general clinical practice, more restrictive criteria may be desirable because of the invasive nature of ONS and its cost-effectiveness profile. We aim to develop a physician-friendly instrument to be used to select patients eligible for ONS.

Methods and materials We identified a set of information necessary to define the severity of migraine (clinical features, number of headache days per month, efficacy of rescue medications) and the pharmacological and non-pharmacological remedies already used by the patient. Migraine provoked disability in the last 3 months and the patient's opinion on his/her own disease and health status were also evaluated.

Results We elaborated a 6-domain questionnaire (demographics, migraine status, previous or current non-pharmacological preventive treatments, previous or current pharmacological preventive treatments, rescue medication, functional disability and quality of life), accompanied by a 3-item checklist, including the essential clinical data needed to identify patients eligible for ONS: 1. migraine diagnosis; 2. more than 15 headache days per month for the last 3 months; 3. previous prophylaxis therapy with adequate doses and duration of at least 1 drug for each pharmacological class, including onabotulinum toxin A, which has been shown to be ineffective.

Discussion The 6-domain questionnaire and 3-item checklist seem to have a suitable balance between the collection of useful clinical data and the ease in their use.

Conclusions Clinical utilization of the questionnaire and checklist would optimize the instrument. However, we consider its current version a valuable starting point to aid physicians in patient selection.

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Neurophysiological study tDCS effects in healthy subjects

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Background Migraine is characterized by a dysfunction of cortical excitability. Evoked potential studies showed that cortical responsivity in migraine fluctuates over time in relation to the migraine cycle (preictal/ictal/interictal) and to attack frequency. The most reproducible abnormality, namely lack of habituation, is detectable during the pain-free interval and it is usually accompanied by a low response amplitude after low numbers of stimuli. It was recently shown that in chronic migraine habituation was normal like during an attack, but evolved to potentiation when patients reversed to an episodic pattern, suggesting that chronic migraine could be considered as a “never-ending attack”. Effective preventive therapy for migraine is still a challenge. A recent study using transcranial direct current stimulation (tDCS) demonstrated that a 15-min session of anodal tDCS over the visual cortex is able to transiently increase habituation in episodic migraineurs and to reduce attack frequency [1]. The optimal stimulation protocol and the precise mode of action, however, still need to be defined.

Objective To study the short- and long-term neurophysiological effects of anodal tDCS of visual and left dorsolateral prefrontal cortex (DLPFC) in healthy volunteers (HV), using the tDCS Cefaly device.

Methods We recorded quantitative sensory test (QST), contact heat evoked potentials (CHEPs), nociceptive Blink reflexes (nBR) and visual evoked potentials (VEPs) in 18 healthy volunteers before and after a single and a series of 5 daily 20-min sessions of tDCS. We applied anodal tDCS over the visual cortex in 9 subjects and anodal tDCS over the DLPFC with the cathode placed over the visual cortex in the remaining 9 subjects.

Results Anodal tDCS of visual cortex increased VEP habituation after 1 session and even more so after 5 days of stimulation. It was able to increase P1N2 habituation and to reduce latency of the P2 CHEP component. After the treatment we found an increased heat pain threshold at the wrist. Anodal tDCS over the DLPFC with cathodal visual cortex stimulation only produced a reduction of nBR sensory thresholds (all $p < 0.05$).

Discussion This study confirms that anodal tDCS over the visual cortex in healthy subjects is able to increase VEP habituation and this effect is more pronounced after long-term stimulation. It is also able to modify habituation of pain-related evoked potentials. These results support the use of this noninvasive neurostimulation method in the preventive treatment of migraine.

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Non-invasive vagal nerve stimulation in patients with chronic migraine and medication-overuse headache: a 9-month follow-up study

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Introduction Medical treatment of patients with Chronic Migraine and Medication-Overuse Headache (CM-MOH) is often challenging. Neuromodulation is emerging as a new therapeutic option for chronic headaches. Gammacore® is a portable non-invasive stimulator that produces a mild electrical signal transmitted to the vagus nerve through the skin. A recent report suggested that migraine patients experience a reduction in the severity of their headache symptoms with Non-invasive Vagal Nerve Stimulation (nVNS) [1].

The aim of the study was to evaluate the safety and the efficacy of non-invasive vagal nerve stimulation (nVNS) for the treatment of headache attacks in patients with chronic migraine and medication overuse headache (CM/MOH) after a detoxification period.

Methods Fifteen CM-MOH patients (1 man, 14 women; mean age \pm SD = 49.9 \pm 15.8 yrs) were enrolled in the study. Patients underwent a 5-day in-patient detoxification period and were then followed for 9 months. Headache attacks during the detoxification period and in the follow up period were treated with repeated nVNS. The clinical characteristics of headaches were recorded in headache diaries.

Results 566 migraine attacks were treated with nVNS during the study. At two-hours, a pain-free response was observed in 165/566 (29.2%). Average initial pain levels was 1.72 \pm 0.7 and dropped to 1.2 \pm 0.5 at 2 hours ($p < 0.01$), using the 0-3 points scale. A significant response to nVNS was observed in 50% of treated patients. Drug abuse was halted in all the treated patients. Rescue medications were used in 90 (15.9%) of the attacks treated with Gammacore®. Treatment-related adverse events were frequent but mild (paresthesia, muscular tension, prickling).

Discussion and conclusions This is the first study that evaluated treatment with Gammacore® in patients with CM-MOH. Hence, results must be viewed cautiously. Our findings show that nVNS could be a safe and efficacious treatment. At two-

hours, a pain-free response was observed in approximately one third of treated patients. Large controlled clinical trials in order to evaluate the long-term efficacy of this treatment are needed.

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Our experience with surgical treatment for migraine and tension-type headache: a modified procedure

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Introduction Recent insights [1] into the pathogenesis of migraine and tension-type headache substantiate the possible role of neuronal hyper-excitability and inflammation involving compressed peripheral craniofacial nerves; these trigger points could be eliminated by surgery, which thus might provide a theoretical therapeutic approach to migraine.

We report the elimination or improvement in forehead migraine headaches through surgical decompression of the peripheral branch of trigeminal nerve (N. Supratrochlearis and Supraorbitalis) following selective endoscopic incision of hyper-active Corrugator Supercilii muscle, depressor supercilii muscle and procerus muscle, and of cervical plexus - C2 (Lesser and Greater Occipital Nerves) following removal of hyper-active

surrounding muscles. Particularly, the aim of this work is to determine whether surgical decompression of forehead trigeminal nerves, performed by means of an innovative minimally invasive endoscopic technique and without the need of general anesthesia, might gain same or improved results compared with the currently adopted endoscopic techniques, in an effort to reduce the invasiveness of this surgery.

Patients and methods Thirty-eight patients who complained of chronic migraine headaches underwent a frontal bilateral selective miotomy procedure of Procerus, Depressor Supercilii and Corrugator Supercilii Muscles by means of video-assisted endoscopic surgery, and an occipital selective miotomy procedure of Occipital, Trapezius, Sternocleidomastoid and Semispinalis Capitis Muscles by means of open surgery.

Results Of the 38 patients included in the study (range, 18 to 73 years), 27 were women and 11 were men. Thirty-two of 38 patients (85%) reported a positive response to the surgery: 15 of 38 patients (40%) observed complete elimination, 17 patients (45%) experienced significant improvement (at least 50% reduction in intensity or frequency), and 6 patients (15%) did not notice a change in their migraine headaches.

Conclusions This study confirms previous literature data, strengthening the role of a peripheral mechanism (trigger points) in migraine headaches. Since the operation has not caused any serious complication or side effects, it can be recommended to patients who suffer from moderate to severe chronic migraine not responding to medications. Moreover, the minimally invasive procedure we described is easy, fast and cost-effective, relying on the use of a single instrument, also reducing the number of postoperative scars from five to one.

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Chronic migraine in cerebral venous sinus thrombosis: a case report

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Introduction Cerebral venous sinus thrombosis (CVST) is an uncommon disease accounting for <1% of all strokes: CVST is more frequent in young adults and children and about 75% of the adult patients are women. Severe headache occurs in more than 90% of adult patients, however, diagnosis is often overlooked or delayed because of high clinical variability. We report a case of CVST presenting initially with migraine-like headache.

Case report A 43-year-old female with clinical history of ovarian dysfunction chronically treated with oral contraceptives and affected by migraine since early childhood reported prolonged fronto-temporal pulsating headache; severity of pain increased over several days and treatment with non-steroidal anti-inflammatory drugs and triptans had no effect; psychological testing and examination showed no occurrence of anxiety or mood disorders. The patient was treated with type A Botulinum toxin for chronic migraine. Gradually the patient developed behavioural symptoms, gait instability and recurrent vomiting. At the neurological examination atypical cranial hypoesthesia was observed. Brain Magnetic Resonance showed an altered signal round area in the pineal gland. Intravenous Magnetic Resonance Angiography showed left transverse sinus thrombosis and partial contralateral compensation and at hematological examination a prothrombin mutation (G20210A) was detected.

Discussion The most frequent symptom of CVST is severe headache, however, in some patients headache is very similar to prolonged migraine attacks. Migraine history, inefficacy of NSAIDs, triptans, BOTOX chronic migraine treatment, family history of thrombosis and assumption of oral contraceptives arouse suspicion for CVST.

Headache caused by decreased intracranial pressure

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We report the case of a 56-year-old woman complaining of diplopia for 2-3 days and nuchal headache of moderate intensity associated with dizziness symptoms, not clearly correlated with body position, for the past 2 weeks. No history of trauma or lumbar puncture.

She presented convergent deficit of abducens nerve bilaterally while the remaining neurological examination did not show other abnormalities; no papilledema. The brain CT scan documented the presence of important smoothing of cortical sulci with ventricular system of small dimensions; two thin extra-parenchymal collections in the frontal area and at the apex bilaterally were reported. Brain MRI confirmed the presence of chronic subdural hematomas at the level of the tentorium and the convexity of both hemispheres, diffuse dural enhancement in the supra- and infratentorial region after administering contrast medium. The radiological data are suggestive of CSF hypotension syndrome. The patient was treated with intravenous hydration therapy and steroids with rapid disappearance of the headache and progressive improvement of vision impairment. The CSF hypotension syndrome predominantly affects middle aged women with an overall prevalence of 5 cases/100,000. Pathognomonic feature is the presence of orthostatic headache but sometimes the correlation with the given posture may fail, with reports of paradoxical headache, relieved by orthostatism. Other typical clinical manifestations are nausea, neck stiffness, tinnitus, hearing loss, photophobia, sixth cranial nerve palsy or radicular symptoms in the upper limbs, changes in level of consciousness including coma.

The pachimeningeal enhancement on MRI is a distinguished feature, often associated with subdural collections (hygromas and hematomas), sometimes with signs of “sinking” of the brain, while thinning of the ventricles is often noticeable. Spinal MRI only very occasionally reveals the exact site of CSF leak. Myelography and possibly the radionuclide cisternography are needed to determine the site of CSF leak. Medical therapy is based on bed rest associated with intravenous hydration, steroids, caffeine, teophylline. If symptoms persist, an epidural

blood patch is the treatment of choice though it is not effective in about 25% of patients and often must be repeated. Surgical treatment should be limited to selected cases [1].

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Thunderclap headache as a presentation of spontaneous spinal epidural hematoma with spontaneous recovery

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Introduction Spontaneous spinal epidural hematoma (SSEH) is a rare spinal cord disorder. Thunderclap headache mimicking subarachnoid haemorrhage as an initial manifestation of this condition has been very rarely reported. Moreover these limited literature case reports headache is usually associated with neurological symptoms and signs of spinal cord involvement and compression, even if the latest ones generally occur later in comparison with cranial pain symptoms.

Objectives To report a case of SSEH exclusively presenting with acute onset severe headache that completely mimicked subarachnoid haemorrhage not accompanied nor followed by any neurological deficit.

Clinical presentation A 48-year-old Asiatic woman presented with sudden onset occipital headache, neck stiffness, discomfort, nausea and vomiting for which subarachnoid haemorrhage was initially suspected. Clinical examination revealed an alert woman with minimal nuchal rigidity. An emergency cranial computer tomography and vessel cranial angio-CT were normal. Lumbar puncture revealed a subarachnoid bleed. Magnetic resonance imaging showed a spinal epidural hematoma located in antero-lateral position to D1 through D7 vertebrae. Dorsal spinal angiogram carried out with selective injection from D5 to D12 levels didn't provide any evidence of vascular malformations nor other relevant conditions were detected. Headache condition slowly improved along three-four weeks. No neurological symptoms nor signs of spinal cord involvement developed, therefore a conservative approach was planned. A follow-up MRI carried out five days later documented a significant improvement of neuroimaging picture. A complete clinical recovery was obtained.

Conclusions The present case confirms that SSEH can sometimes imitate subarachnoid hemorrhage presentation. Moreover it provides the evidence that isolated thunderclap headache can represent the only clinical manifestation of this condition; such

an evidence emphasises the need of an accurate and extensive diagnostic depistage in all thunderclap headache patients including not only traditional procedures aiming to exclude intracranial source of bleeding, but also a more extensive study of CNS.

Drug-resistant Hemicrania Continua responsive to lithium: case report

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Introduction Hemicrania Continua (HC) is a primary headache characterized by an unilateral pain present for more than 3 months, associated with at least one trigeminal autonomic sign, ipsilateral to the headache: conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and facial sweating, forehead and facial flushing, sensation of fullness in the ear, miosis and/or ptosis. It is quite common to have attacks of severe pain on the background of the continuous moderate pain. The distinctive feature is the absolute response to therapeutic doses of indomethacin; for patients with contraindications to the use of this drug, some alternative treatments have been experimented without success.

Materials and methods A 76-year-old woman had a 5-year history of daily and continuous, without pain-free periods, headache of moderate intensity, with exacerbations of short-lasting (10 – 120 minutes) severe pain, located in the left occipital, parietal and temporal regions.

The attacks were strictly unilateral and accompanied by ipsilateral eyelid edema and ptosis, tearing and rhinorrhoea; furthermore, attacks could be triggered by chewing and teeth brushing. Indomethacin was the only drug able to mitigate the pain. Physical and neurological examinations were unremarkable, and the patient's history too, except for hysterioanesthetics (fibromatosis) performed when she was 31-years-old and arterial hypertension treated with candesartan cilexetil. Brain imaging was normal. Assuming a diagnosis of HC we started preventive treatment with several drugs without clinical benefit (pregabalin 150 mg/day, carbamazepine 800 mg/day, sodium valproate 1000 mg/day, lamotrigine 200 mg/day, duloxetine 120 mg/day, and methadone).

On the basis of the reported efficacy of lithium in cluster headache [1], we eventually decided to start a treatment with this drug.

Results Quickly, patient reported an unexpected clinical improvement: pain exacerbations decreased in intensity until disappearing within 7 days. Even after 3 months of follow-up, lithium 750 mg/die continues to be effective, as demonstrated by the limited use of symptomatic drugs.

Discussion We report for the first time a case of drug-resistant HC responsive to lithium. It is still unclear how lithium prevents headache; however, given the limited availability of preventive drugs and the risks correlated to the chronic use of indomethacin, lithium could represent a valid therapeutic option.

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Pure menstrual vestibular migraine

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We describe the case of a young patient affected, from the age of 16, she is now 32, by benign paroxysmal positional vertigo (BPPV) every month during menstruation. Vertigo with nystagmus and neurovegetative symptoms (nausea, vomiting, hypotension) were present for 3-5 days in the month associated with a constrictive non pulsating mild headache involving the whole head, there were no other symptoms during the month. The patient's present history included kinetosis and motion sickness, familiarity for migraine, absence of vertigo and headache during pregnancy and, in absence of menstruation, hyper-PRL secondary to amisulpride. For many years, the patient due to the prevalence of vertigo symptoms, was treated by an otolaryngologist who diagnosed BPPV. The patient was treated with canalith repositioning procedure, with poor results. Instrumental examinations like audiometric tests and vestibular evoked myogenic potential were normal in the interictal phase and during crises, nystagmus was evident only during attack like a left posterior BPPV. Brain MRI with Angio arterial and venous study were normal.

Considering the occurrence of this symptomatology exclusively during menstruation, its duration of about 3-5 days, headache, because of the intensity was considered secondary to vertigo, we diagnosed vestibular migraine (VM) which was treated like a pure menstrual migraine. The patient had regular menstruation without oral contraceptive, we then decided to introduce a short term prophylactic therapy with naproxene 550mg bid starting from 3 days before the period until the fourth day and frovatriptan 2.5mg as rescue therapy with a great success on headache and on vertigo. With this therapy, the patient has been free of BPPV and migraine, confirming the diagnosis of pure menstrual VM for the past third consecutive month.

This case is representative of the important overlap between migraine and vertigo recognized with the name of VM by the In-

ternational Headache Society classification III-beta. This new entity is usually well recognized by headache experts when the prevalent symptom is headache, but it is important to improve the sensibility of headache experts and otolaryngologists, on both headache and vertigo symptoms, to always recognize a VM and treat it in the correct way.

Alternating hemiplegia of childhood or hemiplegic migraine? An atypical case

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Introduction Alternating hemiplegia of childhood (AHC) is a rare disorder characterized by transient recurrent episodes of hemiplegia involving alternatively either side of the body associated with tonic or dystonic attacks, abnormal ocular movement and autonomic abnormalities.

Hemiplegic migraine (HM) is a migraine subtype that includes hemiparesis which can last for hours, days or weeks. It can be accompanied by other symptoms, such as ataxia, coma and paralysis.

For both conditions are known genetic forms. There are some clinical overlaps between AHC and familial HM (FHM) patients, as well as with other forms of paroxysmal neurological disease (episodic ataxia type 2, spinocerebellar ataxia type 6, benign familial infantile epilepsy).

Material and methods We describe a 23-year-old girl with transitory attacks of hemiplegia, lasting 24-48 hours.

Results The patient came to our observation after about 12 hours of a left hemiplegia. No headache was referred. Her neurological examination showed left hemiplegia and transient nystagmus. She was born of a non-consanguineous marriage, at 39 weeks gestation following a normal delivery. The pregnancy and neonatal period were uneventful. She achieved milestones normally during the first years of life. The first symptoms were noticed at 54 months of age when she developed sudden onset right-sided weakness from which she recovered completely in 2 days. There were no associated features like fever, seizures nor loss of consciousness. Subsequently, she developed recurrence of similar episodes of transitory hemiplegia on either side without complete loss of consciousness. The episodes lasted from few hours to few days. Such episodes recurred every 6 months-3 years without leaving any residual deficit. There was migraine personal and family history (mother and brother). Angio-Magnetic Brain Resonance imaging were normal. Genetic investigation for AHC and FMH were negative. Prophyl-

lactic treatment was started with Valproic Acid up to 600 mg/day, well tolerated. She discontinued the treatment after about 7 months. At 18-month follow up, the patient had a complete resolution of the attacks.

Discussion Some findings in our patient are consistent with AHC diagnostic criteria. On the other hand, late onset and no mental and neurological deficit authorize to postulate the HM diagnosis.

Conclusions AHC and HM have widely overlapped pictures with very difficult nosographic framework, without genetic confirmation.

Nummular headache: peripheral or central pain? A pathogenetic hypothesis

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Introduction Nummular headache is a rare primary headache disorder (4.8 ICHD-3beta) characterized by focal and well-circumscribed pain exclusively felt within a rounded or oval/elliptical-shaped area of the head, typically 2 to 6 cm in diameter. The disorder is almost always unilateral and side-locked. The pain is characterized as pressure-like, sharp, or stabbing and is usually mild to moderate in intensity. Sensory changes (hyperesthesia, hypoesthesia, allodynia, paresthesias) are frequently reported in the affected area. The temporal pattern may be episodic or chronic [1].

Case report A 76-year-old man developed a continuous pressure-like mild headache in a circumscribed area of the right parietal region, 6 cm in diameter, associated with allodynia and hyperalgesia of the affected area, interrupted by spontaneous remissions lasting weeks. The medical history was negative for other diseases.

He underwent brain MRI (negative) and infrared imaging with evidence of a hyperthermic region in correspondence to the area affected by pain.

A cold thermal stimulus between attacks feel uncomfortable by the patient not the warm one. We treated the patient with administration of palmitoylethanolamide 600 mg bid with rapid resolution of symptoms.

Discussion From this striking response to the administration of an immunomodulator comes our hypothesis, based on *ephaptic neuronal transmission*. It assumes that the neurons might not communicate only by exchanging information through their synaptic connections, but additionally through the extracellular matrix. Proinflammatory neuropeptides released by nociceptors activate mast cells, which in turn react degranulating various proinflammatory substances including the NGF (Nerve Growth

Factor), CGRP, substance P, IL-1, IL-6 and other proinflammatory agents responsible for the phenomenon of sensitization of peripheral sensory nerve endings. With nerve damage, loss of individuality ensured by the sheaths of the fibres allows the formation of “short circuit” or “ephapse” that would result in the transfer of signal from C-fibres to the adjacent fibres of the sympathetic nervous system which are thus activated, as confirmed by thermographic image.

Conclusions According to our hypothesis, Nummular Headache can be considered a peripheral pain triggered by neurogenic inflammation responsible for the process of peripheral sensitization.

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Hemilingual spasm triggered by trigeminal neuralgia. Case report

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Introduction Hemilingual spasm is a little-known movement disorder, presenting as intermittent paroxysmal involuntary contractions of half of the tongue muscles, first described by Lees et al. in two patients (1986) [1]. It consists of sudden episodes of speech difficulty due to involuntary spasms of half of the tongue. The spasms start as a feeling of stiffness or numbness lasting only seconds, and triggers include talking, eating, and stress. The first cases were considered idiopathic; thereafter few other cases have been reported, secondary to a premedullary arachnoid cyst, a tortuosity of the extracranial internal carotid artery, and a vascular compression along cranial nerve XII, respectively. Here we report the first case of hemilingual spasm triggered by classical trigeminal neuralgia.

Case report A 39-year-old woman complained of attacks of unbearable neuralgic pain within the territory of the maxillary branch of right trigeminal nerve since she was 29. The shock-like pain started in front of the temporomandibular joint and quickly spread to the chin, sometimes involving the ipsilateral side of the tongue. Every painful burst, during from 2'' to 2', was followed by a refractory period. The attacks occurred hundreds of times per day, during both daytime and nighttime. They could appear spontaneously, but were mostly triggered by touching the lips, washing the face, talking, chewing, or swallowing. Sometimes the attacks were associated with mild tearing and injection of the right eye. The most prominent feature, however, was a very painful hemispasm of the tongue that, in

its right half, raised up and shrank, till to cut itself and bleed. The spasm began immediately after the trigeminal pain and ceased with it; the tongue quickly regained its usual shape. Amongst many drugs taken by the patient, only carbamazepine was effective, but at the price of unbearable side effects. In July 2013 the patient underwent an intervention of microvascular decompression according to Jannetta procedure, with complete disappearance of trigeminal pain and hemilingual spasm.

Conclusions So far an association between hemilingual spasm and trigeminal neuralgia has never been reported. The precise mechanism by which trigeminal neuralgia triggers the tongue spasm has to be determined. One could hypothesize the activation of an abnormal lingual-hypoglossal reflex, whose existence has been demonstrated in normal subjects.

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Headache and Arnold-Chiari type 1 in children: case report

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Headache onset in children under five years of age should be assessed, followed and investigated. Among the many causes we must regard the Arnold-Chiari malformation (ACM). ACM is a condition characterized by herniation of a part of the cerebellar tissue in the cervical canal, compressing the spinal cord and resulting in a series of clinical manifestations. The symptoms are related to the compression of the craniovertebral junction. The ICHD-II classification in 2004 and the latest 2013 beta report this headache in secondary forms in Chapter 7 and describe its characteristics. We report the case of a 10-year-old child, presenting to our facility during the past 2 years, because of recurrent episodes of headache since the age of 4. *Family history*: headache in both the maternal and paternal lines. The headache crises were characterized by a throbbing pain, mainly in the temporal, lasting a few hours, responding to drug therapy with paracetamol. Associated symptoms: photo- and phonophobia, fatigue, pallor, and often vomiting. The patient presents neurological examination and psychomotor development normal. EEG: diffuse abnormalities in type sharp-wave under SLI. Both the symptoms and the family history attributed diagnosis of migraine. The type of headache modified in the last period because of the increase of frequency of episodes, not responding to medication, sometimes the onset was in the morning and accompanied by confusion. Thus, it was decided to undergo brain and spinal cord MR: presence of a commitment of the cerebellar tonsils into the foramen magnum,

about 5mm below the same which was associated with reduced CSF perimesencephalic cisterns and expansion of the supratentorial ventricular system with a prevalence of left section. The spinal MR: multiple expansions of the ependymal canal in the spinal dorsal cervical, major in metameric level C6- C7 of the maximum diameter of about 4 cm, to report in terms of hydromyelia. To complete diagnosis we performed PESS and PEM of the upper limbs. The neurosurgical consultation suggested “wait and see.”

Conclusions Our case is important because it emphasizes the importance of developmental guidelines for the diagnostic of headaches in children. The Chiari malformation is considered a minor disease and is poorly described in children, but can be a dangerous condition.

Periodic perimenstrual cruralgia in isolated lumbar root endometriosis: a case report

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A 38-year-old woman reported a two-year history of periodic left anterior thigh pain, which appeared 2-3 days before menstruation, was unresponsive to non-steroidal anti-inflammatory drugs, and disappeared after menses. Her past medical history was unremarkable. Lumbosacral magnetic resonance imaging (MRI) with gadolinium and abdomino-pelvic ultrasonography and MRI were all negative. She was diagnosed with psychogenic pain in another hospital and treated with benzodiazepines, antidepressants and psychotherapy with no effect. Neurological examination was unremarkable except decreased left patellar reflex. A neuropathic origin of her pain was suspected and she underwent electromyography, which showed left L4 mild neurogenic changes and short T1 inversion recovery (STIR) MRI during menstruation that documented left L4 root endometriosis. Pain responded to leuprorelin, confirming the diagnosis of endometriosis.

Isolated endometriosis of the lumbosacral roots or plexus may cause perimenstrual radicular pain and can be diagnosed with STIR MRI during menstruation. The diagnostic algorithm for neuropathic pain may be helpful in cases of pain of unclear etiology.

A new case of hemiplegic cluster

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Background Visual, sensory and olfactory auras accompanying cluster headache are increasingly recognized by clinicians, but only in anecdotal cases coexistence of hemiplegic features have been described. We report a new case of hemiplegic cluster.

Case report We report the case of a 41-year old Caucasian male with a 23-year history of right sided throbbing orbital-temporal region pain, accompanied by ipsilateral autonomic symptoms such as conjunctival injection, tearing and nasal congestion. Attacks were of severe intensity and lasted up to 120 minutes, occurred three times a day for about 2 months and they were followed by months or years of remission. Headache was rarely accompanied by right sided paresthesias and in one case by motor aphasia.

Two weeks before admission, the patient began suffering from the usual headache. He was admitted because few minutes after the onset of an attack, he suddenly developed a right sided weakness. Neurological exam showed a mild right hemiparesis, while headache was remitting. The patient received 325 mg aspirin and hemiparesis resolved in 8 hours. Secondary aetiologies, including transient ischemic attack and stroke were ruled out by head CT angiography, cerebral MRI, EEG and echocardiography. The patient had another episode of transient right sided hemiparesis associated with headache 13 years before, when no diagnostic definition was reached. A cluster-like headache aura status was diagnosed. In the hospital setting the patient experienced 4 attacks of headache, successfully treated with 6 mg subcutaneous sumatriptan. Therapy with verapamil 240 mg/day and prednisone 75 mg/day was started. Headache resolved in 3 days.

Conclusions We described the first Italian case of cluster-like headache aura status. The associations of verapamil plus prednisone were effective in resolving headache. Recognizing hemiplegic cluster is important to prevent the patient from useless and potentially harmful investigations and treatments.

Possible pathogenetic differences among migraine without aura attacks evidenced by electroencephalogram

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Introduction Many studies have been performed to clarify the migrainous pathogenetic mechanism; despite this, many points still need to be elucidated. Electroencephalogram (EEG) is at

present rarely done in migrainous patients since the results of some studies failed to evidence peculiar abnormalities. We describe a case observed in our Headache Center in which we found peculiar features of the EEGs performed during migraine without aura (MO) attacks.

Case report A 23-year-old male student presented to the emergency room (ER), with a history of MO (ICHD-III beta). He had the first attack at the age of 19 years, thereafter these occurred about one every 2-3 months. The attacks were characterized by moderate, throbbing pain, exacerbated by movement, usually localized in the right frontal region with occasional left-side attacks. The episodes were accompanied by photophobia, phonophobia, osmophobia. They usually lasted 4-6 hours and responded well to NSAIDs. He came to the ER for a migraine attack lasting 24 hours with a severe pain in the right frontal region, not responding to NSAIDs. Physical and neurologic examinations, neuroimaging were normal; an EEG evidenced diffuse slowing theta delta rhythm on the right hemisphere. Six hours after admission the pain stopped with indomethacin 50 mg i.v. A follow-up EEG performed the day after, when the painful phase had resolved, was normal. Two months later he performed an EEG, during a MO attack with the usual duration and pain intensity, that resulted normal.

Discussion In the literature there are scattered reports on EEG abnormalities, in particular showing unilateral or bilateral theta-delta and delta activity in migraine with aura (MA) or in basilar, hemiplegic and ophthalmoplegic migraine. Our patient presented MO and the only clinical differences between the attacks here considered were pain's intensity and duration. Based on this finding we hypothesize that only more severe MO attacks could affect EEG activity. There is evidence from neuroimaging studies, in particular functional MRI, that phenomena resembling cortical spreading depression (CSD) are present in MA attacks in humans and it seems that subclinical CSD could be present also in MO attacks. The study of a large series of MO and MA patients, relating their EEGs to intensity/duration of their attacks/aura could contribute to support this hypothesis.

Clinical features of olfactory migrainous hallucination

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Introduction Olfactory migrainous hallucination (OMH) is a rare phenomenon, affecting about 0.1% of migraine patients, not included as migrainous aura in the International Classifica-

tion of Headache Disorders 3rd edition. Recently, 39 OMH cases have been reviewed. However, some clinical aspects remain to be clarified particularly about its frequency, onset and offset.

Case reports We report four patients with OMH thoroughly investigated about their clinical features. OMH attacks frequency in our patients ranged from 2 attacks/year to 3-4 attacks/month. In two cases OMH onset was sudden, in two gradually increasing, in one case with constant and in one with intermittent development, lasting between 3-5 and 30 minutes. In all the cases OMH began before headache, in two cases OMH resolved before pain development, in two cases persisted during the painful phase. The OMH duration varied from 3-4 minutes to 4-8 hours. The offset was sudden in three patients and gradual in one. Smell kind was reported as always unpleasant in three cases, sometimes pleasant in one. All the patients presented a persistence of the same smell during each attack, and the smell perceived was always the same in three patients, in one it was different in the various attacks. Three patients reported osmophobia during the migrainous attacks preceded by OMH. It has been clarified, however, that OMH and osmophobia are two distinct clinical symptoms. The headache associated with OMH presented in all the cases MO features, but in one case OMH presented as an isolated symptom. All patients presented other kind of primary headaches; in all but in one case, OMH started many years after their beginning.

Discussion From our experience, the patient, when properly asked about, is able to describe details that allow a better OMH clinical characterization. We believe that in future prospective studies all the patients with this symptomatology should receive detailed questions on the subject. The clinical acquisitions could support cortical spreading depression as pathogenetic mechanism, e.g. clarifying if OMH could develop progressively; contribute for a possible collocation in the next ICDH for this homeless aura; help in the differential diagnosis with other neurological pathologies, in particular with epileptic olfactive seizures.

Migraine with aura-like episodes in bilateral spontaneous vertebral artery dissection

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Introduction We describe the case of a young woman who presented with episodes fulfilling the ICHD-III beta criteria for migraine with aura (MA), whose diagnostic work-up led to an unexpected diagnosis.

Case report A 29-year-old woman, with no personal history of headache but with a positive family history (mother, twin sister) of migraine with visual aura, came to our attention because of five transient episodes lasting 40-90 minutes occurring over 48 hours of visual disturbances associated with headache. In particular, she described a “dazzling sensation”, blurred vision and scintillating scotomas in the left visual field, that in 5 minutes progressively spread across the entire eye field; in two occasions these visual perturbations were associated with a headache having the clinical characteristics of a migraine (throbbing pain, photophobia, nausea and vomiting) poorly respondent to NSAIDs. There were no recent head traumas, no chiropractor’s procedures; the only comorbidity was autoimmune hypothyroidism. Neurological and ophthalmological examinations were unremarkable. CT of the brain and EEG were normal. A neurovascular ultrasound (nUS) examination detected bilaterally a hypoechogenic thickening of the vertebral artery wall associated with a marked serpiginous stenosis extending from V1 to V3, suggesting a bilateral VAD (vertebral artery dissection), which was confirmed by magnetic resonance angiography. Cerebral MRI did not disclose any ischemic lesions. Laboratory analysis, including hypercoagulability tests, were normal. She was treated immediately with anticoagulant doses of enoxaparin and she has been asymptomatic ever since. When she was discharged, one month ago, nUS detected the first signs of recanalization in the left V1 segment; follow-up examinations are scheduled monthly in the first six months to monitor recanalization and steer proper treatment.

Conclusions Excruciating neck pain is sometimes the presenting symptom of VAD. Rarely, headache mimicking a migraine, even with visual aura, represents the reason for referral; in particular, our patient presented symptoms that fulfilled ICHD-III beta diagnostic criteria for probable MA. A first attack of MA deserves a complete diagnostic work-up in order to exclude potentially threatening secondary causes, as demonstrated by our case, since VAD is a pathological condition that needs urgent treatment considering its high stroke risk (about 80%). This is the first reported case of migraine with visual aura related to spontaneous bilateral VAD.

Vogt-Koyanagi-Harada syndrome: an unusual cause of headache

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Background Vogt-Koyanagi-Harada (VKH) syndrome is an

uncommon idiopathic autoimmune disorder characterized by early neurological symptoms (headache, meningismus) and then bilateral ocular manifestations (uveitis with retinal detachment, optic disk hyperemia). Later auditory (tinnitus) and dermatological disturbances (alopecia, poliosis, vitiligo) occur.

Subject and methods On March 2014, a 45-year-old woman from Macedonia presented with a two-week history of severe headache, photophobia, bilateral blurred vision, red eyes and tinnitus to our Neurological Department. She was previously healthy but overweight. No history of head or ocular injury.

Neurological examination confirmed loss of vision (21/30 in each eye). No signs of meningeal irritation or of long tract motor or sensory involvement were detected. There were no skin lesions or lymphadenopathies. Cranial computed tomography and brain magnetic resonance imaging, with gadolinium and sinus venous study, were unremarkable. Lumbar puncture, twenty days after the onset of symptoms, showed clear cerebrospinal fluid (CSF) and an opening pressure of 15.6 mmHg (abnormal >20mmHg); normal number of cells and level of proteins and glucose. A work-up was performed including: complete blood count, erythrocyte sedimentation rate, rheumatoid factor, angiotensin converting enzyme, lysozyme, HIV, *Borrelia burgdorferi*, *Bartonella* and *Chlamydia* antibodies titers, Pathergy test, CSF analysis for tuberculosis and syphilis, which were unrevealing. An ophthalmologic evaluation including stereoscopic examination and fluorescein/indocyanine green angiography, revealed bilateral inflammatory papilledema and multifocal choroiditis. The optical coherence tomography showed multiple serous detachment of the neuroepithelium and epithelium pigmentosum. Final diagnosis of bilateral uveopapillitis was suggested.

Prednisone 50 mg daily was started, administered orally. At two weeks of therapy partial resolution of the intraocular inflammation and improvement of visual acuity occurred. The patient did not suffer headache at discharge.

Results The patient was diagnosed with partial VKH syndrome, that is an uncommon idiopathic autoimmune disorder occurring primarily with ocular pathological findings and headache. The pathophysiology involves T-cell-mediated autoimmunity against melanocyte-associated antigens in the choroid, meninges, cochlea and skin.

Conclusions The VKH syndrome accounts for about 9.2% in uveitis in the Japanese population, whereas the prevalence is likely to be lower in white and black people. Nevertheless, this disorder should be suspected in our country, especially for immigrants, when headache and possible meningism occur with bilateral blurred vision.

Use of rotigotine in chronic cluster headache

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Introduction Chronic Cluster Headache (CCH) is an infrequent, particularly severe form of Cluster Headache, defined by the absence of remission periods. Preventive medical treatments are few, sometimes ineffective and poorly tolerated. Rotigotine was recently reported as useful in a single patient with CCH resistant to other medical therapies.

Aim To report the results observed using rotigotine in three cases with CCH.

Case reports All patients received a diagnosis of CCH according to ICHD-3 Beta. They all showed normal brain imaging and strictly normal neurological examination. Patients were aged 61, 67 and 49 years respectively. They all had been treated with verapamil, carbolothium and steroids, unsuccessfully. In all cases rotigotine has been started in February 2014.

Case 1: Apart from the mentioned medications, he was treated with Gammacore and pregabalin, which also proved ineffective. Transdermal rotigotine was started at the dose of 2 mg/die. After a few days, only scarce, minor attacks persisted, and were stopped by an increase in posology up to 4 mg/die.

Case 2: Rotigotine was started, titrating doses up to 6 mg/die, but the patient did not report any beneficial effect, and after a month the dopamine-agonist was discontinued.

Case 3: Titration of rotigotine was needed up to 4 mg/die, for persistence of minor attacks with lower doses. Lasting remission has been observed since dose increase.

No adverse event has been reported by the three patients.

Discussion and conclusions Rotigotine is a non-ergoline D3-like receptor agonist. Its availability in the transdermal form and its safety profile make it well accepted by patients. The three subjects whose cases we reported did not show any adverse event at the employed doses. Two of them showed initial but definite benefit from this therapy and are currently free from pain and under follow-up. Based on these outcomes, very recently we decided to start the same treatment in a fourth case. We think that rotigotine should be considered in the management of CCH unresponsive to common treatment.

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Stroke in HIV-positive migrainous patient: emergency department evaluation common pitfalls

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We describe the case of a 33-year-old woman who presented to our Unit reporting sudden onset of mild weakness and sensory loss of the upper right arm. The patient complained also of pulsating headache associated with photo- and phono-phobia, which arised approximately 48 hours before and was partially responsive to non steroidal anti-inflammatory drugs. At admission neurological evaluation revealed only mild right hand weakness (NIHSS: 1). During the evaluation at the Emergency Department (ED) the patient denied any previous history of headache; instead, she reported being diagnosed HIV-positive approximately six-years before (previous history of intravenous drug use). At the moment of hospitalization the patient was in treatment with nevirapine and tenofovir/emtricitabine. An urgent brain computed tomography scan showed no acute lesions whereas a magnetic resonance imaging (MRI), performed 4-5 hours since symptoms' onset, demonstrated feeble left frontal cortical hyperintensity on DWI and FLAIR sequences of suspected ischemic nature. Later blood tests revealed slight hypercholesterolemia and minimal homocysteine elevation; screening for hypercoagulable states returned negative. A subsequent brain MRI scan performed 48-hours from admission showed two small ischemic lesions within the left frontal and insular cortex, much more apparent compared to the basal MRI scan. Cervical ultrasonography was unremarkable and so was transthoracic echocardiography. Transcranial Doppler and bubble study led to a diagnosis of patent foramen ovale with moderate shunt at rest and severe shunt during Valsalva maneuver. During hospitalization, despite having denied any previous history of headache during ED evaluation, the patient reported a 5-year history of severe pain localized to the left eye, preceded by visual disturbances with central scotoma (duration approximately 30 minutes); each episode lasted a maximum of 12 hours with an average frequency of 4-5 times a month. At discharge, a diagnosis of left frontal-insular stroke in migrainous patient was made; we began an antiplatelet therapy and gave no specific indication for PFO closure. In conclusion, this case report highlights two pitfalls of major concern when dealing with a patient complaining of headache and showing focal neurological signs, the first being the high efforts required in some cases to identify a past history of headache when evaluating a patient in the ED setting (repeatedly denied by our patient) and the second being the incomplete reliability of MRI in ruling out ischemic lesions when performed in the hyper-acute phase (only feeble DWI hyperintensity, not conclusive for ischemic lesion, was demonstrated in the first MRI scan).

A case of headache in a patient with SLE

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A 48-year-old Caucasian man was admitted to our Department due to persistent headache resistant to treatment with analgesic agents. The headache started five days before, it began in the frontal-temporal areas and the associated features were the worsening with standing, transient hypoacusia episodes and facial paresthesia.

His history was positive for Systemic Lupus Erythematosus (SLE) with renal involvement, antiphospholipid antibody syndrome, bladder cancer, sporadic episodes of migraine without aura.

His blood test showed only mild thrombocytopenia (Plts 101,000/ml), low complement levels (C3 120 mg/dl, C4 21 mg/dl) and increase in RCP level. Serological findings showed antinuclear antibodies (ANA +++ omogeneous pattern), anti-double-stranded DNA antibodies (dsDNA), anticardiolipin [aCL] antibody IgG 141.40 GPL/ml, IgM 4.02 MPL/ml, anti-beta-2 glycoprotein I IgG 100 UA/ml, IgM 2.9 UA/ml.

A magnetic resonance imaging (MRI) of the brain with and without gadolinium was performed and it showed diffuse thickening of the pachymeninges with gadolinium enhancement. The radiological findings could be suggestive of intracranial hypotension. MRI of the spine was performed to rule out secondary causes of intracranial hypotension (extra-arachnoid CSF collection, meningeal diverticula and bony abnormalities that might have contributed to dural tear) but it showed no significant findings. After neurological evaluation, no more diagnostic studies were performed and the patient was treated with intravenous administration of normal saline solution for 3 days with progressive improvement of the headache.

A month later, a new MRI was performed and it showed no radiological findings of intracranial hypotension suggesting that the headache was due to spontaneous low CSF pressure, according to ICHD 3-beta [1].

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Botulinum toxin type-A therapy in cluster headache: a case report

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Introduction Cluster headache (CH) is a primary headache which can be considered rare if compared to migraine and tension-type headache (TTH). Its rarity as well as its peculiar course characterized by silent periods alternating with active periods are the main causes of misdiagnosis and delayed diagnosis. In the literature there are few studies concerning the neuropsychological features and the quality of life of CH sufferers. The goal of this study was to examine the role of toxin botulinum type-A on this form of primary headache in a patient referring to the Headache Centre of Florence.

Case report A 46-year-old man suffering from chronic CH according to the ICHD-II criteria [1] since the age of 20 years, resistant to conventional pharmacological treatment, with the exception of sumatriptan subcutaneous injectable solution of which the patient now abused. Seizures began with a tenderness or tension at the level of the temporomandibular joint sx that then spread to the eye and the pain became pungent, burning. Sometimes associated with sparkles in his eyes, loss of balance, lacrimation and nasal secretion. Over the past 2 years he had undergone five applications of toxin botulinum type-A (Botox) with a periodicity of about 3 months between each treatment, with a total dosage of 155 U per treatment in 31 sites in the muscles of the head and neck following a standard treatment paradigm.

Results The benefit on the symptoms appeared after the second infiltrative treatment with persistence of effectiveness until February of this year, after an unpredictable interval of about 8 months after the last (V°) treatment due to family circumstances. The patient sometimes reported rare episodes of tension at the level of the temporomandibular joint sx, but unlike the previous episodes, they did not result in real crises and therefore the symptoms were well controlled with no need to take a triptan.

Conclusions The botulinum toxin type-A (Botox) therapy in cluster headache can represent a valid alternative prophylactic therapy in case of failure of conventional therapies.

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A case of prolonged acute confusional migraine

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Introduction Acute confusional migraine remains unclassified by ICHD-III beta, despite being a dramatic clinical manifestation requiring accurate differential diagnosis. We report a pediatric case with prolonged confusional migraine.

Case report A 13-year-old boy was brought to our Emergency Department for headache, dysarthria, difficulty in simple calculations and photophobia. Some hours earlier, while playing basketball, he presented transient right arm sensory and motor deficit for 60', followed by left-side headache and vomiting; he had already experienced a similar episode one year before. His mother had migraine with aura in childhood.

On admission he was confused, unable to write and solve simple calculations; neurological examination was otherwise normal. Physical examination showed only mild systolic murmur. Laboratory tests, echocardiogram and CT-angiographic evaluation were all normal. Rachicentesis showed normal glucose and protein levels and no leukocytes; the detection of neurotropic viruses, anti-NMDA and anti-GAD proved negative. The electroencephalogram (EEG) performed on admission revealed left-side temporal-parietal-occipital slowing. He was put on intravenous acyclovir, dexamethasone and acetaminophen. Headache and confusional state endured for 48 hours, then the child fully recovered. Two days later, the EEG strongly improved. Brain MRI was also performed and proved negative. Considering familiar and personal history, clinical characteristics and evolution, EEG improvement and negative neuroimaging, prolonged confusional migraine was diagnosed. During hospitalization the patient remained asymptomatic; the EEG got normal one month later.

Conclusions Confusional migraine is an atypical variant of migraine presenting with sudden confusional state, usually associated with agitation, visual symptoms, dysarthria, amnesia. Headache precedes or follows the attack, which lasts 1-24 hours, sometimes longer. Neuroimaging is negative; typically the EEG pattern shows diffuse slowing that returns to normal few weeks after the attack. Differential diagnosis includes brain infections, stroke, metabolic disorders and toxic exposure.

Our patient showed typical clinical manifestations of confusional migraine, but the episode was prolonged over 24 hours. In this case an accurate familiar and personal history, clinical examination and EEG rapid improvement allowed the diagnosis.

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Dialysis headache responding to flunarizine

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Introduction A case of dialysis headache resistant to any modification of HD treatment [1].

Case report A 61-year-old, female, married and retired patient came to my referred observation from the dialysis service. *Family history:* Negative for neuropsychiatric, cardiac and cerebral vascular events. The patient's brother and son suffer from headache with sporadic frequency. She has a son with polycystic kidney disease on hemodialysis for the past 10 years.

Past medical history: Appendectomy, bilateral inguinal hernia, hysterectomy for fibroids, ovarian annessiectomy, retinopathy, colon diverticulosis, removal of villous adenoma of the colon, chronic viral hepatitis type B, dyslipidemia and arterial hypertension treated with ramipril 5 mg and amlodipine 5 mg.

Headache history: The patient reports occasional headache for 10 years, which worsened in the last year close to dialysis treatment. Pain occurred 30 minutes after treatment, it was bilateral, of severe intensity, with migraine features. The patient, when goes home, needs to stop any activity. During hemodialysis no

drops or rises in blood pressure neither significant changes in arterial blood gas had ever occurred. She took about 15 tablets of nimesulide per month.

The nephrologists tried to modify the hemodialysis technique using the AFB and the headache disappeared but the method was suspended due to serious muscarinic effects. The bicarbonate HD was reinserted with some parameter variations: HCO₃ from 3.1 to 2.9, Na from 14.2 to 14.6, glucose 33%, 10 mL/h, with poor results. Also, the replacement of various types of membranes KF -201 16 G, polisulfan has been tested with poor results.

At this point, I decided to replace amlodipine 5 mg with flunarizine 5 mg. One month after the beginning of treatment, the patient reported a less severe headache, beginning later on and remitting after paracetamol 500 mg. No change in blood pressure has been observed. At 3 months, the patient was no longer bedridden on dialysis days and was satisfied with her quality of life even though the headache was not completely gone, and was hopefully waiting for transplantation.

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Focus on pharmacological treatment of pediatric migraine*P.A. Battistella**Juvenile Headache Centre, Department of Woman's and Child' Health, University of Padua, Italy;
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Introduction Migraine is the most important cause of pediatric consultations due to headache. The aggregate weighted rate of definite migraine in children is about 12%, and 50% of those with frequent and/or severe migraine do not receive professional treatment; this one should be based on an integrated bio-behavioral and pharmacological approach [1].

Acute treatment Drug approach includes acetaminophen, NSAIDs and triptans. • Acetaminophen and ibuprofen are the first therapeutic choices in the acute treatment of migraine and are well tolerated; however, they may be ineffective in approximately a third of the cases. The triptans can be a useful therapeutic option in adolescents with a good safety profile. • Sumatriptan nasal spray is significantly more effective than placebo and is licensed in Europe from the age of 12 at a dose of 10 mg. Oral almotriptan and rizatriptan, recently approved by the US FDA for the treatment of acute attacks of migraine in adolescents, were demonstrated to be more effective than a placebo. Other triptans, probably effective in children and adolescents, include zolmitriptan nasal spray.

Preventive treatment Most of the studies performed on preventive drugs are outdated and contain several methodological limitations. The literature shows that flunarizine and topiramate have a significantly greater efficacy than placebo; topiramate has been recently approved by the US FDA to prevent migraine in adolescents. For other drugs (including cyproheptadine, amitriptyline, divalproate and levetiracetam) there is not sufficient evidence in children. The results from the use of propranolol are conflicting, whereas nimodipine and clonidine have been shown to be non-effective. The conflicting data regarding efficacy of many preventive drugs are likely due to high placebo response rates, differences in population, methodologies and efficacy measures. Recently, nutraceuticals treatments (coenzyme Q10, riboflavin, magnesium, butterbur and other compounds) have been used in treating pediatric migraine: even if there is no convincing evidence of their effectiveness, the clinical practice impression is that nutraceuticals might have a role in the management of young migraineurs. Further studies are needed based on larger samples, crossover mul-

ticenter trials and patient selection from primary care services.

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Juvenile migraine and allodynia: prevalence and clinical correlations*V. Raieli¹, D. Trapolino², G. Giordano², C. Spitaleri², F. Consolo¹, G. Santangelo¹, F. Vanadia¹, M. D'Amelio³**¹Child Neuropsychiatry Unit, Di Cristina Hospital-ARNAS CIVICO, Palermo, Italy; ²Child Neuropsychiatry School, University of Palermo, Italy; ³Department of Experimental Biomedicine and Clinical Neurosciences, University of Palermo, Italy;**e-mail: vraieli@libero.it*

Background and aims In the past years, several studies have underlined the importance of allodynia during cephalalgic attacks for the comprehension of migraine physiopathological mechanisms, as for its treatment. Nevertheless, there are only two studies about allodynia in the pediatric population, both undertaken in small groups [1]. The aim of this study was to evaluate the prevalence of allodynia during cephalalgic attacks in a juvenile population with primary headaches and to study the correlation between allodynia and other main symptoms of migraine.

Methods A short questionnaire on allodynia was administered to all children seen in a two-year period and diagnosed with primary headache (During a migraine attack, have you ever had an unpleasant sensation when touching your head or combing your hair or wearing an object on your head or neck or to try to avoid touching your head) The cephalic allodynia was diagnosed on one positive answer.

Chi-square and t-tests were used to compare nominal and continuous variables. Odds Ratio, calculated by means of a logistic regression analysis, was used as measure of association of allodynia and migraine characteristics.

Results Two hundred and thirty children suffering from primary headache (105 males, 125 females, aged 4–17 years) were enrolled: 202 children were affected by migraine, 28 (12.2%) by other primary headaches; migraineurs significantly complained of allodynia (37% versus 0%). Pain increased by physical activ-

ity (OR 2.0, 95% CI 1.0, 3.8), patient showed phonophobia (OR 2.3, 95% CI 1.0, 5.1) and nausea (OR 1.9, 95% CI 1.0, 3.7).

Conclusions According to our data allodynia is common during pediatric migraine attacks. The associations between allodynia and physical activity, nausea and phonophobia, even if not described in any previous study on the pediatric population, are supported by several studies on the adult population, showing same correlations. While for physical activity the possible explanation of association is easy to understand considering that increasing pain during physical activities is believed to be a feature of peripheral sensitization of trigeminal neurons which conduct to successive central sensitization. The association with phonophobia and nausea, which involves different mechanisms (cortical and autonomic), suggests involvement of more complex and higher brain centers, because it is difficult to explain these associations based on brainstem mechanism of allodynia alone. Recently, it has been suggested that migraine attack is consistent with a pathological brain state that provoked a derangement of the physiological relationship between different brain networks. On the other hand nausea, phonophobia and allodynia can be present simultaneously and furthermore dopamine is a neuromediator involved in all three disorders and they may imply linked physiopathological mechanisms.

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Headache due to Pseudotumor Cerebri in children: an unusual and not always benign condition

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Introduction Pseudotumor cerebri (PC) is characterized by headache, papilloedema, intracranial hypertension (beyond 250mmH₂O), 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 (IIH). A multidisciplinary approach for prompt diagnosis and a correct treatment is necessary to avoid the complications of PC.

Material and methods We retrospectively reviewed clinical charts of children accepted to our Department of Pediatric Neurology with symptoms of intracranial hypertension suspected

for Pseudotumor Cerebri, over a one year period, from December 2012 to December 2013.

Results Ten children were admitted to our Department of Pediatric Neurology with symptoms of intracranial hypertension (headache, vomiting, diplopia) with normal brain imaging. Blood tests and neuroradiological exams were performed (including thrombophilic and endocrinological panel), and in one patient Cushing Syndrome was diagnosed. Mean age at presentation was 10.6 years with a prevalence among females (7 out of 10), six children of the ten were overweight (BMI > 20). Lumbar punctures showed increased opening liquor pressure in all cases except one (in this case diagnosis on PC was excluded). Evoked Visual Potentials showed a permanent visual loss in one case.

Discussion and conclusions PC is a rare condition in pediatric age. Scientific evidence suggests to define this condition as Pseudotumor Cerebri Syndrome and to reserve the term IIH only for cases of unknown origin.

Our results confirm that 10% of PCS may evolve into a permanent visual loss. For this reason the term Benign Intracranial Hypertension should be abandoned [1]. Moreover, a secondary cause must be searched in prepuberal children.

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Primary headache in childhood: neuroimaging and prescriptive appropriateness

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Introduction In recent years technology has reached great importance in health care and the use of sophisticated diagnostic radiology technologies has increased. However, the amount of radiation dose used to perform a radiodiagnostic examination should be assessed with appropriateness of the medical evaluations. Health protection must be, in fact, a priority objective of the clinician who sometimes contrasts with an “excessive conscientiousness” and an inappropriate use of these investigations, in particular in childhood.

Case report An 8-year-old girl, recently returned to attend her school activities, complained of a sudden and intense headache characterized by a throbbing and intermittent pain of a few minutes. These attacks were characterized by a temporary prostration and suffering states during which the girl shouted loud. The child was therefore referred for medical evaluation and at first she underwent an eye examination resulting in a

refractive defect with the prescription of corrective lenses. After a few days, with the recurrence of the headache, the patient was brought to the Pediatric Emergency Area and she was subjected to a brain CT scan which resulted normal. About 20 days later the child showed a new similar attack and she was brought to the Emergency Department of another city hospital. She received a second brain CT scan and she was discharged with an oral symptomatic prescription (ibuprofen). Because of persistence of the headache attacks in the following period she was referred to the Headache Paediatric Centre. A careful anamnesis and an accurate neurological examination allowed to diagnose a primary headache. Moreover, during an attack, it was enough just to question the child about her pain to automatically reduce the headache spontaneously until it disappeared.

Conclusions Excessive use of CT scans in childhood may be responsible for the development of brain tumours and leukaemia as reported in a recent retrospective cohort study recently published in literature. Therefore, radiation doses from CT scans ought to be kept as low as possible and alternative procedures, which do not involve ionising radiation, should be considered if appropriate [1]. Sometimes, listening carefully to the patient is enough to reach a correct diagnosis.

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Headache, aggressiveness and metacognition in children and adolescents with epilepsy

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Introduction Children with epilepsy are at an increased risk of behavioral and emotional problems [1]. Aim of the study is to investigate the relationship between the seizure disorder, aggressive behavior and metacognition. Subsequently the experimental group was divided according to the presence of headache, to determine if the chronic pain involving higher levels of aggression and lower metacognitive capacity.

Material and methods The sample of 100 subjects, 38 males and 62 females, aged between 8 and 15 years, with a diagnosis of idiopathic epilepsy, was recruited from the Center for the treatment of epilepsy of the Department of Pediatrics and Child Neuropsychiatry of the "Policlinico Umberto I" in Rome. The

non-clinical sample, 100 subjects without epilepsy, with 60 females and 40 males, of the same age, was recruited from primary schools in Rome.

Administered tests: Aggression Questionnaire and Metacognitions Questionnaire.

Results At t-Student test there were no significant differences about aggressiveness between the clinical and non-clinical samples, but there were significant differences about metacognition ($p=.03$) and metacognitive features: Positive Beliefs ($p=.01$), Uncontrollability and Danger ($p=.04$).

ANOVA test shows a significant difference about aggressive feature, between rolandic epilepsy and absence epilepsy about Hostility ($p<.005$), but there were no differences between children with only epilepsy, epilepsy and migraine and epilepsy and TTH. Instead, a significant difference was observed between epilepsy without headache and epilepsy with migraine, epilepsy with migraine and epilepsy with TTH, about metacognitive features: Superstition, Punishment and Responsibility ($p=.04$).

Discussion These results show that there is no relationship between aggressiveness and epilepsy with or without headache, but there is a difference between rolandic and absence. Children with epilepsy report lower levels of metacognition if compared with healthy subjects. Furthermore children with chronic pain in addition to epilepsy present higher levels of Superstition, Punishment and Responsibility.

Conclusions No significant results about aggressiveness are probably due to the pharmacological therapy, which can lower the levels.

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Correlation between abnormal brain excitability, anger management and anxiety in migraine children

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Objective To analyze the possible correlation between abnormal brain excitability and psychological factors in migraine children.

Methods We studied 12 migraine children. Auditory event-related potentials (ERPs) were recorded in three successive blocks to test habituation. Psychological profile was assessed by Picture Frustration Study test for anger management (PFS) and

Psychiatric scales for self-administration for youths and adolescents (SAFA-A scale for anxiety).

Results In migraineurs, all the ERP components (N1, P2, and P300) showed a reduced habituation, as compared to healthy children. In both the second and third blocks, a significant correlation between P300 deficit habituation and SAFA-A (social anxiety subscale) was found. Moreover, the P300 habituation was also correlated with PFS-I (intraggressive anger) in the second block and with the total SAFA-A score in the third block.

Conclusions To our knowledge, this is the first study showing a correlation between abnormal brain excitability, intraggressive anger and anxiety, suggesting a possible role of the latter in producing the migraine phenotype in children.

Childhood periodic syndrome and childhood headaches and the ICHD-III

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Introduction The association between periodic syndrome (PS) and primary headache disorders has long been known, as to be considered, in its various forms, a chapter of migraine. Therefore it was found that the presence of PS could influence the clinical course in young patients suffering from headache. Nevertheless, the ICHD-III removed this entity in the context of primary headaches in developmental age [1].

Materials and methods 866 headache patients, aged between 3 and 16 years represent the study sample. The presence of PS and the diagnosis of headache formulated according to the criteria ICHD-II and III was evaluated. A family history for headache and psychiatric disorders was considered. The following tests: the CBCL and YSR SAFA tests were administered.

Results 423 patients (48.9%) appear to have Mwo, 214 (24.8%) FETTH, 116 (13.4%) Mw (27 M and 22 F), 111 (12.8%) CDH. Patients with PS were 741 (85.5%) without significant differences between M and F. RAP (recurrent abdominal pain) and infant colics are the symptoms most often reported in the PS (74.6%), especially in the group of Mwo and FETTH. Family history of headache was present in 87.1%. Family history of psychiatric disorders was higher in patients with PS (36 vs 15% of patients without PS) and was prevalent in the CDH and FETTH (45.3 and 40.3%). Intensity and frequency of headache crises were reported as very high in the sample of children without PS: the intensity of pain was moderate-severe in 79.8% of patients with PS complains vs. 73.5% of children without PS. Monthly frequency of headache was prevalent (35.8%) in PS,

while in children without PS it was mainly multi-week (38%). 37.2% of patients with PS had a positive score for internalizing and externalizing disorders.

Discussion The presence of PS influences the diagnosis of headaches and characteristics of the headache crises. The different trend of familiarity for headache and psychiatric disorders in patients with PS is newsworthy as if the PS would represent an additional risk factor in individuals who already have a genetic imprinting [1].

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Benign paroxysmal torticollis responsive to flunarizine at 3 months of age

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Introduction Childhood periodic syndromes are thought to represent early life expression of migraine genes that later in life are expressed as migraine headache. Benign paroxysmal torticollis (BPT) is a rare paroxysmal dyskinesia characterized by recurrent stereotypic attacks of torticollis. During an attack, inclination or rotation of the head to one side occurs by itself, or is accompanied by vomiting and ataxia. BPT is often accompanied by signs similar to some of the nonheadache features of migraine, including pallor, hypotonia of one limb, photophobia, tears, ataxia, apathy, and drowsiness. Onset is sudden, without warning, and with a spontaneous resolution of episodes. The episodes most often last hours to days, but may last only a few minutes in some patients. Attacks first manifest during infancy, between ages 2-8 months. They resolve by age 3-5 years. Treatment is not standardized.

Materials and methods We report the case of a previously healthy 3 months breast-fed boy admitted to our Department of Neurology for stereotyped paroxysms of torticollis since the neonatal period with recurrence every 15 days; the duration of torticollis was between 4 and 24 hours. Pallor and irritability accompanied the disorder. There was a family history for migraine. The neurological and eye examinations were normal as the audiometric and vestibular functions. No gastro-oesophageal signs of disease were detected and a video EEG has been performed showing no abnormalities. To rule out secondary causes of torticollis, an ultrasound evaluation of the neck and a MRI of the brain were performed, resulting normal.

Therapy with flunarizine 1mg per day has been started and the

boy has been evaluated in follow-up, showing a progressive reduction of the episodes of torticollis and less intense symptoms.

Discussion and conclusions Our report suggests that a prophylaxis therapy is useful even in very young children affected by BPT with disabling symptoms and high recurrence of attacks. Moreover, low doses of flunarizine can be safe. Flunarizine is a calcium channel blocker and its efficacy and tolerability are well known in migraine treatment. Considering the relationship between migraine and BPT, flunarizine should be considered as a pharmacological approach to BPT.

Maternal attachment style and alexithymia: is there a relationship with their children headache feature and psychological profile?

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Introduction Childhood headache is a complex symptom, where genetic, biological and environmental factors interact with each other. While great attention has been placed on the role of anxiety and/or depression on headache features, few studies have analyzed the relationship between childhood headache and maternal psychological profile. There is evidence that caregivers' attachment styles and the way of management/expression of emotions (alexithymia traits) may influence children's psychological profile and pain expression. However, data dealing with headache are scarce. Aims of our study were to investigate the role of maternal attachment style and alexithymia on: 1) their children headache features (intensity and frequency), 2) their children psychological profile (anxiety, depression, somatization).

Materials and methods Eighty-four children with primary headache (mean age 11.5; s.d. 2.4) and their mother were included. Patients were divided into four groups according to the frequency of attacks (low, intermediate, high frequency, and chronic migraine). Pain intensity was rated on a 2-level graduated scale (mild/moderate and severe pain). The psychological profile was assessed by SAFA Anxiety, Depression and Somatization scales. Attachment style was measured by the semi-projective test SAT and children were divided in "secure" and "insecure" ("avoidant", "ambivalent" and "disorganized/confused") attachment patterns. We used ASQ and TAS-20 questionnaires to assess respectively the maternal attachment style and alexithymia levels.

Results TAS-20 subscale "Difficulty Describing Feelings" showed significant higher scores in mothers whose children reported a "high" attacks frequency compared to those whose children complained a "low" frequency ($p=0.007$). No differences were found in the intensity of pain ($p=0.08$). Alexithymia levels also correlated with children's psychological profile and attachment style. A positive significant relationship between TAS-20 and SAFA-Anxiety total scores was found ($p=0.028$). Moreover, we found a significantly higher score in maternal alexithymia levels in children classified as "ambivalent", compared to those classified as "avoiding" (Total scale: $p=0.002$; Difficulty Identifying Feeling subscale: $p=0.007$). No differences were found between groups in ASQ subscales.

Conclusions and discussion Our results show that maternal alexithymia may influence children headache frequency, anxiety and attachment style. We can hypothesize that mothers' difficulty in expression and management of emotions increases their children anxiety levels; on the other hand, children may express their distress through recurrent headaches in order to be comforted by their mothers.

Childhood headache features and psychological symptoms: the role of attachment style

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Introduction Attachment theory suggests that early interpersonal relationships may be important determinants of psychopathology and pain management. In particular, individuals with insecure attachment ("ambivalent" and "avoiding") styles have been shown to experience more pain than people with secure attachment style. Few studies focused on headache and data on attachment style in pediatric headache are scarce.

The main objectives of the study were 1) to compare the psychological profile in migraineurs children according to their attachment styles; 2) to investigate the relationship between the clinical features of headache (intensity and/or frequency) and the psychological symptoms in patients with different attachment styles.

Materials and methods The intensity of pain was assessed on a four-point scale (from 1 = low to 4 = high) while the frequency of attacks was rated on a four-point scale (from 1 = low to 4 =

chronic). Given the low frequencies, the “not specified”, the “low” and the “intermediate” frequency attacks and the “not specified”, the “low” and the “mild” intensity were collapsed in the same two categories. The psychological profile was assessed by SAFA Anxiety, Depression and Somatization scales. Attachment style was measured by the semi-projective test Separation Anxiety Test. Children were divided into “secure”, “avoidant”, “ambivalent” and “disorganized/confused” attachment patterns.

Results The final sample was composed by 78 participants (boys = 35; girls = 43). Due to their low frequencies, the “disorganized” and the “secure” attachment categories were eliminated from our analysis. Forty-five children (57.7%) showed an “ambivalent” attachment style, while thirty-three (42.3%) patients were classified as “avoiding” style. Compared to the “avoiding”, the “ambivalent” group had higher anxiety levels (SAFA Total: $p=0.002$). When we analyzed the SAFA scales as function of intensity and/or frequency of attacks according to the two attachment styles, the “low self esteem” and “regret” subscales (SAFA Depression) showed a relationship with the intensity of pain in the avoiding group.

Conclusions and discussion Our results suggest a relationship between insecure attachment style and headache in children. In particular, we can hypothesize that assigning more importance to performances (i.e., school, sport), children classified as “avoiding” tend to experience low self esteem and regret if the intensity of pain adversely affects their activity.

Airplane headache: a multicenter study in pediatric age

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Introduction Airplane headache (AH) is a rare form of headache disorder associated only with airplane travel. In ICHD-III, 2013 AH has been classified among headache attributed to disorder of homeostasis (point 10.1.2) [1]; in the literature, AH

has been reported in adults and only in three cases in children.

Methods Prospective study conducted for 6 months in eight Juvenile Headache Centers; inclusion criteria: diagnosis of primary headache (ICHD-III, 2013).

Results Total sample of 569 cases; complete data reported in 478 patients (202 M, 276 F) with mean age at interview of 11.2 years (3-19 years). Headache types: 332 Migraine (M) (69.5%), 103 Tension Type Headache (TTH) (21.5%), 28 M + TTH (5.8%) and 15 other types of headache (3.2%). M are divided into 287 M without aura (MO, 86.5%), 40 M with aura (MA, 12.0%), 5 chronic M (1.5%); TTH are divided into 73 Episodic TTH (ETTH, 70.9%) and 30 Chronic TTH (CTTH, 29.1%).

In our population 209 patients experienced airplane travels (43.7%), while 6 patients presented AH (1.1% of the total sample; 2.9% of total patients experienced airplane travels). AH patients are 4 F and 2 M; mean age 11 years (range 8-13 years). Mean age at onset of headache is 7.5 years. Headache types in AH are 3 MO, 1 NDPH, 1 ETTH and 1 CTTH. Only 2 patients reported in their past medical history allergic rhinitis or sinusitis. 4/6 patients present AH from the first flight and 5/6 in all flights. Headache is mainly bilateral (5/6), frontal (5/6), pulsating (4/6); accompanying symptoms and intensity are variable. In 5 patients AH was triggered by airplane taking-off, and, among these, in 3 also by landing; only 1 presents AH exclusively during the flight. The length of the flight does not seem to impact on AH. Drug therapy, administered in 2 patients, is effective. Paranasal sinus tomography and cerebral magnetic resonance imaging, made in 5 patients, are negative.

Conclusions Our study is the first to study prospectively AH in children and in our patients AHs are different from the cases published in literature.

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Brief prophylactic treatment proposal for the pediatric FETTH

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Introduction Tension-type headache is a frequent primary headache with no specific coded treatment, particularly during childhood. The aim of the present study is to assess the efficacy

and safety of Griffonia simplicifolia/Magnesium complex in a pediatric population with frequent episodic tension-type headache (FETTH).

Materials and methods *Study population* The study population consisted of 53 children (25 males, 28 females) aged between 8 and 12 years (mean 9.03 ± 2.67 years) consecutively referred for FETTH to the Clinic for Headache in developmental age of the Clinic of Child and Adolescent Neuropsychiatry at the Second University of Naples. The diagnosis of FETTH was made according to the pediatric criteria of the International Headache Society Classification 2013.

In order to define headache characteristics at baseline (T0) and after 6 months of treatment (T1), monthly headache frequency and mean headache duration were assessed from daily headache diaries kept by all the children. Headache intensity was assessed on a visual analogue scale (VAS).

Griffonia/Magnesium complex (50 mg and 200 mg, respectively) was orally administered as prophylactic therapy twice a day for 3 months to the enrolled children. To verify the efficacy of the association, we tested the starting frequency (T0) of headache after 3 months (T1) and then we calculated the headache frequency delta percentage to express the decrease in monthly frequency. This index was calculated at T0 and T1 according to the following formula:

$$\Delta = 100 - [(T1/T0) \times 100]$$

All parents gave their written informed consent. The study was conducted according to the criteria of the Declaration of Helsinki.

Results At T0, FETTH mean frequency per month was 6.43 attacks ($SD \pm 1.76$) and at T1 was 1.11 ($SD \pm 1.01$) ($F = 3.02$, $p < 0.001$). Mean delta frequency percentage was 84.11 ($SD \pm 14.27$) at T1.

Conclusions These preliminary findings indicate the potential safety and efficacy of Griffonia simplicifolia/Magnesium complex as brief treatment for the pediatric FETTH.

Motor impairment rehabilitation in pediatric migraine

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Introduction Migraine without aura (MoA) is a painful syndrome, particularly in childhood; it is often accompanied by severe impairments, including emotional dysfunction, absenteeism from school, and poor academic performance, as

well as issues relating to poor cognitive function, sleep habits, and motor coordination.

Materials and methods The study population consisted of 71 patients affected by MoA (32 females; mean age 9.13 ± 1.94 years) compared with a control group of 93 typically developing children (44 females; mean age: 8.97 ± 2.03 years) recruited in schools of the Campania region. The whole population underwent a clinical evaluation to assess the intellectual level, visual-motor integration (VMI) skills, and motor coordination performance, which was assessed using the Movement Assessment Battery for Children (M-ABC). Children underwent training using the Wii-balance board and Nintendo Wii Fit Plus™ software (Nintendo Co, Ltd, Kyoto, Japan); training lasted for 12 weeks and consisted of three 30-minute sessions per week at their home.

Results The two starting populations (MoA and controls) were not significantly different for age ($P = 0.899$) and sex ($P = 0.611$). M-ABC and VMI performances at baseline (T0) were significantly different in dexterity, balance, and total score for M-ABC ($p < 0.001$) and visual ($p = 0.003$) and motor ($p < 0.001$) tasks for VMI. After 3 months of Wii training (T1), MoA children showed a significant improvement in M-ABC global performance ($p < 0.001$), M-ABC dexterity ($p < 0.001$), M-ABC balance ($p < 0.001$), and VMI motor tasks ($p < 0.001$) [1].

Conclusions Our study reported the positive effects of the Nintendo Wii Fit Plus™ system as a rehabilitative device for the visuomotor and balance skills impairments among children affected by MoA, even if further research and longer follow-up are needed.

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Periodic Limb Movement Disorder during sleep (PLMd) can cause impairment in childhood migraine management

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Introduction The relationships between sleep and headaches are complex and manifold. About the variety of phenomena that can disrupt the sleep macrostructure and can impact its restora-

tive function, the periodic limb movement disorder (PLMd) can be considered as the most powerful.

Aim of study is to assess the prevalence of PLMd and migraine and their relationship with disability and pain intensity in a pediatric sample, referred for migraine without aura by pediatricians.

Materials and methods After a preliminary sleep habits screening, 34 migraine subjects affected by MoA (20 M, 14 F) (mean age 9.08; SD \pm 2.28) and 51 volunteer healthy children (28 M, 23 F) (mean age 9.37; SD \pm 1.81) accepted to undergo overnight PSG recordings in the Sleep Laboratory of the Clinic of Child and Adolescent Neuropsychiatry, in order to define the macrostructural sleep characteristics and the prevalence of PLMd. Subsequently, the migraineurs sample was studied in order to define the relationship between disability, pain intensity, therapeutical responsiveness and the presence of PLMd.

Results In the migraineur children group, the individuals with PLMd pathological index (PLMI \geq 5) represent the 26.47% of sample and present higher frequency ($p < 0.001$), intensity ($p < 0.001$), duration ($p = 0.006$) and life impairment as scored in the PedMIDAS ($p < 0.001$) of headache and lower efficacy of prophylactic ($p = 0.001$) and acute ($p = 0.006$) pharmacological treatment than MoA children without PLMd pathological index [1].

Conclusions This preliminary study indicates the potential value of the determination of the PLMd signs, and the importance of the PSG evaluation in children affected by migraine, particularly when the clinical and pharmacological management tends to fail in the attacks control.

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The gut brain connection in pediatric migraine: an open label trial

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Introduction The aims of the present study were to assess the efficacy and safety of dietary supplement of Alpha Lactalbumin with FOS and inulin, specifically designed for pediatric age on frequency, severity and grade of disability related to migraine, in a population of children affected by MoA.

Methods Study population comprised 42 children (22 males) 6-10 years aged (mean 8.97 ± 1.93 years) consecutively referred for MoA to the Childhood Headache Center of the Child and Adolescent Neuropsychiatry Clinic of the Second University of

Naples. The monthly migraine frequency was assessed from daily headache diaries kept by all the children, MoA intensity was assessed on a VAS (visual analogue scale), and grade of disability linked to migraine attacks was assessed using PedMIDAS questionnaire. The whole population was assessed according to the Bristol Stool Chart in order to define the presence of stool problems, and underwent an haematological evaluation in order to survey inflammatory indexes such as ESR and CRP. All parameters were assessed at the beginning of the study (T0) and after 3 months of treatment with the nutraceutical complex.

Results At baseline (T0) MoA children showed normal values of all inflammatory indexes examined (ESR: mean 0.63 ± 0.48 mm; CRP: 0.29 ± 0.14 mg/dL) and not significantly different values at T1 (ESR: mean 0.57 ± 0.33 mm, $p = 0.506$; CRP: 0.33 ± 0.12 mg/dL, $p = 0.164$).

After 3 months of treatment (T1) the studied population showed a significant reduction in MoA frequency (9.81 ± 2.44 vs 6.18 ± 1.73 attacks/month; $p < 0.001$) with no significant reduction in MoA severity (8.03 ± 1.97 vs 7.91 ± 2.15 ; $p = 0.790$) and PedMIDAS score (26.52 ± 11.43 vs 22.48 ± 14.63 ; $p = 0.162$).

According to the Bristol Stool Test evaluation, at T1 MoA children showed a significant higher prevalence of type 2 stool (commonly considered as “normal stool”) compared to T0 evaluation (64.28% vs 38.09% ; $p = 0.029$)

Conclusions The present open trial suggests the potential safety and efficacy for MoA pediatric brief prophylaxis of the Alpha Lactalbumin plus FOS and inulin complex.

Maternal personality traits and pediatric migraine

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Background No studies about the personality of parents of migraine children have yet been conducted. The aim of the present study was to assess the personality profile of mothers of children affected by migraine without aura (MoA).

Materials and methods 269 mothers of MoA children (153 males; mean age 8.93 ± 3.57 years) were compared with mothers of 587 healthy children (316 males, mean age 8.74 ± 3.87 years). Each mother filled out the MMPI-2 questionnaire. The t-test was used to compare age and MMPI-2 clinical basic and content scales between mothers of MoA and typical developing children. Pearson's correlation test was used to evaluate the relation between MMPI-2 scores of mothers of MoA children and frequency, intensity, and duration of migraine attacks of their children.

Results Mothers of MoA children showed significantly higher scores in the paranoia and social introversion clinical basic subscales, and in anxiety, obsessiveness, depression, health concerns, bizarre mentation, cynicism, type A, low self-esteem, work interference, and negative treatment indicator clinical content subscales ($p < 0.001$ for all variables). Moreover, Pearson's correlation analysis showed a significant relationship between MoA frequency of children and anxiety ($r = 0.4903, p = 0.024$) and low self-esteem ($r = 0.5130, p = 0.017$), while the MoA duration of children was related with hypochondriasis ($r = 0.6155, p = 0.003$), hysteria ($r = 0.6235, p = 0.003$), paranoia ($r = 0.5102, p = 0.018$), psychasthenia ($r = 0.4806, p = 0.027$), schizophrenia ($r = 0.4350, p = 0.049$), anxiety ($r = 0.4332, p = 0.050$), and health concerns ($r = 0.7039, P < 0.001$) MMPI-2 scores of their mothers [1].

Conclusions The study highlights the potential value of maternal personality assessment for better comprehension and clinical management of children affected by migraine.

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Pediatric migraine can affect the self-esteem perception

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Introduction The impact of migraine without aura (MoA) on self-esteem has not yet been well investigated. The aims of the present study were to assess self-esteem levels and to verify their possible relationship and correlation with the frequency and intensity of migraine attacks, in a population of children and adolescents affected by MoA.

Methods The study population comprised 185 children (88 males) aged 6-12 years (mean 9.04 ± 2.41 years) and 203 healthy controls (95 males) with mean age 9.16 ± 2.37 years. The monthly headache frequency and the mean headache duration were assessed from daily headache diaries kept by all the children, and MoA intensity was assessed on a VAS (visual analog scale). To further evaluate their level of self-concept, all subjects filled out the Italian version of Multidimensional Self-Concept Scale (MSCS).

Results The two study groups were comparable for age ($p = 0.621$), gender ($p = 0.960$), and z-score BMI ($p = 0.102$). The MoA group showed a significant reduction in the MSCS total score ($p < 0.001$) and in the Social ($p < 0.001$), Affect ($p < 0.001$), Family ($p < 0.001$), and Physical ($p < 0.001$) domains of the MSCS compared with the control group. The Pearson's correlation analysis showed a significantly negative relationship be-

tween MoA clinical characteristics and MSCS scores, and similarly the frequency of attacks was significantly negatively related with the Social ($r = -0.3176; p < 0.001$), Competence ($r = -0.2349; p = 0.001$), Physical ($r = -0.2378; p = 0.001$), and total ($r = -0.2825; p < 0.001$) scores of the MSCS. On the other hand, the MoA duration was significantly negatively related with the Social ($r = -0.1878; p = 0.01$), Competence ($r = -0.2270; p = 0.002$), Physical ($r = -0.1976; p = 0.007$), and total ($r = -0.1903; p = 0.009$) scores of the MSCS [1].

Conclusions Our study first identified differences in self-esteem levels in children affected by MoA compared with controls, suggesting the need for evaluation of self-esteem for better psychological pediatric management of children with migraine.

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Migraine without aura and development learning disorders in school-aged children

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Introduction Migraine without aura (MoA) is a painful syndrome often accompanied by severe impairments, impacting also on cognitive function, and academic performance.

The aim of the present study was to assess the risk to develop learning disorders in an objective way in a population of school-aged children affected by MoA.

Methods The study population was comprised of 83 MoA children (51 males) aged 8-10 years (mean age 9.162 ± 1.423 years) and 141 healthy controls (84 males) (mean age 9.037 ± 1.606 years). Parents of the whole population filled out a validated Italian population questionnaire to screen the risk to develop learning disorders in their offspring (RSR-DSA questionnaire).

Results The two study groups were not significantly different for age ($p = 0.558$) and gender ($p = 0.893$). The MoA group showed a significant higher percentage of subjects considered "at risk for learning disorders" compared with the control group (22.89% vs 9.92%; $p = 0.014$).

Conclusions The present study highlights the high prevalence of risk signs for learning disorders in migraineur children compared to healthy control children, suggesting the need of further research on the relationship between migraine and learning disabilities in school-age children.

Visuo-spatial training effects on migraine without aura in children

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Introduction Migraine without aura (MoA) is a painful syndrome, often accompanied by impairments in motor coordination and visual motor integration ability, particularly in childhood.

Materials and methods Study population consisted of 14 patients affected by MoA (5 females, 9 males) (mean age: 9.35 ± 1.67 years); the control group consisted of 25 normally developing children (10 females, 15 males) (mean age: 9.13 ± 1.96 years) recruited in the schools of the Campania region. The whole population underwent a clinical evaluation to assess visual-motor integration (VMI) skills, and motor coordination performance by Movement Assessment Battery for Children (M-ABC) at the beginning of the study (T0) and after 3 months (T1) of treatment using a training software named "Allenare le abilità visuo-spaziali" [1] at their home.

Results The two groups (MoA and controls) were not significantly different for age ($p=0.726$) and sex ($p=0.937$). M-ABC and VMI performances at baseline (T0) were significantly different in dexterity, balance, and total score for M-ABC ($p<0.001$) and motor ($p=0.004$) tasks for VMI. After 3 months of training (T1), MoA children showed a significant improvement in M-ABC global performance ($p=0.018$), M-ABC dexterity ($p=0.036$), VMI total score ($p=0.025$), and VMI motor task ($p=0.027$).

Conclusions Our study reported the positive effects of the visuo-spatial training system as a rehabilitative device for the visuomotor and dexterity skills impairments among children affected by MoA, even if further research and longer follow-up are needed.

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Headache in pediatric multiple sclerosis: data from Padua case series 2003-2013

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Introduction The association between multiple sclerosis and headache has been studied by several authors in the literature [1]; though, data in children are limited.

Materials and methods We recruited all the pediatric patients diagnosed with multiple sclerosis in our Centre between 2003 and 2013, and we studied the prevalence and the characteristics of headache at onset and at follow-up in this population.

Results Between 2003 and 2013, 16 patients in pediatric age were diagnosed with multiple sclerosis at our Centre (9 females; age range at onset: 2.5 - 14.5 years). In 9/16 patients (4 females), headache was reported at onset or within the first months from disease onset: in 2 cases, headache preceded the onset of multiple sclerosis by years, and was still present at disease onset; in 4, headache was among symptoms of presentation of multiple sclerosis; in the remaining 3, headache onset was reported within 2-6 months from the first symptoms of multiple sclerosis. Two of these 9 patients had a positive family history for headache (data not available in 2/9). At follow-up, headache was reported by 6/9 multiple sclerosis patients with headache at onset or in the first months of disease (data not available in 2/9) and by 1/7 patients without headache at onset or in the first months of disease (data not available in 4/7).

Discussion and conclusions Headache was a common symptom at onset and in the first months of disease in our case series of pediatric multiple sclerosis, also in the absence of family or personal history of headache.

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Hemiplegic migraine with onset in childhood: follow-up of 14 patients

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Background Sporadic and familial hemiplegic migraines (SHM and FHM) are rare paroxysmal disorders characterized by motor aura and headache [1]. In the literature information on the natural history of HM is quite limited, particularly in cases with onset in pediatric age.

Methods Retrospective study of 14 cases diagnosed as HM (ICHD-III, 2013) with onset under 16 years and with a longitudinal follow-up.

Results Fourteen cases (10 females, 4 males): 11 SHM (8 females, 3 males), 3 FHM (2 females, 1 male). Family history positive for migraine without aura (5/14) or with aura non hemiplegic (4/14). Triggering factors were found in 8/14 cases (minor head trauma 3/14, emotional stress 4/14, physical stress 2/14). Age at HM onset: mean 9.2y, range 4-17y (5/14 cases < 6y). Motor aura was preceded or associated with visual (7/14), and/or sensory (5/14) and/or aphasic aura (5/14) or dysarthria (1/14). Mean duration of aura was 22h 40' (range 5'-48h). Between HM attacks, neurologic examination was normal in all cases. Two cases had intellectual disability; in other 2 cases mild neuropsychological deficits were found.

At follow-up: mean age 19.1y (range 10-47y), mean duration of follow-up 11.45y (range 4-38y). The frequency of attacks ranged from 2 per month to less than 1 per year (mean 6-7 every year).

During the follow-up the frequency of HM attacks was quite stable in 6/14, while increased only in one case; 3/14 cases had no longer attacks in the last 2 years. Aura symptoms changed in 7/14 cases and intensity of the aura declined in 2/14 cases. Preventive therapy for HM was prescribed to 4/14 cases.

Discussion and conclusions Data on the natural history of HM are quite limited, particularly in children. In the majority of our cases, the frequency and the type of attacks were quite variable, and in more than half trigger factors were identified. The majority of our patients had a good prognosis, even in cases with early onset of HM and/or prolonged and/or severe HM attacks. During follow-up evolution of FHM cases was similar to SHM ones.

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Incidental findings on brain MRI in children: report of 3 cases

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Introduction: Several studies demonstrate that there is no appreciable difference in the frequency of incidental findings in common headache populations compared with the general com-

munity [1]; recently in a large sample, 6.4% of pediatric migraine patients had incidental white matter findings and incidental findings increase with age [1].

Case report Three children were diagnosed with a primary headache (ICHD-III, 2013): respectively a boy (7 years, case 1) having migraine without aura, a girl (12 years, case 2) and a boy (13 years, case 3) both diagnosed with episodic tension-type headache. Case 1 and 2 had a prolonged history of recurrent headache and a normal neurological examination; their family history was positive for migraine. Case 3 complained of headache since 10 years of age, he had no family history for headache, the neurologic examination was normal except for a congenital strabismus (Brown syndrome in the left eye). Brain magnetic resonance imaging (MRI) of all 3 children showed a small bright white matter lesion (hypointense on T1-weighted image, hyperintense on T2-weighted image and fluid-attenuated inversion recovery) in the frontal left cortex, reagent to contrast and stable at the medium term follow-up (case 1 and 2: 2 years; case 3: 5 years). EEG was normal in all 3 cases.

Discussion and conclusions In our 3 cases, the neuroimaging findings are consistent with a cortical dysplasia or a low-grade glioma; these findings are incidental and do not have any correlation with the headache of our patients (migraine in case 1, tension-type headache in case 2 and 3).

Incidental findings on brain MRI are common and, in the last years, the incidence of these findings is increasing due to the use of higher resolution MRI and to the increasing frequency of radiographic scans [1].

When the lesions are clinically silent and stable on longitudinal neuroimaging evaluation, it is recommended a long-term follow-up of these patients through a multidisciplinary team, while an aggressive approach is restricted to cases with growing, symptomatic or not well-defined lesions.

Clinicians must be aware of the risk of manufacturing morbidity in uncovering incidental and insignificant imaging changes [1], thus MRI is not routinely required where a primary headache diagnosis can be made.

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Migraine without aura, paroxysmal hemicrania or cluster headache? Description of an intermediate phenotype in pediatric age

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Objective To describe the case of a girl, whose headache shares characteristics with migraine without aura (MWA), paroxysmal hemicrania (PH), and cluster headache (CH).

Case report In September 2012, a 12-year-old girl (FN) without history of headache began to suffer from headache attacks of duration shorter than 1 hour. Pain was always unilateral and localized in the orbital region. It was associated with ipsilateral ptosis, miosis, and tearing. From 2 to 4 attacks a day were reported. Attacks could be interrupted after 15-20 minutes by paracetamol administration. Initially, headache was diagnosed as MWA and a prophylactic treatment with amitriptyline (10 mg/day) was suggested. After 2 months, no improvement was obtained. Indomethacin (50 mg x 2/day) led to a weak reduction of attack frequency that, however, remained daily. Moreover, indomethacin could not interrupt the attack. Prednisone was administered at the maximal dose of 1.5 mg/kg/day, which was progressively reduced and stopped after 2 months. The frequency of the attacks dropped to 1 a week for 3 months up to the end of the school year, while no attack occurred during summer. In September 2013, the attacks appeared again and verapamil at the dose of 60 mg x 2/day was started. After 2 months with no clear improvement, FN began to assume topiramate at the dose of 1 mg/kg/day. Her headache improved dramatically and at the present she is headache free.

Discussion and conclusions This interesting pediatric case shows some features that can be difficult to include in a definite phenotype. The young age and the headache dependency on emotional factors (apparently spontaneous resolution during summer) could suggest the diagnosis of MWA. Some characteristics of the attacks, mostly the vegetative phenomena, and their random occurrence during the day addressed to PH, but indomethacin was not fully effective. Clinical characteristics of attacks could also suggest CH, although their frequency was of 1 a week in the period March-May 2013 without therapy. Steroid treatment was partially effective, supporting the possibility of CH, but verapamil did not produce any positive effect. The most effective treatment was topiramate, known to be useful in both MWA and CH.

Epidemiological and clinical features of headache in a Pediatric Emergency Department: a 2-year retrospective study

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Introduction Headache is a common condition in childhood, frequently leading to the Emergency Department (ED) [1]. Aim of this study was to assess the epidemiological characteristics and clinical features of children referring to a Pediatric ED because of headache.

Materials and methods All the patients referred to our Pediatric ED between 01/01/2011 and 31/12/2012 for headache as the main symptom were retrospectively reviewed. For each patient we recorded age, sex, diagnosis at discharge, results of laboratory tests, neuroimaging investigations, consultations, therapies.

Results Six hundred and fifty-three patients were included (280 females, 373 males); the mean age was 9.57 years (range 2-14 years). Two hundred and ninety-seven patients (45.5%) were diagnosed as having primary headache, 293 (44.8%) secondary headache, 25 (3.8%) post-traumatic headache; 38 (5.8%) received a diagnosis that could not clearly account for their headache (e.g. constipation). Migraine (ICHD-III beta) accounted for 4.7% of primary headaches.

Among patients with primary headache, 41 (13.8%) underwent head CT or MRI and 55 (18.5%) received a specialist consultation; 196 (65.9%) received pharmacological treatment; therapy was effective in 148 cases (75.5%).

After discharge, 70 patients (23.5%) with primary headache had their first visit at our Pediatric Headache Center. Only 11 ED visits (3.7%) occurred in patients regularly followed at our Center. We observed 30 "revolving door" visits at the ED (4.5%); none of these patients had been referred to our Headache Center at discharge after the first ED visit.

Acute viral respiratory illness was the most frequent cause of secondary headache (178 patients, 60.8%). Serious neurological disorders (hydrocephalus, brain tumor or seizure) were found in 14 patients.

Discussion and conclusions In our experience, primary headache had almost the same prevalence of secondary headache. Only a minority of children presented headache as a symptom of underlying severe neurological conditions. Collaboration with the Headache Center was fundamental to improve diagnostic work-up and to limit repeated visits.

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