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Edited by: Luigi Alberto Pini, Paolo Martelletti

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XXV National Congress of the Italian Society for the Study of Headaches

Headaches, pain and comorbidity

**Riccione
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Proceedings

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Luigi Alberto Pini
Paolo Martelletti**

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**Proceedings of the XXV National Congress
of the Italian Society for the Study of Headaches**

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PREFACE

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On behalf of the Italian Society for the Study of Headaches (SISC), it gives me great pleasure to present the abstracts of all the scientific contributions that will be presented at the XXV National Congress of our Society, to be held in Riccione from October 7 to October 9, 2011.

The Congress is the main event in which our Society fulfils its aim in providing a forum for physicians involved in all aspects of headache, including research, clinical practice, professional and lay education to meet, discuss and exchange scientific information and ideas. Specialists from different areas have always been involved to reach this goal: from Neurologists to Psychiatrists, from Child Neuropsychiatrists to Pediatricians, from Internists to Pharmacologists, from Psychologists to General Physicians.

The “Open Minded” concept, a key aspect of society, is based on the cooperation between people of different backgrounds and the union of different strengths to reach common goals.

The round table that will be held on the first day also underlines the main topic of this Congress: after the WHO declaration regarding the impact of headache on the quality of life, it is now time to introduce the study and the practice of headaches in the daily routine of hospitals and the public health system, and recognize the special role in treating headaches, namely the chronics one, as part of the healthcare programme in reducing pain.

The different organizing models used by Headache Centres and Clinics will be discussed with institutional decision makers to try to include the headache disease in the list of diseases recognised by the Italian Health System, so as to overpass the “voluntary” role performed by headache doctors and acknowledge the professional medical figure of specialists in the treatment of headache.

The Scientific Committee has put together an exciting programme that will cover all aspects regarding headaches, from molecular genetics to recent advances in therapy. Of relevance, the space dedicated towards the integrated activities with other scientific Societies, such as, the Italian Society of Neuropsychopharmacology (SINPF), the Italian Society of Clinical Neurophysiology (SINC), and the Italian Society of Neurologic Rehabilitation (SIRN) whom promote clinical and scientific research with our Society.

The reading of these congress abstracts will improve our scientific knowledge and stimulate new research strategies.

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

Pharmacological and non pharmacological treatment

Clinical pharmacology of topiramate in migraine prophylaxis: efficacy and safety

A. Ferrari

Headache and Drug Abuse Inter-Department Research Centre, Division of Toxicology and Clinical Pharmacology, University of Modena and Reggio Emilia, Modena, Italy; e-mail: anna.ferrari@unimore.it

Topiramate is approved in antiepileptic therapy and for the prophylaxis of migraine in adult patients. This drug has different mechanisms of action. It modulates voltage-dependent Na⁺ channels, and it seems contemporarily to strengthen the activity of GABA (increasing post-synaptic currents of GABA-A receptors). Moreover, it would reduce the effects of the activation of glutamatergic AMPA/kainate receptor subtype. Topiramate is also a weak inhibitor of carbonic anhydrase, particularly of subtypes II and IV. However, the significant mechanism of action responsible for efficacy in migraine prophylaxis remains to be resolved.

Topiramate is well absorbed by the gastrointestinal tract. Its bioavailability is 80%. T_{max} after oral administration is 1.5–4 h, protein binding is 9 to 41%, V_d is 0.6–0.8 l/kg. It is scarcely metabolized in the liver, and between 55 and 97% of an oral dose is excreted unchanged in the urine, thus minimizing the risk of pharmacokinetic drug–drug interactions. Elimination half-life is 18–24 h. Topiramate is a mild inducer of CYP 3A4 and inhibits CYP 2C19. However, the only interaction observed as a result of induction by topiramate is with oral contraceptive steroids. This interaction occurs in high topiramate dosage (>200 mg/day).

There is scientific evidence that topiramate is effective in reducing migraine frequency at a dose of 100 mg/day in patients suffering from episodic migraine with or without aura. Topiramate also appears to be effective in the treatment of chronic migraine, even in patients overusing acute medications. Hence, it may not be necessary to withdraw patients from medication overuse prior to treatment with topiramate.

Topiramate is generally considered to be safe and well tolerated in migraine treatment. The most common adverse effects are paresthesia, fatigue, anorexia and nausea. Other side effects, probably dose-dependent, include cognitive symptoms such as difficulty with memory, concentration/attention or speech problems. Generally, adverse effects appear to be most pronounced at the beginning of topiramate treatment within the first 2 months and often resolve over time. Rare side effects of topiramate are depression, hallucinations or paranoia, and vision problems such as acute myopia with secondary closed-angle glaucoma. Topiramate treatment is associated with a tenfold increase in the risk of nephrolithiasis. One attractive effect of topiramate is weight loss in many patients. This effect is more evident in patients with a higher body mass index.

The treatment in migraine with optimising circadian cycles and behavioural insomnia

F. Foti¹, A. Bagalà¹, U. Cannistrà², R. Cuzzocrea³

¹Centro Salute Mentale, Palmi, Italy; ²U.O. Neurologia, Catanzaro, Italy; ³S.P.D.C., Melito Porto Salvo, Italy; e-mail: sidera@live.it

Introduction In individuals with migraine, sleep regulation may play an interesting role in headache management. Changes of chronobiological patterns have been identified in some forms of headache, and also in migraine. In headache clinic populations, insomnia is a common sleep disorder and is observed in half to two-thirds of migraineurs. Recent studies have shown that migraine improves by controlling sleep disorders. Practitioners for this reason are considering new strategies that restore sleep homeostasis as a possibility to improve and treat vulnerability to headache [1]. The use of effective drugs in the regularization of the sleep-wake cycle and moods have proven useful in treating some cases of migraine. Agomelatine is an antidepressant that works by stimulating receptors MT1 and MT2, usually triggered by melatonin and blocking 5-HT₂ receptors activated by serotonin. Therefore, this drug could present the requirements needed to be used for the two aspects.

Materials and methods Four migraine patients underwent a series of tests for the assessment of mood, sleep disturbance and simultaneously completed a headache diary before and after administration of agomelatine 25 mg/die for a period of 5 months.

Results Improvement of varying degree was recorded in all four patients.

Conclusions For its dual role in stabilising the sleep-wake cycle and mood, a treatment of agomelatine in four migraine patients has proved to be effective in reducing the number of migraine attacks with an overall improvement in psychological well-being.

References

1. Rains JC, Poceta JS, Penzien DB (2008) Sleep and headaches. *Curr Neurol Neurosci Rep* 8(2):167–175

Fibromyalgia and chronic tension-type headache: efficacy of antidepressants

S. Guerzoni, G. Sandri

Headache and Drug Abuse Inter-Department Research Centre, University of Modena and Reggio Emilia, Modena, Italy; e-mail: simona_guerzoni@libero.it

Fibromyalgia (FM) is a rheumatic disease with chronic pain often associated with chronic tension-type headache (CTTH), even if the relationship between these two diseases has not been completely clarified. Antidepressant drugs have been widely used without strong

scientific evidence of efficacy and without clear depressive symptoms.

The aim of this study was to evaluate efficacy and safety of some antidepressant drugs in patients suffering from FM and CTTH, to compare the clinical improvement with respect to both FM and CTTH symptoms [1].

Methods Thirty-eight patients visited by the Rheumatologic Clinic of the Modena University Hospital in the last 8 months suffering from FM and CTTH (2 males/36 females, aged 50 ± 9.6 years) were treated with fluoxetine (20–40 mg/day) or venlafaxine (75–150 mg/day) for almost 3 months. At starting time and after 12 weeks self-reporting questionnaires were administered for Fibromyalgia Impact Questionnaire (FIQ), and for headache evaluation (HIT-6 questionnaire) and the Beck Depression Inventory (BDI) for depression evaluation.

Results Thirteen (13/38) (34%) patients interrupted antidepressant assumption because of severe or intolerable side effects, or worsening of pain symptoms within the observation period. In the 25 patients who completed the treatment we recorded a significant reduction of FIQ (from 57.02 ± 14.56 – 49.98 ± 16.53 , $p = 0.026$) (t paired test), whereas only in half of these patients the improvement was clinically significant (score >12). Eighteen patients (18/38) (72%) showed a BDI score of ≥ 10 at starting time. After 12 weeks the global BDI was reduced from 24.11 ± 9.5 to 20.22 ± 10.9 , $p = 0.02$; with a clinical improvement of depression in eight cases (44%), whereas the FIQ remained unchanged. The HIT6 questionnaire was reduced from 65 ± 3.1 to 43 ± 6.3 [2].

Conclusions Treatment with antidepressant in FM and CTTH is active in reducing both depressive and non depressive symptoms, whereas the high number of side effects often reduces the compliance of these drugs.

References

1. Wang J, Liu X, Mullins CD (2011) Treatment adherence and persistence with duloxetine, venlafaxine XR, and escitalopram among patients with major depressive disorder and chronic pain-related diseases. *Curr Med Res Opin* 27(7):1303–1313. Epub 2011 May 12
2. Arnold LM, Hudson JI, Keck PE et al (2006) Comorbidity of fibromyalgia and psychiatric disorders. *J Clin Psychiatry* 67(8):1219–1225

Self-reported factors associated with the onset of chronic headache in patients developing medication-overuse headache and who successfully underwent detoxification

M. Allena¹, C. Tassorelli^{1,2}, G. Sandrini^{1,2}, G. Sances¹, G. Nappi^{1,3}, The Comoestas Consortium*

¹Headache Science Centre, IRCCS National Neurological Institute C. Mondino Foundation, University Consortium for Adaptive Disorders and Head Pain (UCADH), Pavia, Italy; ²University Consortium for the Study of Adaptive Disorder and Head Pain (UCADH), Pavia, Italy; ³Chair of Neurology, Sapienza University of Rome, Rome, Italy; e-mail: marta.allena@mondino.it

*F. Blandini, P. Rossi (Headache Science Centre, IRCCS National Neurological Institute C. Mondino Foundation, University Consortium for Adaptive Disorders and Head Pain, Pavia, Italy); R. Jensen, L. Bendtsen, S.B. Munksgaard (Region Hovedstaden, Glostrup Amtssygehuset); M. Lainez, B. Lopez (Fundación de la Comunidad Valenciana para la Investigación Biomédica, la Docencia y la Cooperación Internacional y para el Desarrollo del Hospital Clínico Universitario de Valencia, Spain); Z. Katsarava,

M. Rapsch (Universitätsklinikum Essen, Germany); J.A. Leston, M.T. Goicochea, D. Cerquetti (Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia, Buenos Aires, Argentina); R. Fadic, B. Shand (Pontificia Universidad Católica de Chile, Santiago, Chile); M. Pagani, A. Stoppini (CBIM); S. Spadafora, M. Osa (Isalud)

Migraine or tension-type headache progression from episodic to chronic pattern is realized through a period of time of several months or years, during which an increase of attack frequency occurs.

Medication-overuse headache (MOH) results from the chronification of these primary forms of headaches, as a consequence of the progressive increase in the intake of symptomatic drugs.

The process of transformation from episodic to chronic forms is complex and involves multiple risk factors.

The present survey was performed within the COMOESTAS project [1] (a multicentre study conducted in the last 3 years) to evaluate MOH patients self-reported factors/events associated with the onset of their chronic headache.

At the baseline visit, the clinical interview provided detailed data on headache history; a specific section was focused on the identification of risk factors for developing MOH, including lifestyle parameters, psychiatric comorbidities, type of acute drug used for preliminary episodic headache. Patients were also asked to individualise self-reported possible factors influencing their headache pattern through a list of proposed agents: stressful events at home or at work, head or neck traumas, menopause, undergoing surgery, hypertension, intake of oral contraceptive or hormone replacement therapy (HRT).

Of 529 eligible subjects, 495 patients (392 females and 103 males) with episodic pattern and without drug overuse in the 6 months after the withdrawal phase were included. Mean age of primary headache onset was 18.2 ± 9.6 years, while mean duration of chronic headache and of drug overuse were 5.25 ± 6.8 years and 4.5 ± 5.9 , respectively.

Stressful events were reported by 30.7% of patients as factors that are subjectively associated with chronification. In decreasing order, patients identified neck traumas (4.7%), menopause (2.2%), undergoing surgery (1%), hypertension (0.6%) and others (i.e., intake of oral contraceptive, 2.2%) as factors influencing their headache pattern.

Quite surprisingly the majority of patients (nearly 58%) failed to identify any possible factor associated with the worsening of the disease. Chronification of primary headache is complex and involves multiple risk factors, whose identification should halt the progression of the disease. Moreover, from the preliminary evaluation of data we can infer that for MOH patients the subjective identification is not often easy. Appropriate training and education of these patients is needed to enhance knowledge and to improve over time the management and the outcome of this disabling disorder.

References

1. COMOESTAS Project, EC contract number 215366 (COMOESTAS) FP7—Thematic priority ICT

Developmental age: headaches in neurology and psychiatry

Neurobiological aspects of migraine in childhood and adolescence

D. De Carlo, S. Sartori, I. Toldo, P.A. Battistella

Juvenile Headache Centre, University of Padua, Padua, Italy; e-mail: pierantonio.battistella@unipd.it

Migraine (M) is a common neurologic disorder but the exact mechanism of the process remains elusive. There have been major advances in the scientific understanding of the pathophysiological mechanism of M even if neurobiological basis of M at the molecular level is uncertain. Pathophysiological hypotheses have been formulated within a limited number of paradigms, notably the vascular, neurogenic, neurotransmitter, and genetic/molecular biological paradigm [1].

The efforts performed to reconcile the vascular and the neurological hypotheses led to the modern, integrated view of M as a “neuro-vascular” disorder; in this context, a major pathogenetic step is thought to be the release of inflammatory factors. Many mediators, such as nitric oxide, serotonin, histamine and calcitonin gene-related peptide, have been identified as targets toward which M-specific therapy is directed [2].

M aura is indicative of a reversible cerebral cortical dysfunction that is most probably caused by cortical spreading depression (CSD) that activates the trigeminovascular system in animals [1]. An increased neuronal excitability and reduction of CSD are demonstrated by extensive studies of cellular and animal models with mutation for familial hemiplegic migraine (FHM). Interestingly electrophysiological studies have been performed in a few patients with FHM, showing an increased habituation of visual-evoked potentials and nociception-specific blink reflexes, whereas a deficient habituation has been found in patients with M.

The role of genetics in the mechanism of M is increasing and in most cases M occurs as a multifactorial inherited character. Some authors recently suggested that M may be a channelopathy involving mainly calcium channels; in particular, a “genetic basis” has been demonstrated for hemiplegic M in which mutation of the ion transportation genes CACNA1A, ATP1A2 and SCN1A have been documented [1]. Neuronal hyperexcitability and abnormal glutamate metabolism might have pivotal roles not only in FHM but also in common type M: a susceptibility locus for M has been recently located between two genes regulating glutamate concentrations in the brain; moreover, mutations in KCNK18, gene encoding for a potassium channel, has been associated with M with aura in one family. Conversely, comorbidity between M and other disorders such as epilepsy, psychiatric illnesses or hypercoagulability represent an interesting phenomenon and may result from different mutations in the same gene or mutations in genes located in neighbouring segments in the same chromosome.

Future research is needed to better understand and recognise the mechanisms involved in the genesis of the headache in the paediatric age.

References

1. Tfelt-Hansen PC, Koehler PJ (2011) One hundred years of migraine research: major clinical and scientific observations from 1910 to 2010. *Headache* 51(5):752–778
2. Gupta S, Nahas SJ, Peterlin BL (2011) Chemical mediators of migraine: preclinical and clinical observations. *Headache* 51(6):1029–1045

Headache in children victims of earthquake: new symptom or risk factor to posttraumatic stress disorder?

E. Tozzi, E. Sechi, L. Mattei, I. Ciancarelli

Centro Regionale Diagnosi e Terapia delle Cefalee, Ambulatorio Età Evolutiva, U.O.C. Neuropsichiatria Infantile, Clinica Neurologica, Università di L'Aquila, L'Aquila, Italy;
e-mail: elisabetta.tozzialleva@univaq.it

It has long been known that stress is a trigger factor of the headache attack. It is not always clear if the trigger factor is like or a causative factor of one type of secondary headache. The headache attributed to posttraumatic stress disorder (PTSD) is reported in the ICHD-II classification in the appendix at point 12.9. Epidemiological data are interesting and there are differences among various traumas (child abuse, hospitalization, natural catastrophes) [1, 2]. Also, it is known that psychiatric disorders in childhood headache have been referred by several Authors in over 60–70% of patients.

Objective The aim of this study was to verify if headache, diagnosed in children admitted to our Headache Centre before the 2009 earthquake of L'Aquila, changed in relation to the trauma of the earthquake. The patients were recruited chronologically and consisted of 76 patients (30 males and 46 females) aged 6–18 years. The children lived in the epicentre of the earthquake. The diagnosis of headache was made according to the ICHD-II (2004) criteria. We used the following tests: UCLA PTSD test (child, adolescent and parent form), Migraine Disability Assessment Questionnaire (Ped-Midas) and the drawing test.

RESULTS Migraine without aura (MO) was diagnosed in 62% of patients, tension-type headache (TTH) in 20%, and chronic daily headache (CDH) in 18%.

On the basis of Ped-Midas 18% of patients suffered from minimal headache, 37% light headache, 39% moderate headache, and 6% severe headaches. The patients were re-examined after 1 year from the earthquake: 39% of patients showed worsening of symptoms (79% migraineurs), 25% showed severe worsening (100% migraineurs), and 25% improvement of headache (80% CDH) during the 4–6 months after the earthquake. The PTSD was diagnosed as partial in 65% and was not present in 25%. There was no correlation between UCLA test and Ped-Midas.

Conclusions Headache is conditioned by intrinsic and environmental factors. Family stress is the most important factor in headache modification.

References

1. Feldman JM, Ortega AN, Koinis-Mitchell D et al (2010) Child and family psychiatric and psychological factors associated with child physical health problems: results from the Boricua youth study. *J Nerv Ment Dis* 198(4):272–279
2. Sechi E (2010) Atti del seminario: Progetto terra, ambiente bambino. L'Aquila, ottobre

Headache and alexithymia

B. Bellini¹, A. Cescut², G. Manfrini², V. Guidetti¹

¹Department of Paediatrics and Child and Adolescent Neuropsychiatry, Faculty of Medicine and Odontoiatrics, Sapienza University of Rome, Rome, Italy; ²Department of Psychology, Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy; e-mail: vincenzo.guidetti@uniroma1.it

Introduction Alexithymia is known as the difficulty in identifying, describing and communicating emotions, in distinguishing between emotional experiences and physiological arousal of emotion; it is characterised as a poverty of the imaginative processes, of the cognitive orientation directed towards external reality. It is possible to search for the determining functions of alexithymia and its impact on the state of illness and somatic disorder in the failure or partial acquisition of symbolic capacities and the ability to mentalize experiences assigned to the vicissitudes of the early mother–child relationship whose disregulating effect manifests itself in terms of biological subsystems, in an altered relationship between diverse

chemical systems of diverse autonomous systems (organic disease). Alexithymic tendencies may be exacerbated by traumatic experiences occurring in childhood and can be transmitted to the child essentially as a genetic endowment, but they presumably are also reflected in the child's family atmosphere.

Materials and methods The study compared the scores of four groups: adolescents with headache (AC), their mothers (MC), healthy adolescents (AS), and their mothers (MS). The measures for alexithymia were obtained with TAS-20, while the areas of psychological functioning of the participants were investigated through SCL-90.

Results No significant differences were found, although the mean scores of TAS-20 reported by adolescents headache (AC) were greater than that of adolescents in the control group (AS). Conversely, the mothers of the clinical sample (MC) had lower scores than the mothers of healthy adolescents (MS).

Discussion The results of the work appear to be inconsistent with the evidence coming from studies in adults: Wise et al (1994) compared 100 adult patients affected by migraine and headache tension with a control group of healthy individuals and found that the former demonstrated significantly higher scores of alexithymia, with no differences between the patients with headache tension and those with migraines, while in a study conducted by Yucel et al (2002) on 105 individuals affected with episodic or chronic headache tension between the ages of 18 and 65, further evidence of the significance of the correlation between alexithymia and headaches was found [1, 2].

Conclusions Based on current research it seems that it is not yet clear what the relationship is between alexithymia and headaches in children, also because there are no studies regarding this age group. The results of this study can not be definitive, but should serve as a starting point for further research.

References

1. Wise TN, Mann LS, Jani N et al (1994) Illness beliefs and alexithymia in headache patients. *Headache* 34(6):362–365
2. Yucel B, Kora K, Oezdemir O et al (2002) Depression, automatic thoughts, alexithymia and assertiveness in patient with tension-type headache. *Headache* 42(3):194–199

Spatial attention in migraine children depends on pain characteristics

E. Iacovelli^{1,2}, S. Tarantino¹, C. Vollono¹, A. Capuano¹, C. Casciani¹, F. Vigeveno¹, M. Valeriani^{1,3}

¹Headache Centre, Division of Neurology, Ospedale Bambino Gesù, IRCCS, Rome, Italy; ²Department of Medical-surgical Sciences and Biotechnology, Neurology Section, Sapienza University of Rome, Rome, Italy; ³Centre for Sensory-Motor Interaction, Aalborg University, Aalborg, Denmark; e-mail: elisa_iaco@yahoo.it

Introduction Different physiopathological mechanisms are supposed to work in migraineurs with either imploding or exploding pain. Previous studies demonstrated that tactile-spatial attention modulates the somatosensory N140 component, with increased N140 amplitude for tactile stimuli delivered to the attended hand. The aims of the study were: (1) to evaluate whether migraine children with imploding or exploding pain are different in spatial attention performances assessed with a neuropsychological test for spatial attention; and (2) to investigate the effect of spatial attention on the N140 amplitude in migraine children with imploding or exploding pain.

Methods We studied 11 migraineurs with imploding pain (mean age 11.5 ± 1.5 years) and 9 migraine children with exploding pain (mean

age 11.3 ± 1.7 years). “Deux Barrage” test for spatial attention was administered. Somatosensory evoked potentials (SEPs) to median nerve stimulation were recorded from 31 scalp electrodes in a neutral condition (NC) and in a spatial attention condition (SAC: the subjects had to count tactile stimuli delivered on the stimulated hand).

Results The mean value regarding the R1 of “Deux Barrage” indexes was significantly higher in imploding than in exploding patients. The N140 amplitude increased during SAC, as compared to NC, was significantly higher in patients with imploding than in patients with exploding pain.

Discussion In our study, migraineurs with imploding pain showed a significantly worse performance in “Deux Barrage” test and a higher N140 amplitude increase during SAC, as compared to patients with exploding pain. This suggests not only that spatial attention performances are different between the groups, but also that the brain mechanisms subserving spatial attention are different between imploding and exploding pain patients.

Conclusions Our findings support the possibility that different migraine phenotypes correspond to different diseases.

Which is the true prevalence of primary headaches in childhood?

C. Termine¹, C. Luoni¹, T. Carigi², M. De Simone², S. Crugnola¹, U. Balottin^{2,3}

¹Child Neuropsychiatry Unit, Department of Experimental Medicine, University of Insubria, Varese, Italy; ²Department of Child Neurology and Psychiatry, IRCCS C. Mondino National Institute of Neurology Foundation, Pavia, Italy; ³University Consortium for Adaptive Disorders and Headache (UCADH), University of Pavia, Pavia, Italy; e-mail: cristiano.termine@uninsubria.it

Introduction Prevalence of recurrent headache in the literature is changeable varying from 4 to 20% in pre-school age, to 57–82% at 15: the data vary in accordance with the diagnostic criteria, the methodology and the sources of detection. Therefore, we assessed the concordance between mothers and children reporting the characteristics and the frequency of headache, by the compilation of an anamnestic questionnaire.

Method We recruited a non-clinical sample made up of 425 children (average age 9.58 ± 0.2). The questionnaire given to the children was carried out individually by a clinical expert, while the mothers answered the questionnaire independently.

Results The children related more frequently than their mothers to having had in the past at least one episode of headache (68.7 vs. 52.4%, $k = 0.01$). For all parameters in this group of subjects, the degree of concordance resulted “poor” ($0.001 < k < 0.20$) or “moderate” ($0.21 < k < 0.40$). Similar correlation values were recognised considering the subgroup of children with recurrent headache.

Conclusions The low correlation obtained between mothers and children regarding the prevalence of headache and its features, leads to consider that the compilation of a questionnaire by a single detector should not lead to an appropriate estimate of the prevalence of headache, or to a precise description of its features. These results just partially explain the high variability of the prevalence estimates of headache. Considering our results, an “ideal” epidemiological instrument should supply the information received by the children and their mothers, thus allowing for a better estimate of the prevalence of headache in childhood and adolescence.

Juvenile migraine and the role of the autonomic system: a preliminary clinical study

V. Raieli¹, F. Brighina², F. Consolo¹, M. D'Amelio², G. Giordano¹, M. Moscarelli², L. Paziente¹, M. Saladino¹, G. Santangelo¹, C. Spitaleri¹, E. Vanadia¹, F. Vanadia¹

¹Child Neuropsychiatry Unit, Di Cristina Hospital, ARNAS Civico, Palermo, Italy; ²Department of Experimental Biomedicine and Clinical Neurosciences, University of Palermo, Palermo, Italy; e-mail: vraieli@libero.it

Background and objectives Recent studies suggest a role of the autonomic nervous system in paediatric migraine by the involvement of the trigemino-autonomic reflex. In addition Cranial Autonomic Symptoms (CAS) are frequently reported in adult migraineurs, but the prevalence of CAS in children affected by primary headaches is unknown. Aims of this study were to evaluate the prevalence of CAS during headache attacks in a juvenile population with primary headaches and in order to better understand the relationship between the autonomic system and migraine, to study the relationship between CAS and main migraine symptoms. Finally, to evaluate the General Autonomic Symptoms (GAS) by measuring the frequency of hyperactivity of the vegetative system in a paediatric migraine population with CAS. **Methods** A short questionnaire investigating the presence of CAS was administered to all children. The following CAS were included in our study: conjunctival injection, tearing, eyelid oedema, nasal congestion, rhinorrhoea, red ear, facial flushing, miosis, ptosis, forehead or facial sweating. We also evaluated, in a sample of 24 migraineurs CAS+ (8 males, age range 7–18 years), the frequency of the following GAS over a period of 3 months: orthostatic lightheadedness, dizziness; vasomotor, secretomotor and postprandial symptoms; abdominal pain, cramping, autonomic diarrhoea, obstinate constipation, bladder involvement (incontinence, incomplete emptying), sexual problems, visual and sleep disorders.

Results A total of 110 children suffering from headache (M 46, F 64, aged 4–17 years) were consecutively enrolled during a 6-month period. Ninety-four children (85%) were affected by migraine. The remaining 16 children (15%) were affected by other primary headaches. CAS were significantly more frequent in migraineurs (58/94, 61.7%) compared to non-migraineurs (2/16, 12.50%) ($p < 0.001$). Two or more CAS were found in forty-three (75%) children suffering from migraine with CAS+ during their attacks. The most common signs were flushing, red ear and conjunctival injection. GAS were present in 22 patients (92%) of our sample. Vasomotor (54%) and sleep disorders (54%) were the most frequent.

Conclusions These preliminary findings indicate that CAS are rather common in the course of paediatric migraine attacks and most paediatric migraineurs with CAS also show GAS. These results support the role of the trigemino-autonomic reflex in the pathophysiology of migraine, especially in a subpopulation.

Hot topics in the pathophysiology of headaches

New mutation in ATP1A2 gene in a family with comorbidity of migraine with aura and epilepsy

C. Costa^{1,2}, P. Prontera³, S. Caproni¹, F. Galletti¹, I. Corbelli¹, S. Siliquini¹, P. Sarchielli¹, E. Donti³, P. Calabresi^{1,2}

¹Clinica Neurologica, Università di Perugia, Ospedale S. Maria della Misericordia, Perugia, Italy; ²Fondazione Santa Lucia, IRCCS,

Rome, Italy; ³Sezione di Genetica Medica, Dipartimento di Medicina Clinica e Sperimentale, Azienda Ospedaliera e Università di Perugia, Perugia, Italy; e-mail: costa@unipg.it

Introduction Several epidemiological studies pointed out the association between migraine and epilepsy, with an increased prevalence of migraine in epileptic patients, and vice versa [1]. Migraine and epilepsy share some common pathogenic pathways related to the dysfunction of ionic channels; therefore, it might be hypothesized that channelopathy could be the common background for these disorders, when in comorbidity [2]. The aim of this study was to evaluate a family affected by hemiplegic migraine and epilepsy (febrile seizures and complex partial crisis), assessing the potential role of the ATP1A2 gene.

Methods We isolated the Genomic DNA in the peripheral blood of five patients according to standard methods using Wizard® Genomic DNA purification kit (Promega Corp., Madison, WI, USA). All ATP1A2 gene exons were amplified through PCR, and directly sequenced using an ABI 3100 analyser (Applied Biosystems, Courtaboeuf, France).

Results The 22-year-old proband had febrile seizures at the age of 2. At the age of 19, after suffering head traumas without concussion, he presented two episodes of migraine with aura with right hemiparesis fulfilling the criteria of hemiplegic migraine. All his relatives are affected by migraine with aura, particularly the grandmother, one uncle, and a cousin, who are affected by hemiplegic migraine. The uncle also presented some complex partial crises when he was 11 and 12 years old, and was treated with fenobarbital.

The genetic analysis of the whole family pointed out a heterozygous nucleotide variation of exon 19, leading to Guanine-to-Adenine substitution in place 2620 (c.2620G>A). This variation, determining a Glycine-to-Serine substitution in place 874 (p.Gly874Ser), was not found in 100 healthy controls and was not described in Single Nucleotide Polymorphism or Ensembl databases. Furthermore, its pathogenic role is supported by both the segregation with the disease, and the extracellular domain (amino acids 864–915) of the substitution, in which other missense mutations responsible for familial hemiplegic migraine type-2 were previously described.

Discussion and conclusions The present study provides further evidence of the involvement of ATP1A2 mutations in both migraine and epilepsy, underlying the importance of genetic analysis in families with a comorbidity of both disorders. The genetic analysis could be relevant for the treatment, because of the use of several antiepileptic drugs in migraine prophylaxis, and for pathogenetic purposes, increasing the knowledge on the potential causes of both disorders.

References

1. Haut SR, Bigal ME, Lipton RB (2006) Chronic disorders with episodic manifestations: focus on epilepsy and migraine. *Lancet Neurol* 5:148–157
2. Rogawski MA (2008) Common pathophysiologic mechanisms in migraine and epilepsy. *Arch Neurol* 65:709–714

Allogenic effects of CGRP depends on trigeminal-vascular system activation: results from an *in vivo* experimental model of nitroglycerin-induced sensitization in rat

A. Capuano¹, A. De Corato², M.C. Greco², M. Valeriani¹, P. Navarra², G. Tringali²

¹Department of Neuroscience, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; ²Institute of Pharmacology, Catholic University School of Medicine, Rome, Italy; e-mail: alessandro.capuano@opbg.net

Background CGRP is thought to be a key peptide in migraine and several mechanisms in migraine are mediated by CGRP. However, different evidence pointed out that CGRP is not algogenic per se while CGRP mediates pain in migraine when the trigemino-vascular system is sensitized. Aim of our study was to investigate CGRP-evoked behaviour in NO sensitized rats using a well-established experimental model of nitroglycerin induced sensitization of the trigeminal system [1].

Methods Male Wistar rats were used in this study. CGRP or saline, as control vehicle, were injected into rat whiskerpad and rat face rubbing was recorded for 1 h following injection. Recording time was divided into 5 min blocks and the number of seconds that the animals spend rubbing the injected area with the ipsilateral fore- or hindpaw was recorded for each block. Furthermore, rubbing behaviour was evaluated at different time-points after intraperitoneal injection of nitroglycerin or saline (controls). Additional experiments were performed to investigate CGRP content in different rat cerebral areas following nitroglycerin injection at different time-points. Finally, light aversion behaviour was investigated in rats treated with CGRP; animals previously treated or not, received NO donor injection. CGRP was measured by radioimmunological assay.

Results CGRP locally injected into the rat whiskerpad did not induce face rubbing behaviour significantly different from the control group. However, CGRP injected into the rat whiskerpad of animals previously treated with nitroglycerin at 10 mg/kg induced a significant face rubbing behaviour. The observed effect was time-dependent after nitroglycerin injection, reaching the maximum at 4 h. Nitroglycerin treated animals did not show any rubbing behaviour after locally injected saline (positive controls). Elevated CGRP content was found in the trigeminal ganglia, in the brainstem and, although in a small amount, also in the hippocampus and the hypothalamus after nitroglycerin injection in a time-dependent manner.

In the light–dark paradigm we found that rats treated with nitroglycerin showed a time-dependent light aversive behaviour, that was increased in CGRP treated rats.

Conclusions Our data demonstrated that CGRP induces a painful behaviour in rats only after sensitization of the trigeminal system was induced by NO donor, nitroglycerin. Furthermore, we demonstrated that light aversion, resembling photophobia in migraine, is dependent on trigeminal system activation and is mediated, at least in part, by CGRP action. Moreover, we confirm that genetic, as well as acquired predisposition to trigemino-vascular activation, is the neurobiological basis of CGRP effects in migraineurs.

References

1. Buzzi MG, Tassorelli C (2010) Experimental models of migraine. *Handb Clin Neurol* 97:109–123

Effect of placebo on pain perception and laser evoked potentials in migraine without aura patients

E. Vecchio, C. Serpino, V. De Vito Francesco, K. Ricci, M. de Tommaso

Department of Neurological Sciences, Neuropsychopathology of Pain, University of Bari, Bari, Italy; e-mail: eleonora.vecchio@gmail.com

Introduction Placebo analgesia has been shown to be driven by expectations of treatment effects. Both pharmacological and non pharmacological acute and preventive approaches to migraine seem to be partly supported by placebo effect [1].

We aimed to evaluate the effect of verbal suggestion on the pain perception and brain potentials induced by painful laser stimuli [2] in a cohort of migraine without aura patients compared to age and sex matched controls.

Materials and methods Thirty asymptomatic migraine without aura patients and twenty controls were evaluated by high density (65 channels) laser evoked potentials. Laser stimulus duration was 30 ms. After a basal recording obtained by supra-pain threshold laser intensity, stimuli were delivered on the right hand and the right supraorbital zone after a verbal warning of no pain or strong pain, leaving unchanged the laser intensity. All patients were also submitted to anxiety and depression evaluation by means of Zung scales, MIDAS and allodynia scores. Fifteen patients underwent preventive treatment for migraine, and were clinically evaluated after 2 months therapy.

Results In control subjects, the warning of strong versus no pain caused, respectively, an increase vs a reduction of pain rating and P2 amplitude. In migraine without aura, there was a significant opposite effect on the P2 component, which appeared increased after the no pain warning, especially when the trigeminal zone was stimulated. LORETA analysis revealed a significant increase in the dipole strength at the anterior cingulate and left orbitofrontal levels in migraine patients during the no pain condition. The increase of P2 amplitude in the no pain condition, was positively correlated with frequency of headache and anxiety levels, and showed a negative correlation with the outcome of headache frequency after 2 months preventive treatment follow-up.

Conclusions In migraine patients, the cortical elaboration of pain seemed not to be conditioned by verbal suggestion. The cortical zones involved in orienting attention toward a salient painful stimulus increased their activation after the warning of reduced stimulus intensity. This rigid pattern of pain-related cortical hyper-attention appeared as a negative feature for migraine severity outcome.

References

1. de Tommaso M, Sardaro M, Vecchio E et al (2008) Central sensitisation phenomena in primary headaches: overview of a preventive therapeutic approach. *CNS Neurol Disord Drug Targets* 7(6):524–535
2. de Tommaso M, Difruscolo O, Sardaro M et al (2007) Effects of remote cutaneous pain on trigeminal laser-evoked potentials in migraine patients. *J Headache Pain* 8(3):167–174

Role of cannabinoid receptors in hyperalgesia induced by nitroglycerin: study in animal model of migraine

C. Tassorelli^{1,2}, R. Greco¹, A.S. Mangione¹, G. Levandis¹, G. Sandrini^{1,2}, G. Nappi^{1,2}

¹Headache Science Centre, IRCCS National Neurological Institute C. Mondino Foundation Pavia, Italy; ²University Consortium for the Study of Adaptive Disorder and Headache (UCADH), University of Pavia, Pavia, Italy; e-mail: cristina.tassorelli@mondino.it

Experimental animal models exploring the effects of nociceptive activation of the trigemino-vascular system and aimed to understand the pathophysiology of migraine have suggested the existence of several interactions between the endocannabinoid system and pain mediation in migraine. Extensive evidence has demonstrated a role for the CB(1) receptor in the antinociception. However, recent research suggests that also CB(2) receptors, especially located outside the central nervous system (CNS), play a role in the perception of pain. In this study we evaluated the role of cannabinoid receptors in a

well-known animal model of migraine based on the hyperalgesia induced by nitroglycerin administration at the tail flick. The test was performed in male Sprague–Dawley rats that were pre-treated with nitroglycerin (10 mg/kg, i.p.) or saline (4 h before) and treated with CB1 antagonist (AM251, 4 mg/kg i.p.) or CB2 agonist (AM1241, 4 mg/kg, i.p) 60 min before the experimental tests. The findings have shown that both molecules have a significant analgesic effect in baseline conditions. While, CB1 antagonist abolished nitroglycerin-induced hyperalgesia at the tail flick test, administration of CB2 agonist did not show any analgesic effect. These findings demonstrate that CB1 receptor antagonist at high doses can have analgesic effects in both baseline condition and nitroglycerin-induced hyperalgesia. While, CB2 receptor agonist at the same dose has an analgesic effect only in baseline conditions. The data suggest that pharmacological manipulation of the CB1 receptor may have therapeutic potential in the treatment of migraine.

Polymorphisms in the proinflammatory cytokine genes and response to NSAIDs in migraine attacks

E. Rubino, S. Gallone, P. Fenoglio, P. De Martino, E. Negro, L. Savi, L. Pinessi, I. Rainero

Neurology II, Headache Centre, Department of Neuroscience, University of Turin, Turin, Italy; e-mail: elisarubino@inwind.it

Introduction Migraine is a common neurovascular disorder in which genetic and environmental factors interact. At present, frontline therapies in the acute treatment of migraine include NSAIDs and triptans. Nevertheless, a significant portion of treated patients do not obtain consistent pain relief. Pharmacogenetics bears great promise in optimization of individual specific therapy and providing new targets for drug development [1]. Several studies suggested a role for pro-inflammatory cytokines in the pathophysiology of migraine attack. TNF- α and IL-6 concentrations in the jugular venous blood are significantly increased in the first 2 h after attack onset [2]. The aim of this study was to investigate whether functional polymorphisms in the IL-1 family (IL-1 α , IL-1 β and IL-1RN), IL-6 and TNF- α genes may influence the response to oral NSAIDs administration during migraine attacks.

Materials and methods A group of 290 consecutive patients (82 men, 208 women) with episodic migraine without aura (ICHD-II criteria) were involved in the study. In the first visit, migraineurs were prescribed NSAIDs and were given a diary in order to record the clinical response in three consecutive migraine attacks. A positive response was defined by having a decrease of ≥ 2 points in a 4-point scale intensity of pain, after 120 min NSAIDs administration, in at least two attacks.

Patients were genotyped for functional polymorphisms in the following genes: IL-1 α (−889 C > T), IL-1 β (−511 C > T), IL-1 β (+3,953 C > T), IL-1RN (VNTR), IL-6 and TNF- α (−308 G > A). Statistical analyses were performed using SVS version 7 and SPSS version 18.

Results Migraine patients carrying the A allele of the TNF- α promoter −308 A/G polymorphism showed a significant association with a lack of efficacy after NSAIDs administration in migraine attacks compared to the G allele ($p < 0.01$, OR 2.74, 95% CI 1.19 < OR < 6.29). Remaining polymorphisms had no significant effect on the response to NSAIDs administration in acute migraine attacks.

Discussion Our study showed that a functional polymorphism in the TNF- α gene significantly modulates the clinical response to NSAIDs administration in acute migraine attacks. Patients with a higher

production of the active cytokine during stress showed a significantly lower anti-migraine effect. Our results support a role for TNF- α in the pathophysiological mechanisms of migraine attack.

Conclusions To the best of our knowledge this is the first study that examined the influence of proinflammatory cytokine genes on clinical response to NSAIDs in migraine attack. Further investigations are needed to clarify the underlying neurobiological mechanisms and the potential pharmacogenetic perspectives.

References

1. Ophoff RA, van den Maagdenberg AM, Roon KI et al (2001) Molecular mechanisms of migraine: prospects for pharmacogenomics. *Eur J Pharmacol* 413:1–10
2. Sarchielli P, Alberti A, Baldi A et al (2006) Proinflammatory cytokines, adhesion molecules, and lymphocyte integrin expression in the internal jugular blood of migraine patients without aura assessed ictally. *Headache* 46:200–207

Comorbidity

Cluster headache: a clinical and neuropsychological study in 132 patients

M.P. Prudeniano, M. Rossi, L. Merico, G. Monopoli, I. Sharra, S. Genco, P. Lamberti, P. Livrea

Headache Centre, Neurological Clinic L. Amaducci, University of Bari, Bari, Italy; e-mail: m.p.prudeniano@neurol.uniba.it

Introduction Cluster headache is a primary headache which can be considered rare if compared to migraine and tension-type headache. Its rarity as well as its peculiar course characterised by silent periods alternating with active periods, are probably the main causes of misdiagnosis and delayed diagnosis. Data in the literature concerning the neuropsychological features of this form of headache are lacking. Also the quality of life of cluster headache sufferers needs further studies. The goal of this study was to examine a sample of cluster headache patients referring to a tertiary centre to obtain information on clinical features, neuropsychological aspects and quality of life.

Patients and methods One hundred and thirty-two patients referring to the Headache Centre of the Neurological Clinic “L. Amaducci”, Bari, and receiving the diagnosis of cluster headache according to the ICHD-II criteria [1] were examined. A detailed clinical history was collected. Patients underwent a general and neurological examination. A sample of them underwent the administration of: the MINI psychiatric interview, the Zung Anxiety and Depression Scales, the SCL90R and the SF36. Data were analysed by means of SPSS.

Results More than 90% of cluster headache patients resulted to be affected by an episodic form. The male/female ratio was 7:1. Less than 10% of patients showed an alternating side of pain. Onset age was significantly lower in females than in males. Patients with episodic cluster headache showed a lower onset age than patients with a chronic form. There was a latency of about 10 years between the age of onset and the time of diagnosis. Anxiety was the most frequent disorder found by the MINI interview. The Zung Scales and the SCL90R confirmed a higher prevalence of anxiety than of depressive symptoms. The results of SF36 indicated limitations in both physical and psychical domains with more severe levels in the female group and in chronic cluster headache patients.

Discussion The findings of this study are in agreement with the data in the literature concerning the epidemiology and the clinic features of cluster headache. The delay of about 10 years between the headache onset and the diagnosis indicates the need for widespread

educational programmes directed towards both health workers and the general population. The diffusion of knowledge concerning cluster headache could allow for an early diagnosis and an appropriate management programme, thus improving the state of health and the quality of life of the patients suffering from this highly disabling form of headache.

References

1. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd edn. Cephalalgia 24[Suppl 1]:1–160

Comorbid sleep disorders and migraine clinical presentation: the role of restless legs syndrome

S. Gori, C. Lucchesi, E. Bonanni, L. Murri

Department of Neuroscience, Institute of Neurology, University of Pisa, Pisa, Italy; e-mail: s.gori@med.unipi.it

Introduction The relationship between migraine and sleep is complex and pluridirectional; migraine attacks can preferentially emerge at night time causing awakenings, with subsequent sleep disruption, and sleep disorders are more frequently reported in migraine patients compared to the general population.

An association between migraine and restless legs syndrome (RLS), with a higher prevalence of RLS in migraine patients compared to healthy subjects has been documented in a limited number of studies.

Objective The objective of this study was to assess the prevalence of RLS in a population of migraine patients and to evaluate its possible role on phenotypical expression of migraine, i.e., its possible association with a preferential occurrence of attacks at night time or early morning.

Materials and methods We enrolled 163 consecutive patients (129 women and 34 males, aged 18–77 years) at the Headache Centre of the University of Pisa; patients fulfilled IHS criteria (2004) for the diagnosis of migraine with or without aura. RLS was diagnosed according to the criteria of the International Restless Legs Syndrome Study Group (2003). Patients were divided into three groups according to the preferential occurrence of attacks during the day or at night time-early morning; in particular, patients were defined as “nocturnal-early morning subtype” (at least 75% of migraine attacks occurring at night time/early-morning), “diurnal subtype” (at least 75% of attacks started during the day) and “indifferent subtype” without a preferential emergence of attacks during day or night.

Results and conclusions RLS was diagnosed in 37 migraineurs (22.6%). Migraine patients with RLS showed predominantly a “nocturnal-early morning subtype”, followed by “indifferent subtype” and only a small group showed a “diurnal subtype”.

Restless legs syndrome and migraine are frequently comorbid conditions, especially in patients presenting a preferential occurrence of attacks at night time-early morning. These data emphasise that sleep disorders must be assessed in migraine patients, especially in those presenting a prevalence of nocturnal-awakening attacks, since such an association provides both therapeutic and prognostic implications. Comorbidity between migraine and restless legs syndrome has, indeed, important therapeutic consequences; if both conditions are present, drugs such as gabapentin and pregabalin, should be used as first choice treatment, for both conditions, whereas antidepressant drugs should be, as much as possible, avoided. Moreover, the adequate treatment of comorbid sleep disorders might play a role to prevent the possible transformation from episodic to chronic migraine.

Insulin resistance and migraine: results from a case-control study

S. Sacco, E. Altobelli, F. De Angelis, A. Casalena, A. Carolei

Regional Headache Referral Centre and Department of Neurology, University of L'Aquila, L'Aquila, Italy; e-mail: simona.sacco@cc.univaq.it

Introduction Migraine, and particularly migraine with aura, has emerged as a risk factor for cardiovascular diseases; mechanisms leading to the association are still unclear. Moreover, several studies have demonstrated an adverse cardiovascular risk profile for migraineurs with respect to non-migraineurs including high body-mass index (BMI). Insulin resistance (IR) is a condition in which insulin is less effective in lowering blood glucose; it is present in patients with diabetes mellitus and also in non-diabetic subjects. IR, even in the absence of diabetes mellitus, is an emerging risk factor for cardiovascular disease and analysis of data regarding the association between migraine and IR is conflicting. Aim of the present study was to evaluate the association of migraine and its subtypes with IR.

Methods Consecutive subjects with migraine referring to our Centre and diagnosed, according to the ICHD-II criteria, were included. For each subject a matched control was selected among patients admitted to our hospital for traumatic injuries. Exclusion criteria were represented by diabetes mellitus, BMI > 35, history of overt cardiovascular diseases, and usage of drugs interfering with glucose metabolism. IR was calculated by means of the homeostatic model assessment (HOMA) using a blood sample obtained in the morning after an overnight fasting. Data referring to comorbid risk factors and anthropometric measures were also collected. Informed consent to participate in the study was obtained from each subject. Comparisons were performed by Student's *t* test or χ^2 test when appropriate. Pearson's test was used to assess correlation among variables.

Results Fifty subjects suffering from migraine (88% women) and 40 controls (80% women) have been included so far in the study. Mean age \pm SD was similar in migraineurs (39.7 ± 9.4 years) and in controls (38.5 ± 12.8 years; $p = 0.61$). Among migraineurs, 76% suffered from migraine without aura and 24% from migraine with aura (visual aura in all patients). There was no difference in the prevalence of any cardiovascular risk factor and in BMI (23.6 ± 3.3 vs. 22.3 ± 3.2 ; $p = 0.06$) between migraineurs and controls. Mean \pm SD HOMA values were 1.6 ± 1.1 in migraineurs versus 1.6 ± 0.8 in controls ($p = 0.80$) and 1.7 ± 1.0 in subjects suffering from migraine without aura versus 1.6 ± 1.2 in subjects suffering from migraine with aura ($p = 0.84$). In migraineurs and non migraineurs there was an association between HOMA values and BMI that was anyhow more relevant in the former with respect to the latter group ($\rho = 0.75$; $p = 0.0001$ vs. $\rho = 0.09$; $p = 0.2$).

Discussion Our data indicate the lack of any association between migraine and its subtypes with IR. However, definite conclusions should be drawn with caution because the study is still ongoing and the number of subjects, particularly of those suffering from migraine with aura, is at the moment low.

Psychiatric comorbidity of primary headaches and treatment outcome

D. Cassano¹, A. Amato¹, G. D'Onofrio¹, M.R. Porcaro¹, A.M. Romano¹, V. Pizza², V. Busillo³, C. Colucci d'Amato⁴

¹Territorial Headache Centre, District No. 60, ASL SA, Nocera Inferiore, Italy; ²Headache Centre, S. Luca Hospital, ASL SA, Vallo della Lucania, Italy; ³Headache Centre, Maria SS Addolorata

Hospital, ASL SA, Eboli, Italy; ⁴University of Naples, Naples, Italy; e-mail: info@domenicocassano.it

Introduction The aim of this study was to evaluate the influence of psychiatric comorbidity on headache treatment outcome.

Patients and methods The sample included 262 ICHD-II primary headache patients, 48 males (18.3%) and 214 females (81.7%), aged between 16 and 65 years (mean 38.4), satisfying the ICHD-II criteria for episodic (34%) and chronic migraine (12%), episodic (35%) and chronic tension-type headache (19%). All subjects at the first evaluation visit were administered the Mini International Neuropsychiatric Interview (MINI), a structured interview for the diagnosis of DSM IV psychiatric disorders, opportunely modified for assessment of only mood disorders (major depression, dysthymia, bipolar disorder II) and anxiety disorders (panic attack disorder, GAD). After an accurate psycho-clinical evaluation, they were subdivided into two groups: with and without psychiatric disorders. They received a diary indicating “headache days” (the number of days over a 30-day period during which they experienced a headache) and “severity of headache” (4-point scale: 0 none, 1 mild, 2 moderate, or 3 severe) and advice to take only acute medications; measures of headache disability and quality of life were performed by MIDAS and HIT-6. After 1 month [Baseline (Mo)], these patients received a new preventive therapy, based on the best clinical judgment: antidepressants (only tricyclics), anticonvulsants, beta-blockers, Ca-channel blockers and “others”. From baseline (Mo), follow-up visits were conducted at 1, 3, 6 months. In the first follow-up (M1) preventive therapies were adjusted or changed. At 6-month follow-up, preventive therapy outcome was evaluated considering: “headache activity”, the sum of all headache severity ratings divided by the number of headache days experienced over the target period; “headache related disability and quality of life” by MIDAS and Hit-6 ratings at Mo, M3, M6. “Dropouts” were defined as those patients that missed one or more follow-up visit and failed to reschedule and complete the missed visit. Statistical analyses of data was carried out by the Mann–Whitney test and the χ^2 test with Yates’ correction, as indicated.

Results Of the 262 patients assessed by MINI, 56% (N 146/262) received a psychiatric diagnosis (one or more). According to the psychiatric characteristics patients were subclassified in: 1) Depression only group (N = 35, 13.3%); 2) Depression and Anxiety group (N = 65, 24.8%); 3) Anxiety-only (N = 46, 17.6%); 4) Patients without a psychiatric disorder (N = 116, 44.3%). From baseline (Mo) to 6-month follow-up (M6):

- both groups—with and without psychiatric disorders—showed similar significant rates of improvement in headache activity ($p < 0.2$);
- patients with psychiatric disorders reported significantly greater headache disability than patients without psychiatric disorders ($p < 0.1$);
- patients with two psychiatric disorders reported significantly greater headache disability than patients with one psychiatric disorder ($p < 0.3$);
- patients with psychiatric comorbidity reported a higher use of acute drugs ($p < 0.5$).

Dropouts were mostly patients assuming tricyclics ($p < 0.5$), affected by depressive comorbidity ($p < 0.1$) and by chronic headaches ($p < 0.5$).

Conclusions The characterisation of subsets of primary headache patients with psychiatric disorders can constitute a valid approach to evaluate the impact on headache treatment outcome, conditioning higher drop-outs, overuse of symptomatic drugs and more disabling headache. This differentiation can also be useful to identify optimal behavioural and psychological treatment strategies that, combined with pharmacotherapy, are able to intervene not only on the patients’ headache characteristics but also on important social and emotional aspects of their lives.

Controversies: do trigger factors exist?

Trigger factors in migraine and tension-type headache: open vs structured questionnaires

F. Maggioni¹, E. Mampreso¹, C. Disco¹, M. Margoni¹, M. Bellamio¹, M. Bruno¹, F. Viaro¹, F. Mainardi², C. Lisotto³, G. Zanchin¹

Headache Centres: ¹Department of Neurosciences, Padua University, Padua, Italy; ²SS Giovanni e Paolo Hospital, Venice, Italy; ³San Vito al Tagliamento Hospital, San Vito al Tagliamento, Italy; e-mail: ferdinando.maggioni@unipd.it

Introduction Trigger factors (TFs) avoidance would reduce the related attacks; consequently the identification of TFs is a very relevant aspect of primary headaches management.

Objective To investigate TFs identification with a retrospective and prospective study, comparing open and structured questionnaires.

Materials and methods One group received an open questionnaire (OQ); another group received a structured questionnaire (SQ), listing 40 different TFs, which included and enlarged the series of those considered in previous studies on this topic. Questionnaires were filled in retrospectively and prospectively.

Results Six hundred and three patients (75% women, 25% men) affected by migraine with (n = 60) or without (n = 493) aura or by episodic tension-type headache (n = 50) were included. We considered the number of TFs in relation to the type of administered questionnaire, gender, diagnosis, history of headache, latency between the exposure to the TF and the attack onset. TFs result to be unrelated to the headache duration, frequency, and intensity. We found a clear difference between the number of TFs identified with the SQ (7.7 ± 4.1) and with the OQ (1.6 ± 1.5). TFs more frequently reported were stress, menstruation and sleeping deprivation, both in SQ and in OQ. Odours are reported exclusively by migraineurs, 24% in the retrospective SQ questionnaire; therefore, in a much higher percentage than reported in our paper on osmophobia features in migraineurs [1]. The results of the ongoing SQ prospective study (up to now 210 patients) seem to confirm the main data obtained from the retrospective one.

Conclusions We demonstrated that our SQ, which considers the largest list of TFs available in the literature, is much more suitable than an OQ to identify TFs. Therefore, we stress the relevance of the use of a detailed SQ, particularly in a Headache Centre, in order to increase the possibility of reducing the headache burden.

References

1. Zanchin G, Dainese F, Trucco M et al (2007) Osmophobia in migraine and tension-type headache and its clinical features in patients with migraine. *Cephalalgia* 27:1061–1068

Cigarette smoking may sustain the active phase of episodic cluster headache

M.M. Cainazzo¹, F. Righi¹, I. Tiraferri¹, M. Zappaterra¹, M. Ciccarese¹, G.L. Trianni², L.A. Pini¹, A. Ferrari¹

¹Headache and Drug Abuse Inter-Department Research Centre, University of Modena and Reggio Emilia, Modena, Italy;

²Anti-smoking Centre, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy;

e-mail: cainazzo.michela@policlinico.mo.it

Background Cluster headache (CH) is a severe primary headache disorder characterised by recurrent monomorphic headache attacks manifested through cranial autonomic symptoms; it has a very low prevalence (about 1 in 1,000 people). The most consistent lifestyle feature associated with CH is current smoking. Several studies have indicated that 70–90% of CH patients have a prolonged history of tobacco usage prior to the onset of headache. Tobacco exposure can lead to CH with a mechanism that has not yet been elucidated; probably, toxic agents found in tobacco-based products have a direct effect on the hypothalamus [1]. It has also been speculated that there is a genetic link that predisposes to CH and nicotine addiction [2].

Objective The aim of our study was to explore the relationship between cigarette smoking and the course and characteristics of cluster headache.

Methods Fifty patients, 8 women and 42 men (female and male ratio was F:M = 1:5.25), diagnosed with cluster headache, addressed to our Headache Centre, during the period between October 2010 and April 2011, were interviewed by phone. The overage of the subjects was 47.5 ± 11.7 (mean \pm SD). A specific, standardized questionnaire was administered by a trained post-graduate medical doctor.

Results The age of onset of the cluster headache was 30 ± 13.1 years; the number of cigarettes smoked at onset of CH was 17 ± 11 (F = 12.7 ± 9.1 ; M = 17.6 ± 11.2). Thirty-five patients were current smokers (70%); in the non-smoker group ten patients were included that had never smoked and five patients were former smokers. In the active cluster headache phase the maximum number of cigarettes smoked was 9.4 ± 6.9 cigarettes for women; 6.7 ± 6.1 for men. The mean number of cigarettes smoked per day in the active phase was 2 ± 1.4 for women; 3.1 ± 2.5 for men (*t* test; *p* < 0.05). Among the forty smoking patients, nineteen (47.5%) did not change their smoking habit during the active cluster period; the other nineteen patients (47.5%) smoked fewer cigarettes, the majority (90%) of them because they had a reduced desire to smoke during acute pain. The most interesting result was that the non-smoker group had a shorter mean period of the active cluster headache's phase (6.2 weeks) than the current smoker group (18.2 weeks). The difference was statistically significant (*t* test; *p* < 0.01).

Conclusions These preliminary data suggest that cigarette smoking is an aggravating factor for CH in the duration of the cluster headache's active phase.

References

1. Schürks M, Diener HC (2008) Cluster headache and lifestyle habits. *Curr Pain Headache Rep* 12:115–121
2. Rozen TD (2010) Cluster headache as the result of seconhand cigarette smoke exposure during childhood. *Headache* 50:130–132

Alcohol as a headache trigger: a relationship to be defined

A. Panconesi, L. Guidi, M.L. Bartolozzi, S. Mugnai

Headache Centre, Department of Neurology, Empoli, Italy;
e-mail: a.panconesi@virgilio.it

Alcoholic drinks have been reported to trigger migraine, cluster headache and also tension-type headache. Perhaps only alcohol is a sure migraine dietary trigger, but its importance is still debated. Retrospective studies show that at least one-third of migraine patients referred alcohol as a trigger [1]. However, some questions remain unanswered.

1. Recent prospective studies report that alcohol was not related to headache or only in 4% of migraine attacks.
2. The IHS classification reports that alcohol can provoke an immediate headache (within 3 h) and a delayed headache (hangover headache). In the last case a distinction between usual migraine and hangover headache is difficult and somehow artificial.
3. The alcohol infusion for 3 h ("alcohol clamp" method) does not provoke migraine within 8 h in healthy subjects. Therefore, the immediate headache should be restricted to headache patients or provoked by other components of alcoholic drinks.
4. Alcohol-induced analgesia is well documented. A recent study showed in a rat model of headache that alcohol provokes initial analgesia followed 4–6 h later by increased sensitivity modelling hangover headache. That alcohol induces analgesia seems in contrast with its migraine trigger action. High alcohol blood concentrations lead to vasoconstriction, while small doses have been found to have both vasodilatory and vasoconstrictive activity on cerebral vessels. Both vasodilatation caused by CGRP release and serotonin release from central pain circuits were suggested as a possible mechanism of alcohol related headache. That alcohol is a common trigger of the principal types of primary headaches suggests that these headaches share a pathogenetic mechanism.
5. Hangover headache appears when the blood alcohol concentration declines to zero. Thus, alcohol may have a similar action to other strong vasodilators which provoke migraine when vasodilatation has ended. Congeners and recently acetate were suggested as being responsible for hangover headache, but their involvement is under discussion.
6. Many population-based studies show an inverse relationship between alcohol and migraine. There are significant trends of decreasing prevalence of migraine and non-migraine headache with the increasing number of alcohol units consumed.

In conclusion, many aspects of alcohol-related headaches are discussed [2]. Alcohol as a migraine trigger is probably overestimated. Studies with intravenous alcohol should be performed to definitively evaluate if alcohol itself or other components are responsible for headache induced by alcoholic drinks and to determinate the true percentage of migraineurs experiencing immediate headache.

References

1. Panconesi A (2008) Alcohol and migraine: trigger factor, consumption, mechanism. A review. *J Headache Pain* 9:19–27
2. Panconesi A, Bartolozzi ML, Guidi L (2011) Alcohol and migraine: what should we tell patients? *Curr Pain Headache Rep* 15:177–184

Pain in chronic headaches

Rizatriptan efficacy is not related to the occurrence of cutaneous allodynia in migraine without aura

F. Granella¹, R. Zucco², A. Ferrari³, M.M. Cainazzo³, A. Bonazzi⁴, E. Sternieri³, L.A. Pini³, on behalf of the SISC Regional Section Emilia-Romagna

¹Department of Neuroscienze, University of Parma, Parma, Italy; Headache Centres: ²Reggio Emilia, ³Modena and ⁴Bologna affiliated with the Italian Headache Society for the Study of Headaches, Emilia-Romagna Regional Section; e-mail: franco.granella@unipr.it

Introduction Cutaneous allodynia (CA) is the perception of pain when a non-noxious stimulus is applied to normal skin. Burstein first [1] showed that CA frequently occurs during migraine attacks. He observed that triptan therapy is more likely to provide complete pain relief if administered before rather than after the establishment of CA. However, Burstein's studies were carried out on small case series, while subsequent randomized clinical trials did not confirm a negative correlation between CA and triptans efficacy. Aim of this study was to ascertain if the occurrence of CA was related to the efficacy of triptans in a naturalistic setting.

Methods Consecutive adult outpatients affected by migraine without aura referring to four Emilia-Romagna SISC headache centres were enrolled. During baseline visit, a headache diary was given to the patients, to be filled in at the next migraine attack and patients were instructed to take rizatriptan 10-mg wafer, whenever they considered it was convenient. The diary contained questions concerning demographic variables, headache characteristics, timing of medication, and outcomes at 2 and 24 h, in addition to a 8-item questionnaire on CA [2]. Main outcome was the percentage of pain-free (PF) patients at 2 h after rizatriptan administration in patients with (CA+) and without (CA−) CA.

Results One hundred and seven patients (F 84%; mean age 37.0 ± 9.0 years) entered the study. Mean timing of rizatriptan intake was 79 min after headache onset; pain was mild in 13.1% of the patients and moderate/severe in 86.9%. CA was present in 70.1% of the patients. Two hours after drug administration, 29.3% of CA+ and 50.0% of CA− patients were PF ($p = 0.04$). Sustained PF (SPF) was reached by 21.3% of CA+ and 37.5% of CA− patients ($p = \text{ns}$). Forty percent of patients were PF after early treatment (drug administration within 30 min from onset) versus 32.8% of patients after delayed treatment (drug administration after 30 min) ($p = \text{n.s.}$). Patients with mild pain at drug intake were PF in 78.6% of the cases while patients with moderate/severe pain were PF in 29.0% ($p < 0.0001$). At a multivariate analysis only the severity of pain at the moment of drug intake was significantly correlated with PF ($p = 0.004$) and SPF ($p = 0.05$).

Conclusions The efficacy of rizatriptan 10-mg wafer at 2 and 24 h seems to be mainly driven by the severity of pain at the moment of drug administration.

References

1. Burstein R, Yarnitsky D, Goor-Aryeh I et al (2000) An association between migraine and cutaneous allodynia. *Ann Neurol* 47:614–624
2. Ashkenazi A, Silberstein S, Jakubowski M et al (2007) Improved identification of allodynic migraine patients using a questionnaire. *Cephalalgia* 27:325–329

Chronic headache and fibromyalgia

M.A. Giamberardino, E. Tafuri, S. Di Fabio, C. Tana, G. Costa, A. Fabrizio, G. Affaitati

Headache and Fibromyalgia Centres, Department of Medicine and Science of Aging, G. D'Annunzio University of Chieti, Chieti, Italy; e-mail: mag@unich.it

Introduction Epidemiological studies show a high level of co-occurrence between headache—especially chronic—and fibromyalgia, suggesting common pathophysiological bases between the two conditions [1]. Fibromyalgia (FS) is characterized by a generalized increase in sensitivity to painful stimuli at a somatic level [2]. On this basis, the aim of the present study was to verify: firstly, if the association of FS with headache involves different levels of

hypersensitivity with respect to one condition only, and secondly if, in patients with fibromyalgia plus headache, the hypersensitivity level is a function of headache frequency.

Methods A total of 150 female patients were examined, subdivided into five groups of 30 patients each, who were affected with: (1) fibromyalgia (FS); (2) headache (migraine or tension-type: 8–12 days/month) (H_1); (3) headache (migraine or tension-type: >15 days/month) (H_2); (4) headache (8–12 days/month) plus fibromyalgia ($H_1 + FS$); (5) headache (>15 days/month) plus fibromyalgia ($H_2 + FS$). The groups were age-matched. Headache patients of all groups did not differ significantly regarding the number of years they had been suffering from headache. Fibromyalgia patients of all groups did not differ significantly regarding the number of years they had been suffering from diffuse chronic musculoskeletal pain. In all groups: pain thresholds to electrical stimulation in skin, subcutis and muscle were measured in multiple body sites (deltoid, trapezius and quadriceps) not coinciding with the areas of spontaneous pain; muscle pain thresholds to pressure stimulation were evaluated in the same locations and in the 18 Tender Point sites. Measurement was made in the pain-free interval and with a wash-out of at least 48 h from symptomatic drugs.

Results The lowest electrical thresholds at all body sites and all tissues and lowest muscle pressure pain thresholds were found in group 5 ($H_2 + FS$), followed by group 4 ($H_1 + FS$), group 1 (FS), group 3 (H_2) and group 2 (H_1). The trend for variation among groups was significant ($p < 0.004$).

Conclusions Comorbidity between headache and fibromyalgia involves a higher state of generalized hypersensitivity towards painful electrical and pressure stimuli applied at somatic level with respect to one condition only. The increase in headache frequency—with shift towards chronicity—promotes the enhancement of the hypersensitivity. These results suggest different levels of central sensitization in patients with headache, fibromyalgia or both conditions, which are expressed clinically with higher/wider manifestations of spontaneous pain.

References

1. Affaitati G, Costantini R, Fabrizio A et al (2011) Effects of treatment of peripheral pain generators in fibromyalgia patients. *Eur J Pain* 15(1):61–69
2. Kindler LL, Bennett RM, Jones KD (2011) Central sensitivity syndromes: mounting pathophysiologic evidence to link fibromyalgia with other common chronic pain disorders. *Pain Manag Nurs* 12(1):15–24

Detoxification as first step in the rehabilitation of chronic migraine

M. Fiorillo, A. Negro, L. D'Alonzo, P. Martelletti

Department of Medical and Molecular Sciences, Sapienza University of Rome, Sant'Andrea Hospital, Rome, Italy; e-mail: paolo.martelletti@uniroma1.it

Headache is among the most common neurological symptoms in clinical practice. In some cases of episodic migraine, the headache intensifies into a chronic form, defined as chronic migraine (CM) and such a condition encompasses a headache frequency of 15 days/month, with clinical features similar to those of migraine attacks. The assessment of CM in the US general population ranges around 1.3–2%. Migraine progression from an episodic into a chronic form is realized through a period of time involving several months or years, during which an increase attack frequency occurs. Both Topiramate and OnabotulinumtoxinA can be considered to be safe (Topiramate

AEs > OnabotulinumtoxinA AEs) as well as effective medications, therefore, representing a treatment choice [1]. Regarding drug abusers, the initial relief step always consists of drug interruption [2]. Only after detoxification can a new prophylaxis therapy be commenced, which otherwise would be useless from the start. The feasible diagnostic setting for the tailored treatment of CM based on the application of pharmacogenomics will allow us in predetermining the efficacy of a single drug by avoiding abuse due to non-response of the overused drug. Therefore, detoxification procedures, although with different approaches, must be first carried out before re-prophylaxis treatment with innovative drugs, such as OnabotulinumtoxinA, in order to minimize the risk of relapse into new periods of MOH [2].

References

1. Farinelli I, Dionisi I, Martelletti P (2011) Rehabilitating chronic migraine complicated by medication overuse headaches: how can we prevent migraine relapse? *Intern Emerg Med* 6:23–28
2. Negro A, D'Alonzo L, Martelletti P (2010) Chronic migraine: comorbidities, risk factors, and rehabilitation. *Intern Emerg Med* 5[Suppl 1]:S13–S19

Botulinum toxin

Botox®: an innovative approach to the treatment of chronic migraine

M. Fiorillo, L. D'Alonzo, A. Negro, P. Martelletti

Department of Medical and Molecular Sciences, Sapienza University of Rome, Sant'Andrea Hospital, Rome, Italy;
e-mail: paolo.martelletti@uniroma1.it

Chronic migraine (CM) is defined as migraine occurring more days than not, in patients with previous history of migraine. CM represents the majority of clinical form of headache observed in tertiary headache centres (40–60%). The prevalence of CM in the global population ranges approximately around 2%. People with CM represent a serious subset of headache patients with a high profile of disability, psychiatric comorbidity and economic burden. Since there are few preventative therapies for CM this new indication of BOTOX® represented a great opportunity for this neglected group of CM patients. Two large randomized controlled trials (RCTs) (PRE-EMPT1, PREEMPT2) have shown that treatment with BOTOX® resulted in significant improvements over placebo across a number of primary and secondary endpoints [1]. A standardized injection paradigm of BOTOX® has been developed and validated during the PREEMPT RCTs. This paradigm is based on the application of 155 U of BOTOX® in 31 sites, following the fixed doses fixed sites (FDFS) procedure. Additional 40 U can be injected unilaterally or bilaterally in 3 specific neck/head muscle areas following the Follow-the-pain (FTP) paradigm. A debate on the inclusion in the PREEMPT studies of CM complicated with MOH resulted in a profound criticism of the reliability and clinical application of ICHD-II 2006 classification of CM [2].

References

1. Dodick DW, Turkel CC, DeGryse RE et al, PREEMPT Chronic Migraine Study Group (2010) OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache* 50:921–936

2. Martelletti P (2011) Dispute settlement understanding on the use of BOTOX® in chronic migraine. *J Headache Pain* 12:1–2

SISC guidelines 2011

Non-pharmacological treatments

L. Savi, C. Condello

Headache Centre, Neurology 2, Department of Neuroscience, Saint John the Baptist University Hospital, Turin, Italy;
e-mail: lsavi@molinetto.piemonte.it

Non-pharmacological treatments of primary headaches are useful and too often underestimated options to pharmacological treatments. Many different techniques can be used as non-pharmacological treatments for primary headaches, some of them belonging to traditional medicine (i.e., behavioural therapy, physiotherapy, surgery), while others to alternative medicine (i.e., acupuncture, osteopathy, chiropractic).

These treatments can be very useful in some particular situations, as when a pharmacological treatment is impossible (i.e., pregnancy, lactation, renal failure, liver failure) or when it is preferable to avoid it (i.e., concomitant use of many different drugs for other diseases). Patients generally show a marked preference toward these forms of treatments, since in the majority of cases they prefer to avoid more traditional drugs.

Absence of side effects and contraindications are the principal advantages for the use of these techniques, while the main disadvantages are their being time-consuming, generally expensive and not too easy—sometimes actually impossible—to find far from the bigger Headache Centres, as skilled therapists are often requested.

Many different techniques have been described as useful for the therapy of primary headaches; unfortunately the majority of them are not supported by any demonstration of efficacy, having only being published on anecdotal reports.

Non-pharmacological treatments are described both for symptomatic and prophylactic therapy of almost every form of primary headache; they can be used alone or combined with a pharmacological therapy, a possibility that should definitely be more pursued, as the combination of the two kinds of treatments enhance each other's effects.

The evaluation of the efficacy of all these techniques is extremely difficult for many different reasons, mainly because for the majority of them very few scientifically valid papers are available, and in any case they are extremely heterogeneous, so that meta-analysis is almost impossible to be conducted on them.

Sure demonstrations of efficacy of most non-pharmacologic symptomatic treatments of primary headaches are not yet available. At the moment transcranial magnetic stimulation has gained a level of evidence B as a symptomatic therapy, but the large-scale use of the devices needed for it is impossible.

Conversely, among prophylactic therapies of both migraine and tension-type headache, acupuncture and biofeedback reached a level of evidence A.

In patients with chronic cluster headache, surgical treatments may be the only worthy alternatives when medical therapy is ineffective, impossible for contraindications, or poorly tolerated. Occipital nerve and deep brain stimulation are the techniques that showed the best results, but their efficacy is still uncertain.

Guidelines for primary Headaches of the Italian Society for the Study of Headaches (SISC). Pharmacological treatment

P. Sarchielli¹, F. Granella², M.P. Prudenzano³ on the behalf of the Ad Hoc Committee for the Diagnostic and Therapeutic Guidelines for Primary Headaches

¹Clinica Neurologica, Università di Perugia, Ospedale S. Maria della Misericordia, Perugia, Italy; ²Department of Neuroscienze, University of Parma, Parma, Italy; ³Neurological Clinic L. Amaducci, University of Bari, Bari, Italy; e-mail: paola.sarchielli@gmail.com

Years after the first edition (2001), the Members of SISC Ad Hoc Committee decided to update the therapeutic guidelines for primary headaches in adults. A literature search was carried out on Medline database, and all articles on primary headache treatments in English, German, and French published from February 2001 to December 2010 were taken into account. Only randomized controlled trials (RCT) and meta-analyses were analysed for each drug. If RCT were lacking, open studies and case series were also examined. According to the previous edition, four levels of recommendation (LoR) were defined on the basis of levels of evidence and scientific strength of evidence.

As far as migraine is concerned, triptans are indicated for the treatment of moderate-severe attacks (LoR I), analgesics and non steroidal anti-inflammatory drugs for treatment of mild to moderate attacks or when triptans are contraindicated or ineffective, antiemetics as adjuvant drugs when nausea and vomiting are prevailing. The most consistent evidence for efficacy are available for acetylsalicylic acid (ASA), lysine acetylsalicylate, ibuprofen at higher dosages, naproxen (LoR I), whereas for diclofenac sodium and potassium, ibuprofen at lower dosages, metamizole, ketorolac i.m. and e.v. the evidence of efficacy is more limited (LoR II). Among ergot derivatives the drug class with the best risk/benefit ratio is dihydroergotamine but it is not available in Italy. For combination analgesics the association of ASA + acetaminophen + caffeine (LoR II), acetaminophen + codeine (LoR II) and indomethacin + prochlorperazine + caffeine (LoR I for oral formulation, II for suppository) have the most stringent evidence of efficacy. Among antiemetics only metoclopramide reaches a LoR II. For preventive drugs a LoR I is assigned to propranolol, metoprolol, atenolol among beta-blockers, to flunarizine among calcium channel blockers, amitriptyline among antidepressants, sodium valproate and topiramate among antiepileptics. Bisoprolol, nadolol, cinnarizine, fluoxetine, venlafaxine, gabapentin, pizotifene have a LoR II.

Among drugs for tension-type headache attacks, analgesics and NSAIDs for which evidence of efficacy are available, include ASA, naproxen, acetaminophen (LoR I), diclofenac potassium, ibuprofen, ketoprofene, lumiracoxib, and metamizole (LoR II). LoR I was also assigned to acetaminophen + caffeine, ASA + acetaminophen + caffeine among combination analgesics. Prophylactic treatment for tension-type headache includes: (1) Antidepressants: in particular amitriptyline, mianserine and venlafaxine with LoR II, (2) Miorelaxants: in particular tizanidine with LoR I, and (3) benzodiazepines in particular diazepam with a LoR II and alprazolam with a LoR II.

For acute treatments for cluster headache a LoR I is given to s.c. sumatriptan and oxygen by inhalation whereas sumatriptan spray nasal received a LoR II. For prophylactic drugs only verapamil has a LoR I, whereas all other tested drugs available in Italy (pizotifene, histamine sulphate, lithium carbonate, prednisone) are indicated with a LoR III. Capsaicin, metisergide and histamine sulphate are not available in Italy.

Chronic pain and disability

Sodium valproate in the treatment of medication-overuse headache: an Italian multicentre controlled randomized clinical trial

P. Calabresi^{1,2}, I. Corbelli^{1,2}, S. Caproni^{1,2}, P. Sarchielli¹ on the behalf of the SAMOHA study groups

¹Headache Centre, Neurologic Clinic, S. M. della Misericordia Hospital, University of Perugia, Perugia, Italy; ²IRCCS, Santa Lucia Foundation, European Brain Research Institute, Rome, Italy; e-mail: calabre@unipg.it

Background Medication-overuse headache (MOH) is a chronic disorder associated with high morbidity, disability and great difficulty of treatment [1, 2]. Psychiatric comorbidity in medication-overuse headache is common and should be interpreted as a risk factor for headache chronicity [3]. The management of MOH consists in a detoxification period, limited use of symptomatic acute medications not involved in the abuse and an effective preventive therapy. Sodium valproate, that has been approved by the FDA for migraine prevention, epilepsy, other than for the manic and depressive phase of bipolar disorder, is a promising option for the preventive treatment of MOH [4]. It could be helpful in both reversing the chronic pattern of headache in patients with MOH and improving psychopathological disturbances which often afflict these patients.

Objectives A phase III, multicentre, randomized [1:1], two-arm, double-blind, placebo-controlled, parallel group study has been proposed to verify the efficacy of sodium valproate in the short-term treatment (3 months) of MOH after a 6-day outpatient detoxification regimen.

Study endpoints Primary endpoint is to explore the efficacy of a 12-week treatment with sodium valproate at the dosage of 800 mg/die compared with placebo in reducing the number of days with headache/month (decrease $\geq 50\%$) in patients with medication-overuse headache, following a 6-day outpatient detoxification regimen. Secondary endpoints are: the evaluation of the effect of sodium valproate on psychopathological disturbances complained by MOH patients compared with placebo using ad hoc scales and questionnaires, the determination of the treatment satisfaction and the investigation of the safety and tolerability of sodium valproate at the dosage of 800 mg/day compared with placebo.

Study design Details of changes in headaches and treatment adherence during the study will be recorded in a headache diary. The study for any one subject consists of a 4-week baseline period (during which no study medication will be given), a 6-day detoxification phase (in which drugs abused will be abruptly discontinued) and a 12-week double-blind treatment period. A follow-up visit at 6 months from the beginning of drug administration will also be made to evaluate a possible carry over effect of sodium valproate treatment.

Protocol addendum Genes involved in the mechanism of action of valproic acid or in the pathophysiology of MOH could affect the response to treatment. The aim of the addendum study is to analyze the genetic mechanisms influencing the response to sodium valproate therapy in a sample of patients affected by MOH. Polymorphisms of the genes involved in the pathophysiology of MOH and in the mechanism of action of sodium valproate will be analyzed.

Centres involved in the study This is an AIFA 2006 FARM6TT8SP study. The study started in April 2009 and the last patient was enrolled in May 2011; 11 are the Italian centres involved in the study and 126 the patients enrolled.

References

1. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd edn. Cephalalgia 24[Suppl 1]:1–160
2. Kavuk I, Katsarava Z, Selekler M et al (2004) Clinical features and therapy of medication overuse headache. Eur J Med Res 9(12):565–569
3. Radat F, Creac'h C, Swendsen JD et al (2005) Psychiatric comorbidity in the evolution from migraine to medication overuse headache. Cephalalgia 25(7):519–522
4. Coskun O, Ucler S, Cavdar L et al (2007) Effect of valproic acid on withdrawal therapy in patients with overuse of chronic daily headache medications. J Clin Neurosci 14(4):334–339 (Epub 2006 May 2)

Efficacy of a new educational social network for prevention and abatement of headache and cervical pain in the general population

F. Mongini, C. Milani, A. Ugolini, E. Banzatti, L. Ferrero, A. Piedimonte

Sezione Cefalea e Dolore Faciale, Dipartimento Fisiopatologia Clinica, Università di Torino, Turin, Italy; e-mail: fmongini@unito.it

Introduction In previous longitudinal controlled studies of more than 2,300 local Government employees, a reduction of almost 40% of headaches, shoulder and neck pain and pain killer usage was obtained with a cognitive and exercise program [1, 2]. Following these results data relative to headache and/or neck and shoulder pain were collected from 4,574 residents of the Piemonte Region, through a website program. Subsequently, an educational social network in Italian and English (<http://www.nomalditesta.it>, <http://www.noheadneckpain.com>) for patients and doctors against headache and cervical pain was launched. We report here the results so far obtained.

Method After giving information on their pain characteristics and filling in the MIDAS questionnaire, applicants have free access to demonstration videos and other pertinent text and illustrations. The network is constantly updated with new information. The patient situation may be monitored with daily diaries and with the MIDAS data after 6/12 months follow-up. In a reserved section clinicians have access to educational and scientific material.

Results Up to May 1, 2011 applicants were 1,206 (401 (32%) M; 890 (68%) F) patients and 85 clinicians (51 males, 34 females). Pain conditions were distributed as follows: migraine (M) = 148 (12.3%), tension-type headache (TTH) = 49 (4.1%), myogenic pain in the neck and shoulder area (MP) = 29 (2.4%), M + TTH = 64 (5.3%), M + TTH + MP = 216 (17.9%), M + MP = 513 (42.5%), TTH + MP = 187 (15.5%). The prevalence was significantly higher in females in M ($p = 0.03$ Chi-square), M + TTH + MP ($p < 0.01$ Chi-square) and M + MP ($p < 0.01$ Chi-square). In females the superposition of MP significantly increased the prevalence of headache of any type. MIDAS scores of 400 individuals (260 females, 140 males) were obtained at 6-month intervals and mean values statistically compared (t test) with the data at the baseline. Six months after sign-up there was a significant ($p < 0.01$) reduction of headache days (6.1 vs. 4.5), headache intensity (5.8 vs. 4.8), days of neck pain (7.3 vs. 6.1) intensity of neck pain (4.1 vs. 3.8) days of drug intake (4.8 vs. 3.7). The overall MIDAS score was reduced from 17.9 to 12.8.

Conclusions The social network is an effective tool to analyse, monitor and prevent headache and cervical pain in extensive working

communities and populations. It may also be a support for general practitioners and specialists dealing with patients with headache and cervical pain.

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References

1. Mongini F, Ciccone G, Rota E et al (2008) Effectiveness of an educational and physical programme in reducing headache, neck and shoulder pain: a workplace controlled trial. Cephalalgia 28:541–552
2. Mongini F, Ciccone G, Rota E et al (2009) Long-term benefits of an educational and physical program on headache, and neck and shoulder pain in a working community. J Pain 10:1138–1145

Urine proteomic analysis in patients with chronic headache and overuse of analgesic drugs: possible relation with renal damages

E. Bellei¹, S. Bergamini¹, A. Cuoghi¹, E. Monari¹, A. Tomasi¹, M. Zappaterra², A. Bazzocchi², S. Guerzoni², L.A. Pini²

¹Department of Laboratory, Pathological Anatomy and Forensic Medicine, Proteomic Laboratory, Modena, Italy; ²Inter-Department Headache and Drug Abuse Centre, University Hospital of Modena and Reggio Emilia, Modena, Italy; e-mail: pinila@unimore.it

Introduction Several recent epidemiologic studies have shown that different drugs and agents may cause nephrotoxic acute kidney injury, particularly in chronic patients. The aim of this study was to analyse the urinary protein profiles of patients with medication-overuse headache (MOH), in comparison with healthy subjects. The goal was to identify differences induced by excessive consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans that could be related to nephrotoxicity, namely useful protein targets able to predict potential renal damages.

Materials and methods MOH patients were recruited by the “Headache and Drug Abuse Centre” and the “Unit of Toxicology and Clinical Pharmacology” of the University Hospital of Modena and Reggio Emilia. They were divided into three groups: triptans, NSAIDs and mixture (drugs association) abusers. Healthy donor volunteers, with a history of normal renal function, were also enrolled and used as controls. Second void morning midstream urine samples were collected and then centrifuged to remove cell debris and contaminants. After sample concentration and desalting with specific filter devices, mono-dimensional gel electrophoresis (SDS-PAGE) was performed using 12% resolving polyacrylamide gels. Coomassie colloidal-stained gel images were acquired by a calibrated densitometer and protein bands were analysed with the “Quantity One” software.

Results Urinary proteins were separated by electrophoresis according to their molecular weight (MW). Comparing the patients’ proteomic profiles with those of control subjects, we found a significantly different protein expression at various MW levels. In particular, at high MW (range 80–150 kDa) all patient groups showed a very intensive protein band around 100 kDa, not detectable in the control group. The largest number of differential proteins was observed at medium MW (range 30–70 kDa), where the intensity of five proteins was considerably higher in NSAIDs patients than in control subjects. Finally, at low MW (5–20 kDa) two proteins were evident in triptans and NSAIDs groups.

Discussion The most pertinent proteomic applications in nephrotoxicology can be found in the analysis of renal drug effects, and the

majority of the published literature in this field has appeared in the last decade. The present proteomic research demonstrates the finding of alterations in urinary protein excretion in MOH patients. These proteins will be identified in coming studies, using two-dimensional gel electrophoresis coupled to mass spectrometry.

Conclusions This pattern of urinary proteins, revealed by the use of innovative proteomic technologies, might represent a promising tool for a better understanding of potential nephrotoxicity induced by drug overuse.

Medication-overuse headache: analysis of possible co-morbidities and a medium-term outcome after a standard protocol of withdrawal detoxification

C. Zandrini, G. Veneziano, G. Bono

Fondazione Macchi, U.O. Neurologia, Centro Cefalee, Varese, Italy; e-mail: cinziazandrini@libero.it

Introduction Medication-overuse headache (MOH) is a clinically relevant but heterogeneous entity. The chronic, more or less, long-lasting overuse of acute symptomatic medications by patients with migraine, as well as, with tension-type headache or their association of producing chronic daily refractory headaches, among which MOH, is most frequent. MOH is one of the most common causes of chronic refractory headache. The pathophysiological mechanism of MOH is still unclear. Several different aspects appear to play key roles. Management of MOH is a difficult problem. Aim of our study was to analyse the outcome of a group of patients presenting to our Headache Centre in the last 4 years and identify risk factors for relapse of analgesic overuse.

Methods Two hundred and thirty-eight MOH patients (2007–2011) underwent a standard withdrawal detoxification protocol. One hundred and fifty-one patients (2009–2011), 120 females and 32 males, mean age 48.27, affected by MOH following the International Headache Society criteria were studied. One hundred and ten patients had a history of migraine with or without aura, 20 tension-type headache and 22 with both tension-type and migraine. Patients underwent a standard protocol including hydration, metoclopramide, multivitamins and benzodiazepines i.v., during 5 days, in Day Hospital. At discharge a prophylactic therapy and a symptomatic drug were prescribed. Patients underwent follow-up controls at 3 and 6 months. The overused medications were combination analgesics in 50 cases, triptans alone in 26 cases and in combination with analgesics in 33 cases. We analysed epidemiological and demographic data of the patients (sex, age, schooling, primary headache, trigger factors, hypertension, previous trauma, gastrointestinal disorders, sleep disorders, psychiatric comorbidity, previous detoxifications, type and timing of overuse) that could and to what extent influence a positive outcome.

Results and conclusions Six months after withdrawal, we had complete data for 95 patients (65%): 28 of these patients (28%) had relapsed into overuse and 67 (72%) had not. One year after withdrawal, 50% of patients had not relapsed, patients with migraine had obtained a better outcome than tension-type patients. Our preliminary data acknowledge the important role of trigger factors (64%), psychiatric comorbidity (61%), gastrointestinal disorders (65%), and sleep disorders (52%). We think that good psychological support and behavioural education could play a major role to reduce the prevalence of MOH.

Claim for medico-legal protection by patients suffering for headache: results from a multicentre headache clinic survey

P. Rossi¹, F. Brighina², G. Sances³, E. Guaschino³, A. Puma², S. Talamanca², P. Paladino², M. Avenali³, G. Nappi³

¹INI Grottaferrata, Italy; ²Neurologia, Università di Palermo, Palermo, Italy; ³IRCCS C. Mondino National Neurological Institute Foundation, Pavia, Italy; e-mail: paolo.rossi90@alice.it

Objectives The aim of this study was to evaluate the rates, pattern, outcome, satisfaction with and presence of predictors of claims for medico-legal protection in a clinical population of headache patients. **Design and setting** Three hundred and seventeen consecutive patients attending three headache clinics (Pavia, Grottaferrata, Palermo) were asked to fill in a structured questionnaire designed to gather information about their search for medico-legal protection.

Results Claim for medico-legal protection for headache was reported by 12% of the patients surveyed. The most common reason for not claiming medico-legal protection was “I didn’t know about the existence of medico-legal protection for headache” (58%). Seventy-seven percent of the claims for medico-legal protection were to obtain legal disability status and the remaining ones to enjoy a justified absence from work (Italian Law no. 104). Forty-five percent of the claims for medico-legal protection were filed solely for headache. The most common source of information was the GP (39%). Fifty-five percent of the surveyed patients declared that the evaluation from the medico-legal committee lasted <10 min and only 26% declared to be satisfied with the medico-legal visit. Seventy percent and 30% of the claims under Italian Law no. 104 and disability, respectively, were rejected. Sixty-five percent of the patients receiving the medico-legal protection considered it as not useful. Predictors for claims for medico-legal protection were: living in the north and central regions (OR 3.25, CI 1.1–9.9, OR 3.51 CI 1.2–10); the category of medico-legal impairment as proposed by the Lombardia Region (class A OR 0.09 CI 0.03–0.28, class B1 OR 0.6 CI 0.2–0.8); and not having any other form of medico-legal protection (OR = 0.28 CI 0.12–0.65).

Conclusions This is the first study investigating the claim for medico-legal protection for headache in Italy. Our data indicate that claim for medico-legal protection is infrequent, mainly because of ignorance about the possibility of receiving such protection. Headache sufferers claiming for such protection were those more severely disabled and enjoying other forms of protection. Significant differences emerged between Sicily and the remaining areas of Italy. Patients who have been legally recognized as disabled because of their headache consider it as not being helpful for their needs.

Hypnic headache: possible evolution from migraine?

C. Lisotto¹, F. Mainardi², F. Maggioni³, E. Mampreso³, G. Zanchin³

¹Ambulatorio Cefalee, Ospedale di San Vito al Tagliamento, San Vito al Tagliamento, Italy; ²Centro Cefalee, Ospedale di Venezia, Venice, Italy; ³Centro Cefalee, Dipartimento di Neuroscienze, Padua, Italy; e-mail: carlo.lisotto@ass6.sanita.fvg.it

Introduction Hypnic headache (HH) is a primary nocturnal headache, which occurs exclusively during sleep. Many patients have been reported to have coexistent or pre-existent primary headaches disorders such as migraine and tension-type headache [1].

Materials and methods For the last 13 years we have observed 44 cases fulfilling ICHD-II criteria for HH. All patients underwent extensive investigations, including brain MRI and Angio-MRI, which resulted unremarkable.

Results We diagnosed 44 patients, 38 females and 6 males with HH. The patients' mean age at first observation was 65.0 ± 8.6 years (range 50–83), whereas the mean age at onset was 61.0 ± 9.4 years (range 45–82). The pain was bilateral in 31 patients and unilateral without side shift in 13. Thirty-two (28 females and 4 males) had a chronic headache unremitting from onset. The other 12 patients showed an episodic pattern [2]. Interestingly, 25 patients (23 females and 2 males) had a positive history for migraine and 3 (2 females and 1 male) for frequent episodic tension-type headache. The prevalence of migraine in our case series of HH patients was 56.8%, significantly higher than that of the general population. Out of these 25 patients, 22 had migraine without aura (all females) and 3 had migraine with aura (one was male). Migraine headaches had completely ceased prior to the onset of HH in 21 patients, whereas in the remaining 4 cases migraines were still active and coexisting with HH, even if less frequent and severe as compared with the previous attacks.

Discussion This case series of HH patients is the largest ever reported in the literature. The pathophysiology of HH remains speculative. The variety of drugs reported to be effective in HH underscores the possibility that the pathophysiology might be heterogeneous. In our case series of HH patients, the prevalence of migraine was >55%, suggesting that migraineurs are more likely to suffer from HH, in particular after the age of 50. With advanced age, the function of the hypothalamic-pituitary axis is diminished, and melatonin secretion is impaired.

Conclusions We found a high prevalence of migraine in a large series of HH patients. This observation is suggestive of a possible pathophysiological link between the two conditions. Since for most migraineurs the onset of HH occurred when migraine had already disappeared, it can be hypothesized that in a subpopulation of patients, migraine may evolve into HH, possibly based on greater susceptibility of hypothalamic-pituitary axis derangement.

References

1. Lisotto C, Mainardi, Maggioni F et al (2004) Episodic hypnic headache? Cephalalgia 24:681–685
2. Lisotto C, Rossi P, Tassorelli C et al (2010) Focus on therapy of hypnic headache. J Headache Pain 11:349–354

Rare headache as orphan diseases

Common diagnostic and therapeutic errors in the management of trigeminal autonomic cephalalgias (TACs)

M. Viana^{1,2}, M. Allena³, C. Tassorelli³, G. Sandrini³, G. Nappi³, F. Antonaci^{4,5}

¹Headache Science Centre, IRCCS C. Mondino National Neurological Institute Foundation, Pavia, Italy; ²Università degli Studi Amedeo Avogadro, Novara, Italy; ³Headache Science Centre, IRCCS C. Mondino National Neurological Institute Foundation, University Consortium for Adaptive Disorders and Headache (UCADH) Pavia, Italy; ⁴University Consortium for Adaptive Disorders and Headache (UCADH) Pavia, Italy; ⁵Policlinico di Monza, Monza, Italy; e-mail: fabio.antonaci@unipv.it

Introduction Trigeminal autonomic cephalalgias (TACs) are rare but well defined primary headaches. Despite the fact that the second

edition of the International Classification for Headache Disorder clearly defined them as single entities (code 3), and the presence of recent therapeutic guidelines, frequent diagnostic and therapeutic errors are committed by physicians in clinical practice. The aim of this study was to review all available data related to diagnostic and therapeutic errors in patients with TACs.

Methods We reviewed all the English and Italian literature related to this particular topic. We also collected data derived from the medical history of patient we saw in our practice, as medical errors are rarely described in literature.

Results Many errors in the management of patients with TACs have been described: starting from referral errors (i.e., patients with cluster headache were referred to dentistry etc.), diagnostic delay (a mean of 2.6 years for cluster headache) and the request of investigations. Many headache specialists do not order any neuroimaging in these patients although recommended by diagnostic guidelines as some typical TACs can be secondary to other central nervous system lesions. Misdiagnosis with many other headache and facial pain phenotypes such as migraine with aura, trigeminal neuralgia, sinus infection, are also frequently reported and sometimes they lead these patients to useless and sometimes invasive treatments as dentistry, ENT and even neurosurgery interventions. Also, when the diagnosis is correct, errors in prescribing medication not recommended by therapeutic guidelines were found.

Discussion and conclusions Although very well characterized headache disorders, TACs are frequently not recognized, or if diagnosed are improperly treated, with sometimes serious consequences in outcome in these patients. Better knowledge of these disorders either in primary care physicians or in Headache specialists could really improve the quality of life of the patients suffering from TACs.

Cluster headache and paroxysmal hemicrania in children and adolescents

M. Carotenuto, M. Esposito

Headache Centre for Developmental Age, Department of Child and Adolescent Neuropsychiatry, Second University of Naples, Naples, Italy; e-mail: marco.carotenuto@unina2.it

Background Cluster headache (CH) is a rare illness in children with an estimated prevalence of 0.1%. This condition tends to occur after the age of 10 and is prevalent in males. This rare condition is characterized by clusters of severe pain lasting 15 min to 3 h, characterized by a unilateral pain limited to the orbital, supraorbital or temporal regions and with a clear ipsilateral autonomic features (conjunctival injection, rhinorrhea, eyelid edema, forehead and facial sweating, restlessness and agitation).

Similarly to adulthood, neither symptomatic nor prophylactic treatments have been well documented for children and adolescents. CH can be considered the most painful of the primary headaches, and even if it is a well-defined and recognizable disorder, however, there is a surprising lack of epidemiological specific studies in childhood and adolescence. No precipitating or predisposing risk factors are known, and the few paediatric cases reported in clinical literature cannot identify any one, except the exposition of secondhand cigarette smoke, but no other pathogenetic studies are known. Conversely, a similar address can be considered for paroxysmal hemicrania that could be distinguished in an episodic and chronic subtype. It was firstly described in 1976, with an analogous clinical spectrum to CH, but with more brief attacks and higher frequency and a clear opposite gender preference (F > M). Also, too few studies in paediatric age are present for these types of symptoms to consent a correct clinical assessment and treatment.

Nummular headache: a new case?

A. Tarsitano¹, U. Cannistra², A. Cervarolo³

¹SOC Centre of Medicine Pain, INRCA-IRCSS, Cosenza, Italy;

²SOC Neurology, Regional Hospital Pugliese-Ciaccio,

Catanzaro, Italy; ³Headache Clinic, ASP, Cosenza, Italy;

e-mail: a.tarsitano@inrca.it

Introduction Nummular headache (NH) is a term for a distinct primary headache disorder. Its main feature is that the pain is felt in a small rounded or elliptical area of about 2–6 cm in diameter, usually with well-defined borders. The pain is of mild or moderate intensity with periods of exacerbation or remission [1].

Case report A 40-year-old woman reported, for the last 2 months a pressure type pain in a rounded area in the back inferior parietal on the left side. The circumscribed area was about 2.5 cm in diameter. The pain was described as continuous, of light intensity. She also reported exacerbations of the pain of severe intensity, stabbing and brief length (5 s) with pauses of 10 s and lasting from 1 to 3 h. No triggers were reported. Associated symptoms were not reported. Magnetic resonance imaging showed a light form of S. Arnold Chiari I (her sister is affected by the same malformation), negative neurological exam and middle bulging disc at the C5–C6 level. Anamnestic data referred no trauma. At examination, there were no signs or symptoms of sensory dysfunction in the symptomatic area and no tender pressure points were found. She did not have cutaneous abnormalities in the painful area. No manoeuvre could trigger or bring relief to the pain which was unrestrained and/or worsened with physical activity and cough. At the time, the patient referred episodic light bilateral neck pain and paresthesia in her arms and no other neurological signs.

Discussion Our patient suffered a type of headache which was located in the parietal region and fulfilled the ICHD-II diagnostic criteria for NH (Appendix of ICHD-II coded as 13.7.1). She also had episodic neck pain which never radiated to the head, but presented paresthesia in her arms and headache was unrestrained and/or worsened with physical activity and cough. Are these symptoms and the present type of headache linked to Chiari malformation type I (CMI)? In this case, the localization of the pain did not meet the criteria for Headache attributed to Chiari malformation type I (ICHD-II, code 7.7) and for Primary cough headache (ICHD-II, code 4.2), although the duration corresponded. Furthermore, the ICHD-II criteria reports in the Appendix some novel entities that have not been sufficiently validated by research studies and no specific criteria currently exist to characterise headache attribute to CMI [2].

References

1. Pareja JA, Caminero AB, Serra J et al (2002) Numular headache: a coin-shaped cephalgia. *Neurology* 58:1678–1679
2. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd edn. Cephalgia 24[Suppl 1]:1–160

Primary exertional headache because of incompetence of the internal jugular vein valve

G. Ferrarini¹, M.L. Zedde², N. Marcello³

¹Centro Cefalee, U.O. di Neurologia, Azienda Ospedaliera S. Maria Nuova, Reggio Emilia, Italy; ²Centro Neurosonologia, U.O. di

Neurologia, Azienda Ospedaliera S. Maria Nuova, Reggio Emilia,

Italy; ³U.O. di Neurologia, Azienda Ospedaliera S. Maria Nuova,

Reggio Emilia, Italy; e-mail: ferrarini.giovanni@asmn.re.it

Similar to other conditions, such as transient global amnesia, whose cause is hypothesised to be a cerebral venous congestion, triggered by an internal jugular vein valve incompetence, also in stress-related headache, the hypothesis of an impaired venous hemodynamics as a pathogenetic factor has recently been strengthened; it is thought that the increase in intrathoracic pressure, determined by the Valsalva maneuver, is directly transmitted to the valveless intracranial veins, especially in the presence of an internal jugular vein incompetence (both at the valves and in a troncular shape), with greater difficulty in venous drainage, especially at the junction of straight sinus–confluent sinus.

This condition was evaluated in a non-invasive, dynamic and repeatable manner, by using neurosonological techniques, for both extracranial and intracranial study, with a significant association with clinical symptoms.

Transient global amnesia and migraine: are they related?

G. Dalla Volta¹, P. Zavarise¹, G. Ngonga¹, C. Agosti¹, E. Premi², A. Padovani²

¹U.O. Neurologia, Istituto Clinico Città di Brescia, Brescia, Italy;

²Clinica Neurologica, Università di Brescia, Brescia, Italy;

e-mail: dalla@numerica.it

Introduction Since the initial description by Bender et al the clinical characteristics of transient global amnesia (TGA) have been well described, although we are far from an exhaustive definition of the aetiology and pathophysiology behind the disorder. If the transient dysfunction of the bilateral hippocampi represents the neuroanatomical basis, different hypotheses have been postulated to shed light on the pathological mechanism that leads to this clinical picture, like hypoxic–ischemic events, migraine-related mechanisms, venous flow abnormalities, psychological mechanisms, and epilepsy-related activity [1].

Case report A 70-year-old woman was admitted to hospital for evaluation of repeated episodes of memory loss. She was also affected by hypertension, hypercholesterolemia, anxiety-depression syndrome and migraine without aura (about 6 episodes/month with phono- and photophobia, nausea and vomiting, partially NSAID responsive). From November 2004 to September 2010 our patient experienced seven episodes characterised by sudden onset of memory loss, with inability to form new memories, repetitive questions (anterograde amnesia) and inability to access memories for past events (retrograde amnesia). The patient referred no stress activities before (only in two cases she was performing light housework). Furthermore, the patient remained amnesic for the entirety of the event itself. These attacks lasted <24 h, approximately 4 h. In all cases, the patient reported an intense headache (resembling her usual migraine) which started with the resolution of the amnesic disturbance. After every episode, the patient was admitted to hospital, and in all cases neurological examination was normal except for the cognitive impairment limited to amnesia. She had performed two MRI scans (February 2008 and September 2010) with only a small chronic ischaemic lesion in the right medial temporal cortex, as confirmed by PET scan with a focal hypometabolism in the corresponding region. EEG scans performed during the years and a EEG recording after sleep deprivation were all normal. All episodes fulfilled the current diagnostic criteria for Transient Global Amnesia.

Discussion Data in the literature and our data of up to 200 cases, show that mild vegetative symptoms like headache might be present during a TGA episode [in our sample, we found a TGA recurrence of 9% (18 cases of 200 total cases)]. Six of these presented with headache, two

with migraine with aura. Our patient, however, presented a well clinically defined migraine attack soon after the conclusion of the amnesic episodes. The clinical course, the frequency of the episodes, the absence of clear electrical abnormalities at EEG recording even after sleep deprivation, that makes transient epileptic amnesia less probable, allow us to postulate a migraine-related mechanism behind this specific clinical picture.

Conclusions We suggest that the umbrella term of transient global amnesia might encompass a different underlying mechanism, like an atypical presentation of migraine with aura [2].

References

1. Quinette P, Guillery-Girard B, Dayan J et al (2006) What does transient global amnesia really mean? Review of the literature and thorough study of 142 cases. *Brain* 129:1640–1658
2. Agosti C, Akkawi NM, Borroni B et al (2006) Recurrence in transient global amnesia: a retrospective study. *Eur J Neurol* 13(9):986–989

Placebo/Nocebo

Prevalence of placebo and nocebo effects in migraine patients attending a specialty headache center

I. Rainero, E. Rubino, F. Govone, A. Vacca, L. Pinessi

Neurology II, Department of Neuroscience, University of Turin, Turin, Italy; e-mail: irainero@molinette.piemonte.it

Introduction Placebos are typically defined as inactive substances that elicit a therapeutic response. The opposite of the placebo effect is the nocebo effect, a condition where unpleasant symptoms emerge after the administration of placebo. In randomized clinical trials (RCTs) of antimigraine drugs, a positive response to placebo is observed in about 30% of patients with migraine [1]. However, the response to placebo in RCTs may be influenced by the natural course of the disease [2]. In literature, the prevalence of side effects after placebo administration is about 19% of primary headache patients but the response after nocebo treatment has not yet been investigated. Aim of this study was to investigate the prevalence of placebo and nocebo responses in migraine patients attending an university based Headache Centre.

Materials and methods One thousand four hundred and fifty-six patients were involved in the study. Nine hundred and twenty-four migraineurs (236 men, 688 women, mean age \pm SD = 38.1 ± 13.7 - years) received a tablet containing talcum powder. According to the presence or absence of headache at the time of visit, they were told that the pill might produce reduction or disappearance of pain (placebo effect) or appearance of pain (nocebo effect). A group of 532 migraine patients (138 men, 394 women, mean age \pm SD = 39.9 ± 12.2 years) were used as controls, evaluating the spontaneous remission of the symptom without receiving treatment (natural history). Headache presence or absence in the 4 h after the test were recorded in the diary.

Results A placebo positive response was observed in 36% of migraineurs, while a nocebo positive response was reported by 16% of cases. In the no-treatment group, a significant reduction of pain was observed in 21% of subjects, while appearance of pain was observed in 17% of subjects. Hence, the true placebo effect was 15%. In addition, the reduction of the intensity of the symptoms in patients with migraine without aura was significantly higher than that observed in patients with migraine with aura ($p < 0.01$).

Discussion and conclusions Our study shows that in migraineurs a true placebo effect can be distinguished from the natural history

effect. To the best of our knowledge, this is the first study finding evidence that placebo has a true powerful clinical effect in migraineurs. This effect is more evident in patients with migraine without aura. RCTs in migraine patients should consider this interesting phenomenon in the planning of the study and in evaluating side effects of the pharmacological treatment.

References

1. Bendtsen L, Mattsson P, Zwart JA et al (2003) Placebo response in clinical randomized trials of analgesics in migraine. *Cephalalgia* 23:487–490
2. Price DD, Finniss DG, Benedetti F (2008) A comprehensive review of the placebo effects: recent advances and current thought. *Annu Rev Psychol* 59:565–590

Placebo in migraine: Pros

B. Bellini¹, F. Lucchese², V. Guidetti¹

¹Department of Paediatrics and Child and Adolescent Neuropsychiatry, Faculty of Medicine and Odontoiatric, Sapienza University of Rome, Rome, Italy; ²Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy; e-mail: vincenzo.guidetti@uniroma1.it

There is no unique definition of placebo (or placebo effect), and the most common is “any effect attributable to a pill, potion, or procedure, but not to its pharmacodynamic or specific properties” [1]. The mechanisms of placebo effect have not been definitively understood: we deal with the intriguing field of the mind/brain relationship, psychology and biology. The mechanisms of placebo are related to psychological aspects, as “desire”, “expectation”, “conditioning”. However, the placebo is not only a psychological mechanism, because it is related to the brain structure: studies have evidenced that placebo has implications also in the biological field: antidepressants have an influence both in brain structure and functions.

Placebo is a significant issue in headache disorders. Noteworthy, the placebo rate is higher in headache children than in adults. Studies on triptans showed a response to placebo from 18 to 35% in adults and from 25 to 61% in children and adolescents [1, 2]. In preventive therapy placebo response has been estimated as high as 40–50% in children; in adults, the placebo effect in preventive therapy is about 50% [3, 4].

On the one hand, the high placebo response in headache trials may be an obstacle. On the other, it is an important resource both in the clinical field and in the understanding of the mechanisms involved in triggering and relieving headache [5, 6].

References

1. Wolf S. (1959) The pharmacology of placebos. *Pharmacol Rev* 11:689–704
2. Gawel MJ, Worthington I, Maggiano A (2001) A systematic review of the use of triptans in acute migraine. *Can J Neurol Sci* 28(1):30–41. Review.
3. Winner P (2002) Triptans for migraine management in adolescents. *Headache* 42(7):675–679
4. Ramadan NM, Schultz LL, Gilkey SJ (1997) Migraine prophylactic drugs: proof of efficacy, utilization and cost. *Cephalalgia* 17(2):73–80. Review.
5. Diener HC (2010) Placebo effects in treating migraine and other headaches. *Curr Opin Investig Drugs* 11(7):735–739
6. Mitsikostas DD, Mantonakis LI, Chalarakis NG (2011) Nocebo is the enemy, not placebo. A meta-analysis of reported side effects after placebo treatment in headaches. *Cephalalgia* 31(5):550–561

Lectures

“Alessandro Agnoli” Lecture

Chairs, schools and disciplines: the story of the C. Mondino Foundation at the time of the birth of the neurosciences in Italy

G. Nappi¹, R. Nappi²

¹Headache Science Centre (HSC), University Consortium for Adaptive Disorders and Head pain (UCADH), IRCCS C. Mondino National Neurological Institute, Pavia; Chair of Neurology, Sapienza University of Rome, Rome, Italy; ²CIRNA Foundation Onlus, for the research on headache and clinical neuroscience, Pavia, Italy; e-mail: giuseppe.nappi@mondino.it

In Italy the teaching and treatment of diseases of the nervous system acquired the status of a clinical discipline after the country's unification in 1861. However, “nervous and mental diseases” were to remain within the domain of internal medicine and psychiatry until the early 1900s. A powerful impetus for the development of neuroscience in post-unification Italy was provided by Cesare Lombroso and Paolo Mantegazza, both active in the University of Pavia in Lombardy, a region that was, at the time, one of the main driving forces of the Kingdom of Italy's first two capital cities: Turin and Florence. Known as founders of anthropology and forensic medicine (after Pavia, these disciplines went on to be taught at the universities of Turin and Florence) on the strength of their studies of psychotic behaviours and the devastating physical effects of pellagra, alcoholism, malaria, and endemic cretinism, which they conducted at the University of Pavia in a period in which the Cartesian distinction between mind and brain was being superseded and the antagonism between Darwin and Freud was at its height, Lombroso and Mantegazza must be acknowledged for favouring the first attempt at integration of biological sciences and humanities, through the opening of the Voghera Mental Asylum (in 1887) and Mondino's *Clinica Neuropatologica* (in 1907). In fact, it is Mantegazza's teaching of general pathology that led to the creation of the experimental laboratory in Palazzo Botta where Camillo Golgi, Casimiro Mondino and Ottorino Rossi were trained, as indeed were a number of neuroscientists who influenced the first four decades of the twentieth century (Erspamer discovered 5-HT in '37!). Golgi, future Nobel laureate for his studies of neurons, began his career as an assistant to Lombroso who, from 1863, lectured in nervous and mental diseases and anthropology in Pavia. And it is, of course, no coincidence that, after the years spent in Palermo at the chairs of histology and psychiatry (Mondino) and in “exile” in Florence (Rossi), two of Lombroso's pupils became the first two directors of the *Clinica Neuropatologica* in Pavia, purely devoted to the teaching of nervous and mental diseases and translational research in neurosciences! [1]

Indeed, in the 1900s, Pavia and its university were forerunners of an unusual organisational model. Its creator was Mondino, a talented “manager” who, on arriving from Palermo in 1889, set out to found an institute for the treatment of “nervous disorders”, thereby paving the way for the birth of the Pavia neurological school and showing remarkable foresight, the effects of which are still felt today! [2]

It goes without saying that plenty of water has flowed under the bridges of the Po and the Ticino rivers since the time of Lombroso's physiognomic theories on a Calabrian brigand and Mantegazza's epigenetic model of the lifestyle of cocaine smokers in Argentina; after all, today, at the start of the twenty-first century, the

neurosciences have given us models of neural Darwinism that allow us to study, in parallel, the history of the single individual and his evolution over time!

References

1. Haymaker W (1953) The Founders of Neurology. C. Thomas Publisher, Springfield, IL
2. Nappi G (2011) The XXI Ottorino Rossi Award “New Series”: The Founders of Neurology. *Funct Neurol* 26(2):69–72

“Giovanni Lanzi” Lecture

Neuroimaging between head pain and depression in children

L. Mazzone

Department of Neuroscience, I.R.C.C.S. Bambino Gesù Children's Hospital, Rome, Italy; e-mail: gigimazzone@yahoo.it

In the last two decades the use of neuroimaging techniques has greatly contributed to an increase in knowledge that can help identify the neural circuit abnormalities responsible for psychiatric disorders, as well as for other childhood disorders that can have psychological and emotional implications, including headache.

In childhood, headache can be the expression of psychological difficulties, such as depression, and stressful life events have been frequently implicated in the onset, exacerbation, and maintenance of headache [1]. Conversely, headache itself can be a source of stress, leading to functional impairment. According to the 2004 revision of the International Classification of Headache Disorders (ICHD-II), “Headache attributed to psychiatric disorder” is a new category of secondary headache.

In this sort of “interplay” context, understanding if depression and headache share the same neural circuit abnormalities, or if rather the brain regions involved in depression can modulate or be modulated by head pain, and viceversa, is of crucial importance.

Previous research has indicated several brain regions that may be implicated in the pathogenesis of depression. Amygdala reactivity has been associated with symptom severity during the viewing of facial expressions of emotion in depressed preschoolers [2]. In addition, other brain regions such as nucleus accumbens and frontal cortex have also been postulated in the pathogenesis of depression, and patients with major depressive disorders show perturbed activation in these structures. However, evidence is not yet available regarding the involvement of these brain regions in the pathophysiology of headache. For this reason, neuroimaging, which could help to visualize neural activity in specific brain areas during pain perception, becomes an essential technique.

Indeed, an extensive investigation of the brain areas involved in emotion and pain perception in patients suffering from headache could represent the next step towards the understanding of this complicated interplay. Of course, a precise clinical characterisation of the type of head pain is fundamental to produce clear neuroimaging findings.

References

1. Venable VL, Carlson CR, Wilson J (2001) The role of anger and depression in recurrent headache. *Headache* 41:21–30
2. Gaffrey MS, Luby JL, Belden AC et al (2011) Association between depression severity and amygdala reactivity during sad face viewing in depressed preschoolers: an fMRI study. *J Affect Disord* 129(1–3):364–370

“Federigo Sicuteri” Lecture

Cluster-like headache: a multifaceted problem

G. Zanchin

Centro di Riferimento per le Cefalee della Regione Veneto, Dipartimento di Neuroscienze, Università di Padova, Padua, Italy; e-mail: giorgio.zanchin@unipd.it

Introduction It is well known that clinical features, which at the beginning are virtually indistinguishable from those of a primary headache, may later turn out to be related to a secondary cause. As in our previous study of rarer trigeminal autonomic cephalalgias [1], we carried out a comprehensive review of the literature on symptomatic cluster-like headache (CLH), with the aim of highlighting the main features that could lead to an early suspicion of a secondary condition.

Materials and methods We identified 156 CLH cases published from 1975 to 2008. The more frequent pathologies in association with CLH were the vascular ones (38.5%, $n = 57$), followed by tumours (25.7%, $n = 38$) and inflammatory infectious diseases (13.5%, $n = 20$). Eighty cases were excluded from further analysis, because of inadequate information. The remaining 76 were divided into two groups: those that formally satisfied the ICHD-II diagnostic criteria for cluster headache (CH), “fulfilling” group (F), $n = 38$; and those with a symptomatology in disagreement with one or more ICHD-II criteria, “not fulfilling” group (NF), $n = 38$.

Results Among the aims of this study was the possible identification of clinical features leading to the suspicion of a symptomatic origin. In the differential diagnosis with CH, red flags resulted, both for F and NF, older age (42.7 years) at onset. For NF, abnormal neurological/general examination (73.6%); duration (34.2%), frequency (15.8%) and localization (10.5%) of the attacks; headache intensity, described as moderate by 7.9% of CLH patients.

Conclusions We stress the fact that, on first observation, 50% of CLH cases presented as F, perfectly mimicking CH. Therefore, the likelihood that a secondary cause is responsible for a clinical picture mimicking a primary CH, albeit low, should always be considered to provide a correct diagnosis and appropriate treatment [2]. In this context, besides accurate clinical evaluation, the importance of neuroimaging cannot be overestimated.

References

1. Trucco M, Mainardi F, Maggioni F et al (2004) Chronic paroxysmal hemicrania, hemicrania continua and SUNCT syndrome in association with other pathologies: a review. *Cephalalgia* 24:173–184
2. Mainardi F, Trucco M, Maggioni F et al (2009) Cluster-like headache. A comprehensive reappraisal. *Cephalalgia* 30:399–412

Lecture

The e-clinical chart: a great help

R. Rapisarda¹, B. Panascia², F.P. Alesi³

¹U.O. Anestesia Rianimazione e Medicina del dolore Policlinico Vittorio Emanuele, Catania, Italy; ²Specialista in anestesia, rianimazione e medicina del dolore, Catania, Italy; ³Università di Palermo, Palermo, Italy; e-mail: sararapi@yahoo.it

After almost twenty years of management of patients with headache, we felt the need to develop a computerized tool that not only would facilitate the clinical consultation, but also make the collected data more detectable retrospectively. First of all we designed the sections of the clinical chart trying to encode all possible data. The data encoding would allow us to aggregate the information for many analyses.

The second phase of our work was to realize the computerized tool. The result does not claim to be perfect and can be refined through experience. Database and software are stored in a central server and the authorized personnel can access the programme through the local network using personal accounts. The system recognizes the users. Their identifier codes are used to sign the printouts (eg: prescription, diagnosis) with the relevant first and last name.

The e-clinical chart includes many different controls through the various sections to avoid false or missing data. Moreover, with the purpose to avoid errors, the names of cities, education, marital status, and other data may be selected from drop-down menus. All the changes are tracked and the table of the corrections can be viewed easily. The records in the tables include: changed field, old data, new data, date of the correction and author of the change.

Some automatic options help the user filling in the e-clinical chart: the fiscal code can be calculated by the system, the IHS-2004 can be obtained by selecting the criteria from the specific tables.

We have been using the software since 2009 and no longer use paper medical records. The software allows us to perform many descriptive analyses based on number of visits (also according to single doctor), drug prescriptions, diagnosis (by description or IHS code). The automatic compilation of periodic reports sent to the ASL results particularly useful. We have enhanced the efficiency saving human resources and time for research and archiving folders.

Presently we are thinking of creating a web-based version of our medical records. This would allow us to use it both in intranet environment and through the internet.

JOINT SESSIONS

SISC–SIRN: Headache and chronic pain in rehabilitation

Chronic pain in rehabilitation

S. Paolucci

Fondazione S. Lucia, IRCCS, Rome, Italy; e-mail: s.paolucci@hsantalucia.it

Although pain is a frequent and relevant complication of several neurological diseases, affecting activities of daily living, rehabilitation results and quality of life, epidemiological data both on its frequency and treatment are not very exhaustive. Neuropathic pain is caused by diseases or trauma that produce lesions in the central [e.g., stroke, spinal cord injury, multiple sclerosis (MS)] or peripheral (e.g., surgery, diabetic neuropathy, herpes zoster) nervous system.

In particular, chronic pain after stroke occurs in nearly 30% of stroke survivors, though the range is very wide (11–55%). The most common forms of chronic post-stroke pain are shoulder pain, central post stroke pain (CPSP), painful spasticity, and tension-type headache. CPSP is a presenting symptom in a quarter of patients, but usually develops 3–6 months after stroke.

Similarly, pain is common in patients with multiple sclerosis (MS), but estimates of its prevalence have varied widely. Estimates of the prevalence of pain in MS range from 29 to 86%. The presence of pain in patients with MS is associated with increased age, duration of illness, depression, degree of functional impairment, and fatigue. Several different types of pain are found in patients with MS, including extremity pain, trigeminal neuralgia, Lhermitte's sign, painful tonic spasms, back pain, and headache.

Also the epidemiology of painful diabetic neuropathy (PDN) has not been well established: the prevalence of pain ranges from 10 to 20% in patients with diabetes and from 40 to 50% in those with diabetic neuropathy.

Because of the high prevalence of pain in patients with neurological diseases, it is necessary to educate physicians, who, in most cases, do not consider pain an important concern in these patients. In fact, only a minority of patients are adequately evaluated and treated. In fact, neuropathic pain is often difficult to treat; the treatment response is mostly moderate, and the dosage is limited by side effects, particularly in elderly patients. Moreover, there are only a few randomised controlled studies on treatment of neuropathic pain and there are no published trials on polypharmacy for these patients.

Chronic head and neck pain syndromes: local pharmacological treatments

M.G. Buzzi, F. Rizzi

IRCCS Fondazione Santa Lucia, Rome, Italy;
e-mail: mg.buzzi@hsantalucia.it

Local pharmacological treatment (LPhT) of head and pain syndromes is not the most common therapeutic approach, even though it may represent a useful option in some conditions. Among those, lack of response or low compliance, as well as limitations due to other diseases or side effects, are the most common causes to avoid use of systemic treatment. Besides, recognition of local factors, either clinically relevant or strongly suggested by identified pathophysiological mechanisms underlying the pain syndrome, may lead to approach the pain with LPhT, in order to minimize the activity of local factor or to abort the pain cascade mechanisms stemming from a certain, identified trigger point. LPhT has a further advantage which is represented by the possibility of repeated administration over time without any long-term side effects (unless antibodies to the compounds are generated). Controversies are about the mechanisms of action that specific substances have in reducing pain. This is the case for Botulin Neurotoxin A (BoNTA) which has been widely used in pre-clinical trials to reduce the burden of chronic migraine (CM). In fact, the acetylcholine-mediated muscle activity which is reduced by BoNTA does not represent the main mechanism mediating reduction of pain in this syndrome. The inhibition of Glu and CGRP release from nerve terminals and subsequent reduction of sensitization mechanism, is indeed the most credited (and expected) mode of action of BoNTA. The experience in other conditions in which BoNTA is locally administered, such as spasticity due to CNS injury, shows, in fact, that the pain that accompanies spasticity improves before muscle tone is reduced. Conversely, studies with BoNTA in chronic tension-type headache (CTTH) do not provide clear data. Local anaesthetics to reduce tender point sensitivity (by blocking peripheral nociceptors) in CTTH or to block nerve activity in several forms of headache are easy to understand. This is the case of great occipital nerve (GON) block in cluster headache (CH) or CM or new daily persistent headache (NDPH) in which some of the peripheral components of more complex conditions may serve to inhibit pain presentation for a limited

period of time. No relief is obtained in CTTH. Adding steroids to anaesthetic during the same procedure does not increase the effectiveness of the treatment. In CH, intranasal or sphenopalatine ganglion (SPG) lidocaine application as well as intranasal cocaine may serve to abort the acute pain, the latter being limited by legal and abuse-related problems. More recently, local opiates have also been tested. Alcohol injection or lidocaine application is used to reduce and temporarily abort trigeminal neuralgia (TN) pain. They are particularly useful in those refractory to medical management and in those who are unable or unwilling to undergo neurosurgery treatment. Interestingly, local application of capsaicin cream has been recently introduced to reduce pain and itching following herpetic neuralgia. Capsaicin, the neuro-active ingredient of hot pepper, depletes nerve terminals from pro-inflammatory substances, to reduce local sensitization and pain, therefore acting as a neurotransmitter-modulating drug.

Headache attributed to neck disorders are represented by cervicogenic headache (CGH), headache attributed to retro-pharyngeal tendinitis and headache attributed to cranio-cervical dystonia. The treatment of choice of CGH is represented by blockade of a cervical structure or its nerve supply, and this is also a mandatory criterion to diagnose CGH according to the international guidelines (ICHD-II), whereas local botulin toxin is the treatment of choice for cervical dystonia. There is no standard protocol for using local muscle-relaxant substances (either cream or injection).

Most chronic pain syndromes, however, should not be treated only by reducing the symptom but also regarded as multi-modal conditions and approached through association of other long-term rehabilitation procedures including relaxation, physical therapy and psychotherapy, to reduce the role of physical and/or psychological factors favouring pain chronification or being consequences of the chronic pain.

Non invasive brain stimulation techniques in chronic pain syndrome: pathophysiological insight and therapeutical perspective

F. Brighina¹, F. Giglia¹, M. de Tommaso², B. Fierro¹

¹Università di Palermo, Palermo, Italy; ²Università di Bari, Bari, Italy; e-mail: fbrighina@unipa.it

Chronic pain represents a relevant medical condition with detrimental effects on life quality. Patients with chronic pain may not respond to standard pharmacological therapies and may require other alternative approaches to relieve symptoms. In 1991, Tsubokawa et al [1] effectively treated 12 patients with chronic central, drug-resistant neuropathic pain with motor cortex stimulation (MCS) by dural implanted electrodes. In the following years, new opportunities came with the introduction of techniques able to perform non invasive painless brain stimulation through application of magnetic or electric currents on the scalp. Firstly, transcranial magnetic stimulation (TMS), that works through magnetic fields, was shown able to induce direct neuronal stimulation and, when given in repeated pulses (repetitive TMS: rTMS), long-lasting plastic changes, whose effects depend on the stimulation frequency used: increased or decreased excitability following low-or high-frequency rTMS, respectively. In the last few years, transcranial direct current stimulation (tDCS) that works through low-intensity direct electric currents applied on the scalp, showed ability to modulate cortical activation according to stimulation polarity (anodic → facilitation; cathodic → inhibition) with plastic effects overlasting stimulation. The first evidence of efficacy of motor cortex rTMS for control of chronic pain was

reported by Migita et al (1995) [2] that showed pain reduction in two patients treated by low-frequency (0.2 Hz) rTMS. Since then, evidence of the potential effect of motor cortex rTMS on pain control has been reported in patients as well as in pain models in healthy subjects. Interesting results on pain syndromes came also by stimulation of another cortical area: the dorsolateral prefrontal cortex (DLPFC). First indicated as a valid stimulation area for the treatment of depressive states, recently the DLPFC has also been considered a potential target for nociceptive control [3].

DLPFC stimulation can be effective in pain control significantly increasing the threshold for thermal and pain sensation in healthy subjects and reducing clinical symptoms and the need for analgesic drugs on postoperative and neuropathic pain. Moreover, DLPFC rTMS has been found effective for the treatment of other pain conditions such as chronic migraine and fibromyalgia. More recently, evidence of pain reduction in patients and in pain models in healthy subjects on both motor cortex and DLPFC have also been reported by application of tDCS. As concerns mechanisms underlying analgesic effects, it seems that motor cortex stimulation may act by decreasing the somatosensory-discriminative aspect of pain, while stimulation of DLPFC may effect the affective-emotional aspect of pain, reducing the unpleasantness of a perceived stimulus [4].

References

1. Tsubokawa T, Katayama Y, Yamamoto T et al (1991) Chronic motor cortex stimulation for the treatment of central pain. *Acta Neurochir Suppl (Wien)* 52:137–139
2. Migita K, Uozumi T, Arita K et al (1995) Transcranial magnetic coil stimulation of motor cortex in patients with central pain. *Neurosurgery* 36:1037–1039
3. Lorenz J, Minoshima S, Casey KL (2003) Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain* 126:1079–1091
4. Zaghi S, Heine N, Fregni F (2009) Brain stimulation for the treatment of pain: a review of costs, clinical effects, and mechanisms of treatment for three different central neuromodulatory approaches. *J Pain Manag* 2:339–352

Chronic headaches and psychopathology: a comparison of psychotherapies

M. D'Ippolito, E. Azicnuda, D. Silvestro

Post-Coma Unit, IRCCS Santa Lucia Foundation, Rome, Italy;
e-mail: mg.dippolito@hsantalucia.it

Diseases involving chronic pain are particularly disabling, because pain influences every aspect of the person's life: autonomy is limited, working and social habits are often impaired, as well as relationships. Chronic pain is often associated to the presence of mood disorder, particularly depression, anxiety and adaptation disorders. The choice of the therapy depends on the type of pain, from its intensity and from the patient's response to the treatment.

For chronic pain control, the psychotherapy or the psychological support can be useful treatments and can be associated with the pharmacological therapies. Specific techniques (e.g., biofeedback, relaxation therapies, etc.) allow to work on some aspects, such as adaptation and self-control abilities, allowing the patient to reduce the pain and associated behavioural disturbances. Instead, psychological counseling, offers the patient a space where to treat psychological suffering and manage pain, by means of recognition of dysfunctional

reactions and through the analysis of emotions, hopes, beliefs, inner resources and capabilities.

The Gestalt Therapy and the Transactional Analysis which analyze and use the body and mental processes in their complex interaction: cognition, the emotions' physiology, the memories, the imaginative, the body movements, and language, represent possible psychotherapeutic approaches in patients suffering from chronic pain syndromes.

Joint session SISC–SINC

rTMS and tDCS: Neurophysiological bases and safety

F. Brighina, G. Cosentino, A. Palermo, G. Giglia, B. Fierro

University of Palermo, Palermo, Italy; e-mail: fbrighina@unipa.it

Non-invasive brain stimulation is principally based on the application of magnetic fields and more recently also of direct electric currents through the scalp. Two techniques are currently employed: Transcranial magnetic stimulation (TMS) and Transcranial direct current stimulation (tDCS). TMS acts through magnetic pulses that can easily go through the scalp without distortion and induce potential action in the underlying cortical neurons. TMS can be delivered in single stimuli or in repeated pulses at different stimulation frequency: repetitive TMS (rTMS). rTMS can induce plastic effects depending on stimulation frequency (≤ 1 Hz \rightarrow inhibition; > 1 Hz \rightarrow facilitation) and last after stimulation (short- and long-term plasticity) proportionally to intensity and duration of the train. Initially employed on motor cortex, where it is clinically used to explore integrity of motor pathways, TMS has been then applied over non-motor cortical areas for studying cognitive processing. In this domain the technique has been employed to induce virtual lesioning (i.e., subtle and transitory functional disruption) of a given area to evaluate its role in a specific cognitive function. Single-pulse TMS or brief rTMS trains have been used during cognitive tasks in precisely timed tasks to disrupt cognitive processing (online paradigms); differently, longer low-frequency rTMS has been used before cognitive task (offline paradigm) to depress cortical activity of specific areas. Moreover, rTMS because of its ability to induce long-lasting facilitatory and inhibitory effects has been employed for therapeutical purposes applying stimulation in repeated sessions (once or twice daily or on alternate days) with the hypothesis to obtain cumulative plastic effects to counteract abnormalities of cortical excitability and activation showed to play a pathophysiological role in several neuropsychiatric diseases.

tDCS acts through application of low-intensity (1–2 mA) direct electric currents on the scalp. Differently from TMS, tDCS is not able to induce direct activation of cortical neurons but can act by modifying cellular polarization in a direction that depends on the current stimulation polarity employed: anodic currents favour depolarization, increase of spontaneous neuronal activity and facilitation; cathodic currents induce hyperpolarization, decrease of spontaneous activity and inhibition. As for rTMS, tDCS is able to induce long lasting facilitatory and inhibitory effects and has been employed also for studying cognitive functions and in therapeutic, rehabilitative protocols. tDCS is easier to use and less expensive than TMS requiring only, a cheap and portable device. As for safety concerns, no relevant side effects have been reported and both techniques can be considered safe if used in adequate stimulation intensity and duration ranges.

The rTMS and tDCS in primary headaches: basilar mechanisms and evidence of efficacy

M. de Tommaso

Dipartimento di Neuroscienze Cliniche e Organi di Senso, Università di Bari Aldo Moro, Bari, Italy; e-mail: m.detommaso@neurol.uniba.it

Introduction Non-invasive brain stimulation techniques aim to induce an electrical stimulation of the brain in an attempt to reduce chronic pain by directly altering brain activity. They include repetitive transcranial magnetic stimulation (rTMS), cranial electrotherapy stimulation (CES) and transcranial direct current stimulation (tDCS).

Objectives To evaluate the possible mechanisms of action of brain stimulation technique in primary headaches and the present evidence of their efficacy.

Results Based on the theory that sTMS may disrupt cortical spreading depression, sTMS has been studied and shown to be effective as an acute treatment for migraine with aura. The rTMS of the dorso lateral prefrontal cortex reduced headache frequency in chronic migraine patients [1], while the stimulation of the motor area were able to modulate pain rating and cortical responses by laser stimuli in migraine patients [2]. The low frequency rTMS of the vertex reduced migraine frequency, though not in a significant way in regard to placebo. The safety of TMS (sTMS) in clinical practice, included as an acute migraine headache treatment, is supported by biological, empirical, and clinical trial evidence. Single-pulse TMS may offer a safe nonpharmacologic, nonbehavioural therapeutic approach to the currently prescribed drugs for patients who suffer from migraine. The TDCS was effective in modulating somatosensory nociceptive and non nociceptive responses in normal subjects and migraine without aura patients.

Conclusions Few studies support the evidence of positive effects of rTMS and TDCS in primary headache, but considering the theoretical basis and the safety of these procedures, multi-centre studies would contribute to confirm their potential role in primary headaches treatment.

References

1. Brighina F, Piazza A, Vitello G et al (2004) rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. *J Neurol Sci* 227:67–71
2. de Tommaso M, Brighina F, Fierro B et al (2011) Effects of high-frequency repetitive transcranial magnetic stimulation of primary motor cortex on laser-evoked potentials in migraine. *J Headache Pain* doi:10.1007/s10194-010-0247-7

Short-term synaptic plasticity in migraine motor cortex: evidence by preconditioning of high-frequency repetitive transcranial magnetic stimulation (rTMS) with transcranial direct current stimulation (tDCS)

G. Cosentino, S. Talamanca, P. Paladino, S. Vigneri, A. Palermo, B. Fierro, F. Brighina

Dipartimento di Biomedicina Sperimentale e Neuroscienze Cliniche (BioNeC), Università di Palermo, Palermo, Italy; e-mail: gcosentino80@gmail.com

Background Brief trains of 5-Hz repetitive transcranial magnetic stimulation (rTMS) delivered at stimulation intensity equal or up to 120% of the resting motor threshold (RMT) determine in healthy

subjects a progressive facilitation of motor evoked potentials (MEPs) likely due to facilitatory mechanisms of short-term presynaptic plasticity. In a recent work we showed an opposite response of migraine motor-cortex to 5-Hz rTMS when delivered at different stimulation intensities: MEP facilitation at 110% and paradoxical MEP inhibition at 130% of the RMT. These results seem to provide evidence of both hyper-responsivity and self-limiting hyperexcitability capacity in migraine, in line with studies supporting the concept that under conditions of cortical hyperexcitability inhibitory mechanisms of homeostatic plasticity could be activated. To support this hypothesis, in the present study we applied in migraine patients cathodal transcranial direct current stimulation (tDCS) to reduce experimentally the level of motor-cortical excitability and subsequently assess the motor-cortical response during the 5-Hz rTMS trains delivered at high stimulation intensity.

Methods Ten patients affected by migraine with aura received brief trains of 5-Hz rTMS to the motor cortex at an intensity of 130% of the RMT, with recording of the EMG traces evoked by each stimulus of the train from the contralateral abductor pollicis brevis (APB). This interventional protocol was preconditioned by 10 min of cathodal tDCS delivered at 1 mA intensity.

Results As expected MEP decreased significantly in size during trains of 5-Hz before tDCS preconditioning. Conversely, after inhibitory preconditioning with cathodal tDCS, 5-Hz rTMS trains determined a reduction in the first MEP size and a trend toward MEP facilitation during the trains.

Conclusions Inhibitory cathodal tDCS preconditioning is able to normalize the response of migraine motor-cortex to rTMS trains at 130% of RMT. This support the hypothesis that in migraine motor cortex the mechanisms of short-term presynaptic plasticity evaluated by 5-Hz rTMS trains could be affected interically by an abnormal increased cortical excitability level.

Effects of theta burst stimulation protocols on visual cortex habituation

A. Perrotta¹, E. Iezzi¹, A. Nardella², M. Bolla², A. Ambrosini¹, F. Pierelli³

¹Headache Clinic, INM Neuromed IRCCS, Pozzilli, Italy;

²IRCCS Neurological National Institute C. Mondino, Pavia, Italy;

³Department of Medical and Surgical Sciences and Biotechnologies, Sapienza University of Rome, Polo Pontino, Latina, Italy; e-mail: armando.perrotta@uniroma1.it

Introduction Habituation deficit of stimulus-evoked cortical responses represent a key physiopathological feature of migraine cerebral cortex. It has been demonstrated that repetitive transcranial magnetic stimulation (rTMS) is able to modify the excitability of visual cortex in both migraineurs and healthy subjects. More recently, two new rTMS protocols have been introduced: continuous and intermittent theta burst stimulation (cTBS and iTBS), potentially involved in long-term potentiation/depression-like effect at cortical level. The study was designed to test whether cTBS and iTBS have effects on habituation of pattern-reversal visual-evoked potentials (VEP).

Methods In 10 healthy volunteers and 10 patients with episodic migraine without aura during the interictal phase, VEP habituation (percentage change between the first and the sixth block of six sequential blocks of 100 responses) was measured before and 5, 15, 30 and 60 min after application of either continuous or intermittent theta burst stimulation (cTBS/iTBS; 600 total pulses at 80% phosphene threshold).

Results In healthy subjects iTBS reduced the phosphene threshold by an average of 9%, no differences were detected with cTBS. In migraineurs no changes were detected in phosphene threshold after both cTBS and iTBS. No significant changes were detected in the 1st block VEP amplitude after both iTBS and cTBS in both healthy subjects and migraineurs. In healthy subjects the VEP habituation pattern disappeared (dishabituation) after both iTBS and cTBS between 5 and 30 min after TMS. In migraineurs no effects were detected after iTBS, on the contrary, cTBS induced a transient VEP habituation 15 min after stimulation.

Conclusions Our data confirm a different functional state of the visual cerebral cortex between healthy subjects and migraineurs during the interictal phase. It is difficult to say in which way both cTBS and iTBS modulates visual cortex in healthy subjects and because in migraineurs these modulations are largely lacking. As there is strong evidence that the modulatory effects of different rTMS interventions are critically dependent on the functional state of activity of the stimulated cortex, these could partially explain the differences between healthy subjects and migraineurs. Further studies are needed to better characterise the effect underlying the different protocols of the TBS.

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

E. Vecchio, C. Serpino, V. De Vito Francesco, K. Ricci, M. Delussi, G. Franco, M. de Tommaso

Department of Neurological Sciences, Neurophysiopathology of Pain, Aldo Moro University, Bari, Italy;
e-mail: eleonora.vecchio@gmail.com

Introduction Non-invasive brain stimulation techniques induce an electrical stimulation of the brain in an attempt to reduce chronic pain by directly altering brain activity. In this case-control study we compared the effects of transcranial direct current stimulation (tDCS) of the left primary motor cortex (M1) and left dorsolateral prefrontal cortex (DLPFC) both on subjective pain and on evoked responses induced by laser stimulation (LEPs).

Methods The study was conducted in a cohort of 25 migraine patients without aura during the inter-critical phase, and 10 age- and sex-matched non-migraine healthy controls. Among migraine patients, we stimulated left DLPFC area in 17 cases and M1 area in 8 cases. Evoked laser potentials were recorded in basal, sham and during tDCS, by stimulating the contralateral hand and supraorbital zone. For tDCS a constant current of 2 mA intensity was applied for 20 min. For sham stimulation, the electrodes were placed in the same positions as for real stimulation, but the stimulator was turned off after 30 s and thereafter received no stimulation for 10 min. The one-way ANOVA was used to analyse the data where the LEP latency, amplitude, N2–P2 amplitude, and the laser pain rating were variables, the session (baseline, tDCS and sham) within subject factor. To compare the variables across the three different sessions, a post hoc multiple comparison Bonferroni test was applied to the single groups.

Results We found a significant reduction of N2–P2 amplitude among cases who received tDCS of the left M1, while the stimulation of DLPFC gave no significant change in any LEPs parameters.

Discussion Only few studies with small sample size examined the effects of tDCS on chronic pain and gave conflicting results [1, 2]. Therefore, there is limited evidence that tDCS to the motor or sensory cortex may have short-term effects on chronic pain.

Conclusions Our results are in agreement with recent reports [1] demonstrating that tDCS over the motor cortex significantly ameliorated acute pain perception and various symptoms related to chronic pain syndromes. Further studies are needed to clarify the possible role of tDCS in the management of migraine.

References

1. Antal A, Brepohl N, Poreisz C et al (2008) Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. *Clin J Pain* 24:56–63
2. O'Connell NE, Wand BM, Marston L et al (2010) Non-invasive brain stimulation techniques for chronic pain (Review). The Cochrane Collaboration published in The Cochrane Library. Issue 11

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

M. Bolla¹, A. Perrotta², A. Ambrosini², C. Tassorelli¹, M. Serrao³, A. Priori⁴, F. Pierelli⁵, G. Sandrini¹

¹IRCCS Neurological National Institute C. Mondino, Pavia, Italy;

²Headache Clinic, IRCCS INM Neuromed, Pozzilli, Italy;

³Neurorehabilitation Unit, Sapienza University of Rome, Polo Pontino-ICOT, Latina, Italy; ⁴IRCCS Ospedale Maggiore Policlinico Foundation, Milan, Italy; ⁵Department of Medical and Surgical Sciences and Biotechnologies, Sapienza University of Rome, Polo Pontino, Latina, Italy; e-mail: monica.bolla@mondino.it

Spinal direct current stimulation (sDCS) has been recently proven to modulate nociceptive withdrawal reflex (NWR), an objective and sensitive tool for pain investigation, suggesting its possible application as an anti-nociceptive treatment. The NWR temporal summation threshold (TST) that develops in parallel with the temporal summation of pain and that, in turn, reflects the level of facilitation in pain processing, is considered a sensitive tool to study neural plasticity processes linked to central sensitization of pain pathways, a mechanism thought to be involved in the genesis and maintenance of several pain conditions. To best characterise the potential analgesic effect of sDCS and its possible application in chronic pain, the aim of our study was to investigate the effect of sDCS on TST in a group of healthy volunteers.

Subjects and methods Ten healthy volunteers without any personal history of pain conditions and depression were enrolled in the study. The study protocol comprised recordings of TST at right leg before sDCS stimulation (baseline) and immediately (T0), 30 min (T30) and 60 min (T60) after DCS offset. To detect the TST the sural nerve was stimulated using a constant current train of five individual 1-ms pulses delivered at 200 Hz repeated five times at a frequency of 2 Hz. The subjects rated the psychophysical pain sensation for the first and fifth stimulus on a numerical rating scale. sDCS treatment consisted of a 2 mA, 15 min direct current stimulation where electrodes were positioned in correspondence to the spinal process of the tenth thoracic vertebra and to the right shoulder. Each subject underwent three treatment conditions (anodal, cathodal and sham) tested randomly in a double-blind, cross-over design, with an inter-session elapse of at least 1 week. The terms of anodal or cathodal refer to the electrode positioned at the spinal level. In sham session no efficacy stimulation passed after the first 10 s stimulator switched on.

Results TST was significantly increased at T30 and T60 min after anodal sDCS, whereas cathodal and sham stimulation left TST unchanged across sessions. A trend in the reduction in pain perception

rated by NRS was found, however, without reaching statistical significance.

Discussion and conclusions Our data demonstrated that sDCS is able to modulate TST in healthy volunteers. In consideration of our assumption these results may suggest a possible application of sDCS in chronic pain conditions encouraging further investigations in pain pathologies.

Pros on the therapeutic use of rTMS and tDCS in migraine

M. de Tommaso¹, F. Brighina²

¹University of Bari Aldo Moro, Bari, Italy; ²University of Palermo, Palermo, Italy; e-mail: m.detommaso@neurol.uniba.it; fbrighina@unipa.it

Techniques of non invasive brain stimulation, based on delivering of magnetic fields and more recently also on application of electric currents through the scalp, showed increasing interest in the scientific community in the last few years. Transcranial magnetic stimulation (TMS) is able to induce direct activation of cerebral cortex through very fastly increasing magnetic fields. When given in repeated pulses, repeated TMS (rTMS), the technique is able to induce changes in cortical excitability that depend on stimulation frequency (1 Hz or lower → inhibition; higher than 1 Hz → facilitation) that could persist even after the end of the train depending on the intensity and the duration of the stimulation. Differently from TMS, tDCS cannot induce direct neuronal activation but can act by modifying cellular polarization in a direction that depends on the current stimulation polarity employed: anodic currents favor depolarization, increase of spontaneous neuronal activity and facilitation; cathodic currents induce hyperpolarization, decrease of spontaneous activity and inhibition. Based on such peculiarities, both techniques showed ability to induce relevant and long lasting modulation of cerebral cortex excitability and activity and have been studied as potential tools for treatment of several neuropsychiatric diseases in which dysfunction of cortical excitability and activation have been described and considered to play a relevant pathophysiological role. In this respect, also migraine and in particular migraine with aura, where abnormalities of cortical function have consistently been found, could represent good therapeutic targets for the application of such non invasive brain stimulation techniques. Even if only a few therapeutic prophylactic trials have been until now carried out on small series, both techniques show good potential for efficacy being able to induce long lasting plastic effects. Thus, it is time that rTMS and tDCS be explored in multicentric randomized controlled trials on an adequate number of patients, to evaluate their efficacy for treatment of migraine.

Cons on the therapeutic use of rTMS and tDCS in migraine

A. Ambrosini¹, M. Valeriani²

¹Headache Clinic, INM Neuromed, IRCCS, Pozzilli, Isernia, Italy; ²Headache Centre, Neurology Division, Bambino Gesù Paediatric Hospital, IRCCS, Rome, Italy; e-mail: anna.ambrosini@neuromed.it; m.valeriani@tiscali.it

Although in the past 50 years many efforts have been made to improve knowledge on migraine pathophysiology, the true core of the disease is

still far to be completely understood. Many neurophysiological studies have been performed, in order to elucidate if there is, and what is a neurophysiological behaviour common to each migraine patient. Some outstanding results have been reached, such as the identification of reduced brain response habituation to repetitive stimuli as a common marker in migraineurs. Other methods, such as transcranial magnetic stimulation (TMS), however, have given conflicting results, as a part of investigations suggested increased cortical excitability in migraineurs, other studies showed normal or lower excitability, and some of them found a higher instability of cortical excitability in migraineurs than in controls. Several TMS investigations suggested a possible reduction of cortical inhibition as the main neurophysiological abnormality in migraine, but this was not confirmed by studies applying sophisticated analyses of evoked potentials.

The use of repetitive TMS (rTMS), able to modify cortical excitability, proved useful in some pathological conditions, such as depression and neuropathic pain, and it has been proposed to be relevant in migraine treatment. However, several elements raise doubts about the effectiveness of rTMS as a preventative treatment of migraine. First, the main neurophysiological defect in migraine is still far to be known. Second, even if a defect were definitely found, its correction would not necessarily lead to a clinical improvement. Third, since migraine is a paroxysmal disorder, in which attacks are separated by pain-free interictal intervals, a prophylactic treatment should have a sufficiently long-lasting effect. Unfortunately, there is only weak information about the duration of the rTMS effect even in diseases in which this technique was proved effective. Fourth, low frequency TMS—which should reduce cortical excitability—was not superior to placebo in migraine prophylaxis.

Single pulse TMS has been shown effective in disrupting cortical spreading depression, which is known to be at the basis of the migraine aura. Its use during aura by means of a portable device was able to treat the following migraineous pain in some migraineurs (39%) but its therapeutic effect was very low and not larger than placebo effect (22% responders).

In conclusion, though fascinating, the therapeutic use of TMS in migraine needs many other studies which should also demonstrate the advantages of TMS, as compared to the common pharmacological treatments, in terms of effectiveness, patients' compliance and side effects.

Joint session SISC–SINPF

Clinical pharmacology of amitriptyline chloridrate plus chlordiazepoxide and real life experience for the prophylaxis of migraine

L. Triggiani¹, G. Santamarena², R. Corona¹

¹Centre for the Diagnosis and Treatment of Headaches and Facial Pain, Order of Malta Hospital, Rome, Italy; ²Neuropsychology Service, San Giovanni Battista, Order of Malta Hospital, Rome, Italy; e-mail: ltriggiani@gmail.com

Background Migraine is linked to anxiety and depression. The conditions may share common biological causes since antidepressant drugs are used in migraine prophylaxis, and the serotonin agonists used to treat migraine may decrease depression. Amitriptyline is one of the most commonly used medications in migraine prophylaxis. The use of a fixed dose of amitriptyline combined with chlordiazepoxide, a benzodiazepine derivative, may be effective for the prophylactic treatment of migraine.

Methods A real life observational study was conducted among patients of a Headache Centre. Male and female patients over 18 years of age were eligible for inclusion in the study if they met International Headache Society criteria for migraine and presented two or more attacks per month lasting more than 48 h and minor depressive comorbidity. Tablets with a fixed dose of amitriptyline chloridrate (14.15 or 28.3 mg, respectively, equivalent to 12.5 or 25 mg of base amitriptyline) plus chlorthalidopoxide (5 or 10 mg) were administered once daily for the prophylactic treatment of patients. Follow-up examination was scheduled every 3 months.

Results Forty-seven patients, respectively, 38 women and 9 men, were included in the study. Mean age was 45.9 ± 13.0 years, without differences between women (45.9 ± 13.2) and men (45.8 ± 13.1). Twenty-six patients (55%) attended the follow-up examinations while 21 (45%) missed the follow-up examinations and thus were considered drop-out. Seven patients went on 25/10 mg and 19 on 12.5/5 mg treatment. Mean duration of treatment was 6.3 ± 3.0 months. Sixteen patients (61.5%) had a reduction of the number of migraine attacks equal or over 50%, 6 patients (23.1%) had a reduction of the number of attacks <50%, while 4 patients (15.4%) did not show an improvement. None of the patients reported serious adverse side effects and only 2 (7.7%) required a reduction of the dose because of excessive daytime sleepiness.

Conclusions The co-existing relationship between migraine, depression, and anxiety disorders can have important clinical implications. Treatment of one condition could help prevent progression to one or both of the other two. Although information about drop-out patients is not available, the results of the present study seem to indicate that the use of a fixed dose of amitriptyline combined with chlorthalidopoxide is an effective treatment for the prophylaxis of migraine as 61.5% of the patients who completed the study had a more than 50% reduction of the number of attacks. Amitriptyline is a first-line agent for migraine prophylaxis and is the only antidepressant with consistent evidence supporting its effectiveness for this use. Chlorthalidopoxide has a medium to long half life but its active metabolite has a very long half life. The drug has amnestic, anxiolytic, hypnotic and skeletal muscle relaxant properties. The combination of amitriptyline and chlorthalidopoxide may have a synergistic effect thus permitting to use low dosages of the two drugs and minimizing the risk of side effects. These results need to be validated by a specific randomized clinical trial.

Migraine throughout the life cycle: treatment through the ages

C. Mencacci, G. Cerveri

Dipartimento di Neuroscienze, A.O. Fatebenefratelli e Oftalmico, Milan, Italy; e-mail: Giancarlo.cerveri@fbf.milano.it

Migraine is prevalent in women during the fertile age. Indeed, both neuroendocrine events related to reproductive stages (menarche, pregnancy, and menopause) and menstrual cyclicity and the use of exogenous sex hormones, such as hormonal contraception and replacement therapy, may cause significant changes in the clinical pattern of migraine [1].

Levels of sex hormones fluctuate throughout the female life cycle, and these fluctuations may trigger, intensify, or alleviate migraine. Estrogen variations are highly implicated in modulating the threshold to challenges by altering neuronal excitability, cerebral vasoactivity, pain sensitivity, and neuroendocrine axes throughout the menstrual cycle and not only at the time of menstruation. On the other hand, estrogen withdrawal may really constitute a triggering factor for migraine in women with peculiar characteristics of vulnerability with menstruation or following the discontinuation of exogenous estrogen, as happens with hormonal contraception during the fertile age or with hormone therapy at menopause. In addition, exogenous estrogen may contribute to the occurrence of neurological symptoms, such as aura. The menstrual cycle is the result of a carefully orchestrated sequence of interactions between the hypothalamus, pituitary, ovary, and endometrium, with the sex hormones acting as modulators and effectors at each level. The primary trigger of Menstrually-related migraine (MM) appears to be the withdrawal of estrogen rather than the maintenance of sustained high or low estrogen levels. However, changes in the sustained estrogen levels with pregnancy (increased) and menopause (decreased) appear to affect headaches. Headaches associated with oral contraceptives (OC) use or menopausal hormonal replacement therapy may be related, in part, to periodic discontinuation of oral sex hormone preparations. The treatment of migraine associated with changes in sex hormone levels is frequently difficult and the patients are often refractory to therapy. Based on what is known of the pathophysiology of migraine, we have attempted to provide a logical approach to the treatment of headaches that are associated with menses, menopause, and OCs using preventive medications and hormonal manipulations.

Drugs can be used both preventively and therapeutically to combat the headache that results in some women from such fluctuations. Migraine seriously impairs the quality of life in those who suffer from it and exacts a high socioeconomic cost in lost productivity [2]. About half of all persons with migraine go undiagnosed. To avoid misdiagnosis of migraine, clinicians must be prepared to recognize atypical presentations, including life cycle related presentations.

References

1. Stovner L, Hagen K, Jensen R et al (2007) The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia* 27(3):193–210
2. Lipton RB, Stewart WF, Simon D (1998) Medical consultation for migraine: results from the American Migraine Study. *Headache* 38(2):87–96

Headache clinical aspects

Migraineurs show more anatomical variants of the circle of Willis and brain lesions: special aspects in migraine with aura

C. Cavestro¹, L. Richetta², M.R. L'Episcopo¹, E. Pedemonte¹, S. Duca³, C. Di Pietrantonj⁴

¹Headache Centre, Department of Neurology, San Lazzaro Hospital, ASL CN2, Alba, Italy; ²Department of Neuroradiology, Maggiore Santissima Trinità Hospital, Fossano, Italy; ³Department of Neuroradiology, Koelliker Hospital, Turin, Italy; ⁴Regional Epidemiology Service SeREMI, ASL AL, Alessandria, Italy; e-mail: cicaves@alice.it

Background Some reports documented vascular alterations in brain MRI in migraineurs and a relation between circle of Willis (Circle) variants and lacunar brain infarcts [1]. Migraine with aura is also linked to a higher frequency of stroke. We examined anomalies of the whole circle of Willis and their relationship with vascular brain lesions in migraineurs, to identify any possible vascular mechanism in migraine and relation with stroke.

Methods We studied, with a cohort controlled study, the circle of Willis in migraineurs seen consecutively in our Headache Centre, and in non-headache controls, using angio-MRI of the brain. Statistical analysis used: ANOVA, Scheffè's criterion, and *t* Student test.

Results We recruited 270 migraineurs, 66 with aura (MA) and 159 controls. Anatomical variants were detected in 108 (40%) migraineurs and 34 controls (21.4%). We found a significant association between MO and variants [OR = 2.4 IC 95% (1.5–3.9)] and between MA and variants [OR = 3.2 IC 95% (1.6–4.1)]. Unilateral posterior variants with basilar hypoplasia are statistically associated only with MA compared to controls [OR = 9.2, IC 95% (2.3–37.2)]. Thirty-three percent of MO and 24% of MA sufferers present some kind of brain lesion, included 2% of infra-tentorial lesions. We did not find any statistical association between the presence of Circle variants and ischaemic lesions in MRI [OR = 1.5 IC 95% (0.68; 1.94)], or with infra-tentorial lacunar lesions [OR = 1.58 IC 95% (0.48–5.24)].

Conclusions Anatomical variants of the Circle of Willis were significantly more frequent in migraineurs; posterior anomalies were more frequent in MA, suggesting a vascular mechanism provoking changes in cerebral blood flow, thereby stimulating cortical spreading depression; recent neuroradiologic data support this thesis [2], showing that in subjects with unilateral fetal emergency occipital ipsilateral cerebral blood flow is similar to that of ischaemic stroke.

References

1. Kruit MC, van Buchem MA, Launer LJ et al (2010) Migraine is associated with an increased risk of deep white matter lesions, subclinical posterior circulation infarcts and brain iron accumulation: the population-based MRI CAMERA study. *Cephalalgia* 30:129–136
2. Wentland AL, Rowley HA, Vigen KK et al (2010) Fetal origin of the posterior cerebral artery produces left–right asymmetry on perfusion imaging. *Am J Neuroradiol* 31:448–453

Migraine in patients with colonic sensorimotor activity and irritable bowel syndrome

E. Pucci¹, M. Di Stefano², F. Racca², R. Fasulo², G. Sandrini¹, G.R. Corazza², G. Nappi¹

¹Headache Science Centre, IRCCS National Neurological Institute C. Mondino Foundation and University of Pavia, University Consortium for the Study of Adaptive Disorder and Headache (UCADH), Pavia, Italy; ²1st Department of Medicine, University of Pavia, IRCCS S. Matteo Hospital Foundation, Pavia, Italy; e-mail: emio.pucci@mondino.it

Background and objectives We have recently shown that in patients with migraine and functional dyspepsia an alteration of postprandial gastric sensorimotor function is evident [1]. Alterations of both visceral sensitivity and motor activity are also described in irritable bowel syndrome (IBS) due to alterations of serotonergic pathways, which proved to be also responsible for migraine pathophysiology. An association between IBS and migraine was previously described and the aim of this study was the evaluation of recto-sigmoid sensorimotor activity in IBS patients with and without migraine.

Patients and methods Twelve patients with migraine without aura (ICHD-II criteria) and IBS (39 ± 10 years, range 28–60, 11 females, 5 constipated), 18 patients with IBS (42 ± 13 years, range 29–72, 14 females, 7 constipated) and 10 healthy volunteers (28 ± 6 years, 9 females) underwent the recto-sigmoid barostat test as previously described [2]. IBS diagnosis was made according to the Rome III criteria. After an overnight fast, a double lumen polyvinyl tube with an adherent, infinitely compliant plastic bag (1,200 ml capacity), finely folded, was inserted through the anus as far as the recto-sigmoid junction. The perception and discomfort thresholds were investigated during fasting and the postprandial period (200 kcal, 200 ml liquid meal) through a series of rectosigmoid distentions; at the end of each distention, patients were asked to assess the sensation using a standardized scale from 0 (no sensation) to 6 (pain), were 1 = perception and 5 = discomfort. During the test, postprandial modification of rectosigmoid tone, as the difference between mean 60-min postprandial volume and mean 30-min fasting volume was also evaluated.

Results Results are expressed as 25th to 75th percentile. As expected, perception thresholds were not different among the three groups of patients. On the contrary, in IBS patients discomfort threshold was significantly lower than in HV, but no difference was found between patients with and without migraine. IBS patients with migraine (+12 to +33%) and without migraine (0 to +12%) showed a postprandial rectosigmoid tone modification significantly different compared to healthy volunteers (−84 to −12%; *p* < 0.05). Postprandial rectosigmoid tone modification was more profoundly impaired in IBS patients with migraine than patients without migraine (*p* < 0.05).

Conclusions In IBS patients, the presence of migraine is associated to a more severe alteration of postprandial motor activity, but does not influence sensitivity pathways.

References

1. Di Stefano M, Pucci E, Miceli E et al (2007) Postprandial motility index is significantly reduced in patients with migraine and dyspepsia. *Gut* 32(4):A268 (suppl 1)
2. Di Stefano M, Miceli E, Missanelli A et al (2006) Meal induced rectosigmoid tone modification: a low caloric meal accurately separates functional and organic gastrointestinal disease patients. *Gut* 55(10):1409–1414

Headache and functional dyspepsia: a neurogastroenterology research

E. Pucci¹, M. Di Stefano², E. Miceli², G.R. Corazza², G. Sandrini¹, G. Nappi¹

¹Headache Science Centre, IRCCS National Neurological Institute C. Mondino Foundation and University of Pavia, University Consortium for the Study of Adaptive Disorder and Headache (UCADH), Pavia, Italy; ²1st Department of Medicine, University of Pavia, IRCCS S. Matteo Hospital, Pavia, Italy; e-mail: ennio.pucci@mondino.it

Introduction Several patients with headache often present functional dyspepsia. At present, no data are available on the pathophysiological mechanisms responsible for this association.

Objectives The aim of this study was to verify whether an alteration of post-prandial gastric tone or sensitivity may explain this association.

Materials and methods Thirty-five patients (22 F, 13 M, mean age 32 ± 8 years) affected by functional dyspepsia with (18 patients) and without (17 patients) migraine without aura (ICHD-II), took part in the study. Diagnosis of functional dyspepsia was made according to the Rome II criteria. As a control group, 14 age- and sex-matched healthy volunteers (HV) were enrolled. All subjects underwent gastric tone measurement in fasting condition and after the administration of a 200 ml liquid meal by barostat (computer-controlled system connected to a double-lumen extrusion and an anelastic balloon placed at its distal end, which is introduced into the stomach). After minimal distending pressure (MDP) determination, which represents the pressure applied against the balloon by abdominal content, pressure was set at MDP +2 mmHg and gastric volume (GV) was measured for 30 min during fasting and for 60 min post-prandially. At fasting and after the end of the GV measurement an evaluation of perception of discomfort thresholds (DTh) was performed by sequential ramp distensions in stepwise increments starting from MDP (2 mmHg, 2 min duration). At the end of each distension, the subject scored the sensation on a 0–6 scale (1 = perception threshold, PTh; 5 = DTh). Gastric volume and accommodation were calculated as difference between mean post-prandial and mean fasting volume.

Results Mean post-prandial GV increase and fasting PTh and DTh were similar among the three groups. DTh after meal was lower in dyspeptic-migraine patients than in HV and dyspeptic without migraine.

Conclusions Patients with migraine and functional dyspepsia may be characterised by meal-induced hypersensitivity of the stomach.

Migraine and recurrent epistaxis: clinical-therapeutical issues

V. Pizza¹, A. Agresta¹, V. Busillo², D. Cassano³, C. Colucci d'Amato⁴

¹Headache Centre, S. Luca Hospital, ASL SA, Vallo della Lucania, Italy; ²Headache Centre, Maria SS Addolorata Hospital, ASL SA, Eboli, Italy; ³Territorial Headache Centre, District No. 60, ASL SA, Nocera Inferiore, Italy; ⁴University of Naples, Naples, Italy; e-mail: vpizza@libero.it

Introduction There is little literature concerning primary headaches associated with recurrent epistaxis. The aim of this study was to define in a sample of migraine patients with a history of recurrent epistaxis, the clinical characteristics of such association and therapeutic response to Ca-channel blockers.

Materials and methods A sample of 20 migraine without aura patients (ICHD-II) (13 F, 7 M), mean age 28.8 (range 20–41), with a history of recurrent epistaxis was selected. Only one case presented an episode of epistaxis of such entity to require emergency care aid. In 17 patients the headaches happened generally during the day and was associated to recurrent episodes of moderate degree epistaxis. The remaining two migraine patients presented higher frequency of attacks, occurring exclusively during sleep, constantly accompanied by episodes of moderate epistaxis.

All patients underwent a neurological, ear-nose-throat and cardiological check-up. Their blood pressure was monitored with Holter and they underwent routine laboratory exams, PT, PTT, fibrinogen, AT-111, d-dimer tests, EEG, TC or MR brain scan, and a high resolution TC of osteo-meatus complex of the facial mass. The patients were prescribed 5 mg doses of flunarizine and given advice on keeping a diary to check headache activity and the frequency of epistaxis and asked to return for follow-up (1, 3, 6 months).

Results All the tests resulted normal. All patients checked at 3- and 6-month follow-up showed significant ($p < 0.05$) reduction in the frequency of the attacks and absence of the episodes of epistaxis.

Discussion In the literature cases of primary headaches associated with recurrent epistaxis are rarely described. The migraine without aura patients sample reported associated episodes of recurrent epistaxis in absence of any risk factor for nose-bleeding.

The pathogenesis of this complaint in migraineurs could be connected to the complex vascular disorder at the basis of the headache itself. Considering these points, the prevention therapy with a Ca-channel blocker, such as flunarizine, not only determined a significant reduction in the frequency episodes of headaches but also the disappearance of epistaxis.

Conclusions With all the methodological limitations of this study, it seems possible to state that migraine associated with recurrent epistaxis could represent an uncommon variety of headache, more frequent in women, with a good response to active blood vessel drugs such as Ca-channel blockers.

References

1. Jariour IT, Jariour LK (2005) Migraine and recurrent epistaxis in children. *Pediatr Neurol* (2):94–97

Palinopsia in migraine with and without aura patients

I. Corbelli^{1,2}, V. Belcastro^{1,3}, L.M. Cupini^{2,4}, A. Pieroni^{1,2}, C. D'Amore^{1,2}, S. Caproni^{1,2}, G. Gorgone⁵, E. Ferlazzo⁶, F. Di Palma², P. Sarchielli^{1,2}, P. Calabresi^{1,2}

¹Neurologic Clinic, S. Maria della Misericordia Hospital, University of Perugia, Perugia, Italy; ²IRCCS Fondazione Santalucia, Rome, Italy; ³Neurologic Clinic, S. Anna Hospital, Como, Italy; ⁴Neurologic Clinic, S. Eugenio Hospital, Rome, Italy; ⁵Casa di Cura Madonna della Catena, Laurignano, Cosenza, Italy; ⁶IRCCS, Centro Neurolesi Bonino-Pulejo, Messina, Italy; e-mail: lileum@libero.it

Background The experience of retaining a visual image of objects remaining in the field of view after the patient has looked away or returning after a short delay is known as palinopsia [1, 2].

This study was aimed at investigating the frequency of the visual phenomenon of palinopsia in patients with migraine with and without aura.

Materials and methods We interviewed 63 patients with migraine with aura (MA), 137 patients with migraine without aura (MO) and 226 sex- and age-matched healthy control subjects using an ad hoc semi-structured interview/questionnaire. The interview was divided into four classes of variables for statistical testing: presence or absence of palinopsia; temporal variable; phenomenological variable; conditions in which palinopsia was likely to occur.

Results Palinopsia occurred in 19/200 patients (9.5%); 10/63 of them had MA and 9/137 MO (14.2% vs. 6.6%, $\chi^2 = 9.7$, $df = 1$, $p = 0.002$). Patients with palinopsia had a significantly lower migraine attack frequency than those without this visual phenomenon (4.3 ± 0.3 vs. 14.4 ± 0.2), $z = 7.1$, $p < 0.0001$). There was a tendency for palinopsia to last for seconds, rather than minutes or hours. No patients had an emotional response to the visual phenomenon and they found the experiences neutral. None of the healthy control subjects complained of the phenomenon of palinopsia.

Discussion The mechanism of visual perseveration is not fully understood. There are currently no studies that have clearly defined which cerebral areas and connections are involved in the pathogenesis of these symptoms [1, 2]. In our study we found that recurrent episodes of visual perseveration were referred to by about 10% of patients interviewed. In particular, palinopsia was seen more frequently in MA patients than in MO patients. Palinopsia is probably under diagnosed in patients with migraine. Further investigations are needed to assess whether migraineurs are particularly susceptible to the development of recurrent episodes of visual perseveration.

References

1. Santhouse AM, Howard RJ, Ffytche DH (2000) Visual hallucinatory syndromes and the anatomy of the visual brain. *Brain* 123(Pt 10):2055–2064
2. Ffytche DH, Blom JD, Catani M (2010) Disorders of visual perception. *J Neurol Neurosurg Psychiatry* 81:1280–1287

Reduced effects of pacing respiration at 0.2 Hz on heart rate variability in migraineurs

M. Delussi¹, A. Papagni², B. Di Gennaro², A. Federici²,
M. de Tommaso¹

¹Department of Neurological and Psychiatric Sciences, University of Bari, Bari, Italy; ²D.I.M.O., University of Bari, Bari, Italy; e-mail: m.delussi@gmail.com

Introduction Stroke volume and arterial pressure changes within the respiratory cycle affect heart rate variability (HRV) by cyclic changes in afferent baroreceptor modulation of brainstem autonomic control. HRV increases along with duration of the respiratory cycle, because greater respiratory changes in stroke volume are allowed. Maximal HRV is obtained by slowing respiratory rate to 0.2 Hz [1]. This practice is employed in yoga techniques to reduce somatic effects of psychic stress by modulating autonomic activity.

Materials and methods Effects of slowing respiration to 0.2 Hz on HRV were assessed in 11 migraineurs (M; 22–49 years; 9 f.; 2 m) and in 42 controls (C; 19–43 years; 22 f.; 20 m). ECG was recorded during 20 min relaxation, while breathing at spontaneous rate (S) which in all of the subjects was 0.25–0.35 Hz. Afterwards subjects breathed 6–7 min at 0.2 Hz paced rate (P). Time series of heart period were calculated from R–R intervals, in the last 5 min of S and P conditions. Frequency spectra of HRV were obtained by FFT. Spectral power was

assessed in the bands: VLF (0.02–0.04 Hz); LF (0.04–0.15); HF (0.15–0.4); TOT (total: 0.02–0.4 = VLF + LF + HF). LF/HF ratio was calculated as an index of sympatho-vagal balance.

Results The results (ms^2/Hz ; $M \pm SE$) were:

TOT S: C = 654 ± 91;	VLF S: C = 71 ± 7;	LF S: C = 351 ± 64;	HF S: C = 232 ± 36;	LF/HF S: C = 2.22 ± 0.36
TOT S: M = 364 ± 87;	VLF S: M = 53 ± 12;	LF S: M = 176 ± 51;	HF S: M = 136 ± 134;	LF/HF S: M = 1.48 ± 0.29
TOT P: C = 1085 ± 163;	VLF P: C = 63 ± 7;	LF P: C = 205 ± 29;	HF P: C = 817 ± 136;	LF/HF P: C = 0.51 ± 0.09
TOT P: M = 421 ± 99;	VLF P: M = 61 ± 18;	LF P: M = 92 ± 19;	HF P: M = 269 ± 83;	LF/HF P: C = 0.59 ± 0.13

Two-ways ANOVA and Bonferroni tests indicated that TOT P and HF P were greater than TOT S and HF S in C (TOT < 0.05; HF < 0.0001), but not in M. TOT P and HF P values in C were greater than TOT P (<0.05) and HF P (<0.05) values in M. LF/HF P value was lower than LF/HF S value in C (<0.0001), but not in M.

Conclusions Slowing respiration from spontaneous rate to 0.2 Hz increased HRV in healthy subjects but not in migraine patients, mainly increasing vagal activity, as it results from changes in HF and LF/HF values. Our data suggest that the respiration dependent increase in HF, which can limit negative somatic effects of psychic stress [2], is impaired in migraine.

References

1. Bernardi L, Porta C, Gabutti A et al (2001) Modulatory effects of respiration. *Autonom Neurosci* 90:47–56
2. Thayer JF, Brosschot JF (2005) Psychosomatics and psychopathology: looking up and down from the brain. *Psychoneuroendocrinology* 30:1050–1058

Migraine outcome in postmenopausal women: are there predictive factors?

L. Savi¹, C. Condello¹, V. Massone¹, E. Novelli², M.B. Anoaica¹,
L. Pinessi¹

¹Headache Centre, Neurology 2, Department of Neuroscience, University of Turin, University-Hospital Saint John Baptist, Turin, Italy; ²Department of Biostatistics, San Gaudenzio Clinic, Novara, Italy; e-mail: lsavi@molinetto.piemonte.it

Introduction Common experience shows that in the course of reproductive life changes in hormonal levels can be associated with significant headache modifications.

In the general migraineurs population prevalence decreases with age, but at menopause migraine can either regress or worsen or even stay unchanged.

Objective To the best of our knowledge the possible factors associated with the different courses of headache after menopause onset have not yet been identified. In previous studies we identified as positive prognostic factors the presence of menstrual migraine and dysmenorrhoea. To confirm these data and look for new predictive factors, we enlarged our sample.

Materials and methods We evaluated 472 post-menopausal women suffering from migraine according to the ICHD-II criteria. Among them we only considered the 376 cases of natural menopause. We asked them to fill in a form in order to investigate if and how the characteristics of migraine changed after menopause, age at menarche, age at menopause, association between menses and migraine,

presence of dysmenorrhoea, number of pregnancies, use of oral oestro-progestinic pills.

Results Migraine improved after menopause in 86 (22.9%) natural menopause patients. Seventy-five (87.2%) of the 86 patients whose migraine improved after menopause had migraine attacks correlated to the menstruation, while only 208 (71.7%) of the patients whose migraine worsened or remained unchanged had this correlation ($p < 0.05$). Age at menarche was slightly younger in the improved (12.4 ± 1.6) vs worsened ones (12.9 ± 1.7), but this small difference was nevertheless statistically significant ($p < 0.05$). Surprisingly, nor presence of dysmenorrhoea or use of oestro-progestinic pills showed a statistically significant relationship.

Discussion During menses the oestrogen withdrawal following the priming of the late luteal phase seems to trigger migraine. Stabilization of oestrogen level, as it occurs during menopause, with a constant relative prevalence of oestrogen over progesterone, may effectively reduce the occurrence of migraine attacks.

Why a younger age at first menstruation should predict a better outcome after menopause is not clear.

Conclusions According to our data, the association of migraine attacks with periods during reproductive life and a younger age at menarche seem to significantly predict a headache improvement after menopause.

More studies are needed to assess these tendencies. If these data will be confirmed this will be a very useful indication in order to tailor the best therapy for women approaching the menopausal period.

Psychophysiologic and psychometric profiles in primary headaches and their utility in clinical practice: a preliminary study

M.E. Terracciano¹, R. Pozzolante¹, E. Bagoj¹, C. Mundi¹, A. Graziano²

¹S.C. Neurologia, Azienda Ospedaliera O-U. OO.RR., Foggia, Italy;

²Associazione Promozione Interculturale Neuroscienze (A.S.P.I.N.), Italy; e-mail: mterracciano@ospedaliriunitifoggia.it

Objectives The aim of the present study was to investigate the psychophysiologic profile (at rest and under stressing and relaxing stimuli) and the psychometric profile of patients with primary headache (muscle-tensive, migraine, mixed headache) compared to non-headache control participants. The study's utility was to apply psychophysiologic and psychometric profiles in clinical practice through non pharmacological therapies such as electromyographic and thermal bio-feedback, relaxation therapy and supportive psychotherapies in headache patients.

Methods To achieve the psychophysiologic profile, 70 subjects (50 headache patients and 20 healthy participants) were exposed to three consecutive stressing stimuli (mental arithmetic, sentence completion, modified Stroop test) and three consecutive relaxation exercises of autogenic training (quiet, heaviness, warmth). Physiological variables were measured at baseline, stress, relaxation and recovery. Measurements were made through bio-feedback instrumentation and included frontal electromyogram (EMG), skin temperature (T), galvanic skin reflex (GSR) and heart rate (HR). To achieve psychometric profile all subjects were tested through State-Trait Anxiety Inventory (STAI), State-Trait Anger Expression Inventory (STAXI) and Toronto Alexithymia Scale (TAS).

Results Preliminary results showed a marked variability of psychophysiologic parameters at rest and under stressing and relaxing stimuli both in headache patients and healthy participants. Moreover, STAI, STAXI and TAS items scores in headache patients were higher in comparison with healthy participants.

Discussion and conclusions These preliminary results suggest the utility of achieving further data before applying psychophysiologic and psychometric profiles of headache patients in clinical practice because of psychophysiologic variability at rest and under stressing and relaxing stimuli in headache patients and healthy subjects. The variability of the psychophysiologic profile probably depends on the different individual ability to respond to stressing and relaxing stimuli both in headache patients and in healthy subjects.

Probable cluster headache, probable migraine or cluster-migraine?

C. Lisotto¹, F. Mainardi², F. Maggioni³, E. Mampreso³, G. Zanchin³

¹Ambulatorio Cefalee, Ospedale di San Vito al Tagliamento, San Vito al Tagliamento, Italy; ²Centro Cefalee, Ospedale di Venezia, Venice, Italy; ³Centro Cefalee, Dipartimento di Neuroscienze, Padua, Italy; e-mail: carlo.lisotto@ass6.sanita.fvg.it

Introduction Cluster headache (CH) is a clearly defined form of primary headache. When the attacks fulfil all but one of the criteria A–D for CH, established by the International Classification of Headache Disorders (ICHD-II) [1], probable CH should be diagnosed. This entity indeed requires one of the following conditions: (1) attacks lasting >180 min, (2) attacks without local autonomic signs or restlessness, (3) sporadic (<1 every other day) attacks. In the past “cluster-migraine” was considered an atypical variant of CH [2], but this entity was never categorized, being not sufficiently validated.

Materials and methods For the last 13 years we have observed 240 patients suffering from CH. Out of these cases, 23 (12 males and 11 females) could not fulfil all the criteria for CH. All the patients have been followed-up for at least 3 years.

Results The patients' mean age at first observation was 39.5 ± 13.7 years (range 22–72), whereas the mean age at onset was 35.7 ± 11.0 years (range 21–55). In this population we could distinguish four different subgroups. Three subgroups could be diagnosed with CH except for: (1) duration >3 h, ranging 4–8 h (7 cases) (2) absence of local autonomic signs or restlessness (1 case) (3) sporadic attacks, with no cluster periodicity (6 cases). We could also identify a fourth subgroup of nine patients without cluster pattern and attacks' duration borderline between CH and migraine without aura (MO), usually lasting 3–5 h.

Discussion The first subgroup overlaps with probable MO. Criteria for each disorder are not fully met and patients are labelled as probable MO or probable CH, either of which could have features of the other. The fourth subgroup does not fulfil criteria either for probable CH or probable MO, therefore the old definition of “cluster-migraine” may be still appropriate, even if this term might be considered a regression to the time when CH was considered a variant of migraine.

Conclusions Patients sometimes present with clinical scenarios having characteristics of both MO and CH, but either do not fully meet ICHD-II criteria for either disorder or have sufficient symptoms and signs to allow both diagnoses to be present. These occasions provide diagnostic challenges and account for the controversial form of cluster-migraine. Patients with symptoms overlapping CH and MO likely reflect the inherent clinical variability in each of these two disorders, rather than distinct diagnostic entities in their own right.

References

1. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd edn. Cephalalgia 24 (Supplement 1):1–160
2. Kudrow L (1980) Cluster headache. Mechanisms and management. Oxford University Press, New York, pp 3–9

Psychological profiles in tobacco and drug abusers

M. De Paola¹, A. Ferrari², C. Raimondi¹, L. Neri², M. Zappaterra², P. Vandelli¹, L.A. Pini², M.M. Cainazzo²

¹Servizio di Psicologia, Anti-smoking Centre, AOU Policlinico di Modena, Italy; ²Headache and Drug Abuse Inter-Department Research Centre, University of Modena and Reggio Emilia, Modena, Italy; e-mail: depaola.maria@policlinico.mo.it

Background Medication-overuse headache (MOH) and tobacco smoking are disorders which share repetitive behaviours that persist with minimal self-control despite significant negative consequences [1]. Both conditions have multifactorial origins, cause enormous individual and social costs and are difficult to treat. Patients with medication abuse and chronic headache have, as smokers, a high frequency of psychiatric comorbidity or psychological distress. Moreover, the quality of life, prognosis and treatment are modified by depression, anxiety, panic or obsessive disorders [2]. The aim of our study was to evaluate, using specific and validated tests, the analogies and differences, with respect to the psychopathological profile, between drug abusers and smokers.

Materials and methods Twenty-three smokers and thirty MOH patients, aged 25–70 years, attending our anti-smoking and headache centre were enrolled. Patients were studied with the subsequent tests: symptom check list (SCL-90), short-form health survey (SF-36), self-assessment anxiety (SAS) and depression (SDS) scale (Zung W.W.K). The study began in March 2011 and will end in August 2011. The enrollment will include 120 people, 60 with medication-overuse headache (MOH); 60 smokers and a sex- and aged-matched control group.

Results In smokers the score for the quality of life, evaluated with SF-36, for physical health was 47.55 ± 8 (mean \pm SD) and for mental health was 47.18 ± 10 ; in MOH patients, the scores were, respectively, 32.60 ± 9 and 32.80 ± 8.2 . (*t* student test $p < 0.001$ between groups). In smokers, the self-assessment anxiety scale's score was 31.30 ± 12 and the self-assessment depression scale's score was 32.48 ± 11 ; in MOH patients the scores were, respectively, 47.08 ± 13 and 50.85 ± 16 (*t* student test $p < 0.001$ between groups). In the psychopathological dimensions of SCL-90 the values were worse in patients with chronic headache (MOH) compared with smokers (S); in particular for somatization (MOH 1.94, S 0.80, $p < 0.001$), depression (MOH 1.95, S 0.78, $p < 0.001$), anxiety (MOH 1.56, S 0.59, $p < 0.001$) and sleep disorders (MOH 2.41, S 0.98, $p < 0.01$); instead, there were no differences for the values of interpersonal sensitivity and paranoid (*t* student's test between groups).

Conclusions These preliminary data suggest that the psychological well-being of headache patients is more impaired than smokers.

References

1. Radat F, Lanteri-Minet M (2010) What is the role of dependence-related behavior in medication-overuse headache? *Headache* 50:1597–1611
2. Curone M, Tullo V, Mea E et al (2011) Psychopathological profile of patients with chronic migraine and medication overuse: study and findings in 50 cases. *Neurol Sci* 32:S177–S179

The prevalence of syncope in migraine patients: an effect on dopaminergic overreactivity

R. Iannacchero¹, F. Arabia², U. Cannistra¹, E. De Caro¹

¹Headache Centre, Regional Department of Neurosciences, A.O.P.C. Catanzaro, Italy; ²Syncope Unit, SOC Cardiology, A.O.P.C. Catanzaro, Italy; e-mail: rosarioiann@tiscali.it

Objectives Migraine is an episodic neurovascular disorder characterised by recurrent migraine attacks and autonomic nervous system dysfunctions occurring during vomiting related to headache attacks. Dopaminergic mechanisms activated during migraine attacks may be capable of inducing pre-fainting or fainting symptoms unrelated to the vomiting itself.

Materials and methods We examined 95 consecutive patients referring to our Headache Centre, diagnosed with migraine according to the ICHD-II criteria, investigating specifically the possible occurrence of syncopal episodes.

The diagnosis of syncope was made according to the criteria established by the E.S.C task force. All patients with syncope were subjected to baseline ECG, Holter monitoring, echocardiogram, tilt testing, EEG and TC of the head.

Results Eleven migraine patients were identified with at least one specific syncope. The current mean age of the patients is 36.4 ± 8.4 years (range 18–45); whereas their mean age at first observation was 28 ± 10.6 years (range 21–42). There was no significant differences between the age of onset of the disorders. We did not find any correlation between the migraine severity and frequency and the occurrence of syncope.

Discussion Orthostatic hypotension and syncope are well known to occur during some migraine attacks, while a symptomatology ascribable to impaired orthostatic tolerance can be provoked by means of the oral administration of low dosages of the DA agonist bromocriptine (2.5 mg). In addition, bromocriptine also provoked this symptomatology in patients with a personal history of syncope who had never suffered from migraine.

Conclusions Our observations, seem to suggest that those asystolic rhythms related to extreme sinus bradycardia or to A–V block may be induced by a peripheral mechanism mostly attributable to a phenomenon of hyperresponsiveness to DAergic drugs.

Palmitoiletanolamide in migraine: an open trial

L. Savi, C. Condello, V. Massone, L. Pinessi

Headache Centre, Neurology 2, Department of Neuroscience, University of Turin, University-Hospital Saint John Baptist, Turin, Italy; e-mail: lsavi@molinetto.piemonte.it

Introduction Palmitoiletanolamide (PEA) is a bioactive lipid, composed by palmitic acid and ethanolamine. It showed an autacoids effect, modulating mast-cells degranulation in human tissue, and an analgesic function, binding the CB2 receptor for endocannabinoids and the TRPV1 receptor for capsaicin. These very receptors seem to have a role in the pathogenesis of migraine attack, as well as the degranulation of mast-cells that occurs in the meningeal vessel.

Objective To investigate the usefulness of PEA in the prophylaxis of migraine headache.

Materials and methods We enrolled 25 patients suffering from migraine headache diagnosed according to the ICHD-II criteria, with <10 crises per month, who had not received any prophylaxis in the 3 months before the beginning of PEA introduction.

We gave them ultra-micronized PEA 1,200 mg/die for the first month, followed by ultra-micronized PEA 600 mg/die for the following 2 months, and asked them to fill in the headache diary.

Results Twenty patients completed the study, with 45% of them showing a clinical benefit from the drug. Data of the third month of treatment were compared to data observed before treatment with a *T*-test: the results were not statistically significant, but show a trend toward the reduction of the number of crises and the number of days of migraine per month ($p = 0.09$). Conversely, we observed a

statistically significant reduction in the number of days with associated symptoms of migraine ($p = 0.03$). No patient showed side effects and 65% of them decided to continue prophylaxis with the compound.

Discussion A good percentage of our patients showed slight improvement of symptoms after 3 months of treatment. Sixty-five percent of treated patients decided not to leave the drug after the end of the trial, as they experienced subjective improvement of their headache and no side effects.

Conclusions Use of PEA seems very safe in migrainous patients; there are hints that, particularly in patients with a low frequency of attacks, this compound could be an interesting prophylactic option. A larger sample, evaluated in a double-blind trial, is necessary to confirm the efficacy of this compound.

Could fronto-turbinalis sinus morphometry be predictive for outcome of fronto-turbinalis sinus expansion headache (FTUSEH) after sinus microsurgery?

G. Sanges¹, M. Feleppa², M. Gamerra³, G. Sorrentino³, R. De Luca⁴, M. Merone⁵, L. Cacace⁶, M.E. Bigal⁷

¹Headache and Cervico-facial Pain Service, A.S.L. NA 3 South, Naples, Italy; ²Department of Neurology, Hospital G. Rummo, Benevento, Italy; ³Otolatric and Cervico-facial Pathology Unit, San Leonardo General Hospital, A.S.L. NA 3 South, Castellammare di Stabia, Italy; ⁴Cybernetic Engineering and Mathematics Application Department, Salerno University, Salerno, Italy; ⁵Mathematics, Castellammare di Stabia, Italy; ⁶Surgical Pathology Service, M. Scarlato General Hospital, A.S.L. SA, Scafati, Italy; ⁷Merck Research Laboratories, Whitehouse Station, NJ, USA; e-mail: ciaiko16@libero.it

Introduction Frontal sinus expanded into the pneumatic medium turbinatum (FTUSE), an anatomical variant, is related to chronic headache by means of an increase of its internal pressure not related to an abnormal contact between opposite mucosal surfaces [1, 2]. Minimal endoscopic sinus surgery (MESS) is the treatment of choice, followed by the stable remission of headache. Usually the confirmation of an increased pressure is done in the first phase of surgery by means of the direct puncture of the sinus with the Gamerra's needle connected to a digital manometer. The aim of this experimental work was to propose a non-invasive predictive test to estimate the possible outcome of the headache after MESS.

Methods The experimental design of this study contemplated the inclusion of a number of consecutive patients. Inclusion criteria were:

1. Daily headache, moderate-to-severe, fronto-supra-orbital, for at least 12 months.
2. Positivity of Ewing's and/or Grunwald's points.
3. Normal neurologic evaluation and neuroimaging.
4. Frontal sinus expanded into the pneumatic medium turbinatum in CT scans.

Exclusion criteria: abnormal "contact points".

By means of "Volume View Rendering" technique permitted by 3D CT last generation scan we calculated the volume of FTSE. Pre-surgical measure of sinus pressure was done by its direct puncture. The sinus pressure was assessed through the non-invasive procedure described above and compared with the pressure data obtained by the pre-operative puncture of sinus, usually significantly higher than the environmental pressure. Lateral laminectomy of pneumatic medium turbinatum was performed in all patients.

Discussion The anatomic variant of frontal sinus expanded into the pneumatic medium turbinatum with a pressure gradient supports the

possibility of a headache not related to an abnormal "contact point" [1, 2]. This condition, that represents a novel nosographic entity ("fronto-turbinalis sinus expansion headache" or FTSEH) can be susceptible of a complete stable remission after MESS. The documentation of the pressure gradient by means of a non-invasive technique is the gold standard in this clinical condition.

The application of the law of perfect gases to the data obtained by means of "volume view rendering" allowed by 3D CT last generation scan can assess in a non-invasive way the internal pressure of the structure examined, thus obtaining suggestive data about the outcome of the intervention on a sinus under high pressure. Preliminary experimental results are interesting but more data are necessary to establish the cut-off for the optimal surgical indication.

References

1. Behin F, Bigal M, Lipton RB (2005) Surgical treatment of patients with refractory migraine headache and intranasal contact points. *Cephalalgia* 25(6):439–443
2. Clerico DM (1995) Sinus headaches reconsidered: referred cephalgia of rhinologic origin masquerading as refractory primary headache. *Headache* 35:185–192

The hidden headache in the emergency room

A. Granato¹, G. Relja¹, G. German², S. Musho Ilbeh¹, G. Servillo¹, M. Zorzon¹, G. Pizzolato¹

¹Department of Medical, Technological and Translational Sciences, Headache Centre, University of Trieste, Trieste, Italy; ²Information Science and Telecommunications, University of Trieste, Trieste, Italy; e-mail: antonio_granato@hotmail.com

Background Patients entering the emergency department (ED) with the chief complaint of headache represent a critical problem. However, data on the prevalence of headache in the ED setting in patients presenting with a non-headache disease are scarce.

Objective To assess headache prevalence in patients admitted to the ED for non-headache disease.

Methods A 5-year retrospective analysis of the records of all patients admitted to the EDs of the Province of Trieste, complaining of a non-headache disease as the main symptom was performed. Patients who reported also headache as an associated symptom were enrolled. Headache was classified by the ICHD-II criteria whenever the presence of adequate information in the patient's record made it possible. Demographic characteristics, reasons for admission, type of headache, ED diagnoses and ED discharge were analysed with SPSS 14.0.

Results Out of 397,768 patients admitted to the ED, 2,037 (0.5%) patients with headache as an associated symptom were enrolled. Among these patients, most frequent causes of admission were bodily discomfort (59.3%), losing consciousness (10.4%), and thoracic pain (9.6%). One thousand sixty-five (52.3%) patients were classified as having primary headache (7.3%), secondary headache (75.6%), and not otherwise specified headache (17.1%). The remaining 972 (47.7%) patients had ED diagnoses, mainly cardiologic (19.9%) and otorhinolaryngologic (13.9%), not related to headache. One thousand six hundred and fifty-eight patients (81.4%) were referred to the general practitioner, 379 (18.6%) were admitted to medical (339 patients, 89.4%) or surgical (40 patients, 10.6%) wards.

Conclusions A high percentage of patients admitted to the ED for non-headache diseases suffer also from mostly secondary forms of headache. Almost half of the patients were discharged with ED diagnoses not related to headache. In these cases, the headache was not classifiable, although a tension-type headache due to stress conditions related to the disorder that caused ED admittance is most likely.

Orthostatic headache complicated with convexity subarachnoid haemorrhage

E. Ferrante¹, A. Citterio², L. Valvassori², I. Arpino³, F. Rubino³, L. Porrinis³, L. Quilici², M. M. Ferrante², G. Pero²

¹Centro Cefalee, Niguarda Cà Granda Hospital, Milan, Italy;

²Dipartimento di Neuroscienze, Niguarda Cà Granda Hospital, Milan, Italy; ³Rianimazione, Niguarda Cà Granda Hospital, Milan, Italy; e-mail: enricoferrante@libero.it

Background The majority of SAHs are of aneurismal origin and non-traumatic convexity SAH is rare.

Objective We present a patient with orthostatic headache from intracranial hypotension complicated with convexity subarachnoid haemorrhage (SAH) by cortical venous thrombosis treated with epidural blood patch (EBP).

Design and methods A 52-year-old female had a moderate left hemiparesis and an episode of tonic-clonic seizures. She had a 13-day history of severe, occipital orthostatic headache. The headache appeared after an epidural injection of a local anaesthetic and steroid because of chronic low back pain. The left hemiparesis recovered progressively after 48 h. Later on, the patient had three mild partial sensitive seizures on her left side (tingling and numbness) and was treated with carbamazepine 800 mg/day with complete control of symptoms.

Results EEG showed epileptiform discharge on the right temporal side. Brain CT revealed a small right fronto-parietal cortical SAH. Brain MRI showed a small right fronto-parietal convexity SAH with focal oedema and diffuse pachymeningeal enhancement. Brain MRI venography was normal. Cerebral angiography showed no flow signal in a few frontal and parietal convexity veins in the correspondence of the SAH, a finding suggestive for cortical venous thrombosis (CVT). Laboratory test for thrombophilia was unrevealing. A diagnosis of intracranial hypotension (IH), after an accidental dural puncture during an epidural injection of drugs, was made. Twenty days after the headache onset, the patient was treated with a lumbar autologous EBP (20 ml). The headache disappeared within a few minutes after the procedure. After 2 months cerebral angiography showed restoration of the flow signal in the right fronto-parietal cortical veins. After 9 months brain MRI was normal and EEG was unchanged. At 18-months follow-up the patient was asymptomatic with carbamazepine 800 mg/day therapy.

Conclusions Our case suggests that the intracranial hypotension, in addition to the orthostatic headache, which was the main symptom, can very rarely cause convexity SAH by CVT. In these cases, the treatment with EBP [1] alone can solve both IH with orthostatic headache and SAH by CVT, without the use of intravenous heparin followed by oral anticoagulants.

References

1. Ferrante E, Arpino I, Citterio A et al (2010) Epidural blood patch in Trendelenburg position pre-medicated with acetazolamide to treat spontaneous intracranial hypotension. *Eur J Neurol* 17:715–719

Thunderclap headache

F. La Marra¹, A. Feola¹, G. Granata¹, A.M. Marra¹, F. Piccirilli¹, F. Sandolo², M. Granata¹

¹Headache Centre, U.O.C. Clinical Immunology A, Department of Clinical Medicine, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; ²Department of Radiology, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; e-mail: massimo.granata@uniroma1.it

A 43-year-old woman presented to our Centre with a “violent headache”. The patient, who already suffered sporadically from migraine without aura, complained of the sudden onset of a headache that had quickly reached the maximum pain intensity. The pain made her totally unfit and every change in posture caused vertigo, nausea and vomiting. Nevertheless, the neurological exam was substantially negative and the CT scan, performed in emergency, did not indicate hemorrhage or lesions detectable through this method; besides, there was no fever and inflammatory markers were not significant. We started forthwith the investigation in accordance with the 2004 IHS guidelines for suspicion of thunderclap headache [1]. During hospitalization, there was an attenuation of pain but not of postural dizziness, so we planned a lumbar puncture (LP) [2]. Before carrying out the LP, we had the patient undergo a brain MRI and MRA. This time the images showed intracranial hypotension due to the presence of a diffuse, symmetric and bilateral thickening of the pachymeninges. The caution used before doing the LP was providential. An MRI of the spinal CSF excluded secondary causes of hypotension. The patient was treated with rehydration with about 4 l of physiological solution daily for 3 days with rapid improvement of symptoms. The brain MRI control showed no more signs of CSF hypotension. Final diagnosis was headache attributed to idiopathic low CSF pressure [1].

References

1. Edlow JA, Panagos PD, Godwin SA et al (2008) American College of Emergency Physicians Clinical Policies Subcommittee Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute headache. *Ann Emerg Med* 52:407–436
2. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd edn. *Cephalalgia* 24(Suppl 1):1–160

Post-lumbar headache: report on 201 consecutive lumbar punctures

F. Pauri, F. Sovani, G. Fiermonte, C. Lepre

Dipartimento di Scienze e Biotechnologie Medico-Chirurgiche, Sapienza Università di Roma, Rome, Italy; e-mail: flavia.pauri@uniroma1.it

Introduction Lumbar puncture (LP) is a common procedure for diagnosis and anaesthesia. Headache is a common sequela of this procedure irrespective of the indication. The incidence of post lumbar puncture headache (PLPH) reported in the literature varies from 30 to 40% of performed LPs. PLPH seems to be prevalent and more severe in females than males. Also, taller patients tended to record a shorter pain delay upon rising than smaller patients, which was also shown for younger patients compared with older patients. A high BMI disposed for a slow change in pain intensity upon rising and reclining, which may reflect a constricted epidural space. In specific pathologies such as dementia, the severity is mild and the frequency seems to be lower, about 2%.

Objective Aim of our study was to verify the incidence of PLPH and to find a possible correlation with the demographics of the patients (age and gender), the clinical history, the diagnosis, the cerebrospinal fluid (CSF) cytological and immunological results, and the performance procedure of the lumbar puncture.

Method Data from 201 consecutive LPs were collected. Volume, cell numbers and protein amount in CSF taken from the patients were considered, as well as immunological responses, and viral responses when available. Anamnestic data and demographic information were also collected. All patients were asked about the presence of PLPH and referred its characteristics, when present.

Results No significant side effects, such as infectious diseases, occurred after LP. PLPH and local back pain were the only disease associated symptoms complained by our patients. PLPH occurred in 36 cases of 201 LPs (17.82%) with significant higher frequency in females than in males. PLPH was higher in patients with a clinical history of headache, but did not correlate with number of lumbar puncture/patient, trouble in the LP execution, expertise of the performer physician. Statistical analysis showed a positive association between the incidence of PLPH and CSF immunological profile suggestive of multiple sclerosis (MS) ($r = 0.3$; $p < 0.01$).

Discussion Our study confirmed higher prevalence of PLPH in females. Females are more sensitive to pain and able to discriminate different levels of pain than males. Fluctuations in levels of female hormones could modulate the pain threshold during the menstrual cycle, changes in neuronal excitability, cerebral vascular reactivity, and neuroendocrine activity. An interesting result concerns the positive correlation between PLPH and MS. Probably the complex pathogenesis of MS could interfere with pain threshold too, but further studies are needed to clarify this datum.

Central sensitization, persistent pain in headache: implication of the interventional procedures for diagnosis and treatment

A. Tarsitano¹, R. Iannacchero²

¹U.O.C. Centre of Pain Medicine, INRCA, IRCCS, Cosenza, Italy;

²Regional Headache Centre, Regional Hospital Pugliese-Ciaccio, Catanzaro, Italy; e-mail: a.tarsitano@inrca.it

Introduction Nerve blocks, RTF procedures and neurostimulation are reasonable therapeutic options in patients with head and neck pain. In addition, the peripheral nerve procedures can also be effective in primary headache disorders, such as migraine and cluster headache (CH).

Discussion The mechanisms by which these procedures work are still not clear. Migraine and CH are believed to centrally mediate primary neuropathic mechanisms and it is unclear how blocking cervical roots or trigeminal nerve branches might affect these processes. Improvement, might in the long-term, be correlated with pathophysiological factors important in the production of persistent pain. It has become clear in recent years that central sensitization at the first nociceptive synapse level (spinal trigeminal nucleus or dorsal horn) can be an explanation for persistent neuropathic pain and headache. Central sensitization is a prolonged but reversible increase in the excitability of neurons in the central nociceptive pathways, activated by nociceptor inputs. It manifests as pain hypersensitivity, hyperalgesia, allodynia and aftersensations. More recently, several studies have shown that changes in microglia, astrocyte, membrane excitability, gap junctions and gene transcription, can all contribute to the maintenance of central sensitization in addition to dependent synaptic plasticity activity. It is a real phenomenon that contributes to inflammatory, neuropathic, dysfunctional pain disorder, and headaches included [1].

Conclusions The interventional procedure, when indicated, can result in rapid pain relief and allodynia, and effects may last for several weeks. A study of the literature, however, shows that there is no widely accepted agreement among headache specialists as to the optimal technique, type and indications [2]. There is a need to perform more rigorous clinical trials to clarify the role of interventional procedures in the management and diagnosis of various headache disorders, and to aim at standardizing the techniques used for the various procedures in this setting.

References

1. Woolf CJ (2011) Central sensitization: implication for the diagnosis and treatment of pain. *Pain* 152(3 Suppl):S2–S15.
2. Ashkenazi A, Blumenfeld A, Napchan U et al (2010) Peripheral nerve blocks and trigger point injections in headache management—a systematic review and suggestions for future research. *Headache* 50:943–952

Data from a “call centre” in a headache centre: a 3 months experience

E. Mampreso¹, F. Maggioni¹, C. Lisotto², F. Mainardi³, G. Zanchin¹

Headache Centres: ¹Department of Neurosciences, University of Padua, Padua, Italy; ²S. Vito al Tagliamento Hospital, S. Vita al Tagliamento, Italy; ³SS Giovanni e Paolo Hospital, Venice, Italy; e-mail: edoardo.mampreso@libero.it

Introduction The direct and indirect burden of headaches is noteworthy [1]. It is a common experience that after a visit patients may seek to contact the Headache Centre by phone for different reasons. Only one paper [2] focused on volume and nature of these phone calls.

Aim of this study was to analyse the different characteristics of phone calls of headache patients.

Materials and methods A “call centre” phone number (mobile phone), dedicated to our headache patients, was activated from December 2008 to February 2009, 6 h/week divided into 3 days. During this period 360 patients were visited, 85% females, 88% migraineurs.

Results We received 88 phone calls, on average, 28.2 days (4–180) after the visit. The call duration was <5 min in 43.2%, 5'–10' in 30.7%, 10'–15' in 17%, 15'–20' in 5.7%, over 20' in 3.4%. Second calls were 11. Calls came mostly from females (80/88) and from migraineurs (78.4%); 12.5% from chronic daily headache patients, 5.7% from episodic cluster headache patients, 3.4% from other headaches patients, none from tension-type headache. Phone call motivations were listed in different categories, with the possibility of assigning the motivations to more than one: adverse events of attack therapy (3/88 calls, triptans), on prophylaxis (35/88, about 50% topiramate); additional information on attack therapy (11/88), on prophylaxis (40/88); ineffectiveness of attack therapy (11/88), on prophylaxis (24/88, days elapsed from the beginning of prophylaxis to the phone call being 19.2 ± 9.6); other comorbid diseases (11/88 calls); other reasons (22/88, none about headache diary).

Discussion and conclusions Our data showed a very different behaviour of our patients from what has been reported by Loder & Geweke [2], whose data showed a much higher number of calls. Reasons for that could be various, among which difference in the population (Loder reported 48% of calls from patient with a primary psychiatric diagnosis); and difference in explanations given during the visit. Our data stress, in general, the relevance of detailed information during the visit, particularly on prophylaxis. However, despite the accurate explanation given on the latency of action of prophylaxis, we received many calls on this topic too early (mean 19.2 days) to evaluate properly the apparent ineffectiveness of the drug prescribed. This fact highlights the anxious reaction of patients when they do not see a prompt improvement, therefore the information about the delayed action of preventative therapy should be faced with greater attention during the visit.

References

1. World Health Organization (2001) The World Health Report 2001. WHO, Geneva
2. Loder E, Geweke L (2002) Volume and nature of telephone calls in a specialty headache practice. *Headache* 42(9):883–887

Features of individual headache attacks in medication-overuse headache: analysis by means of an electronic diary

C. Tassorelli, M. Allena, M. Bolla, P. Rossi, G. Sandrini, G. Nappi, and the COMOESTAS Consortium*

Headache Science Centre, IRCCS National Neurological Institute C. Mondino Foundation, University Centre Consortium for Headache and Adaptive Disorders and Head Pain (UCADH), Pavia Section, Pavia, Italy; e-mail: cristina.tassorelli@mondino.it

*G. Sances, F. Blandini, M. Berlangieri, (IRCCS National Neurological Institute C. Mondino Foundation, Pavia); R. Jensen, L. Bendtsen, S.B. Munksgaard (Region Hovedstaden, Glostrup Amtssygehuset); M. Lainez, B. Lopez (Fundación de la Comunidad Valenciana para la Investigación Biomédica, la Docencia y la Cooperación Internacional y para el Desarrollo del Hospital Clínico Universitario de Valencia, Spain); Z. Katsarava, M. Rapsch (Universitaetsklinikum Essen); J.A. Leston, M.T. Goicochea, D. Cerquetti (Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia, Buenos Aires, Argentina); R. Fadic, B. Shand (Pontificia Universidad Católica de Chile, Santiago, Chile); A. Stoppini, M. Landro, A. Cantoni (CBIM), S. Spadafora, M. Osa (Isalud)

Medication-overuse headache (MOH) often evolves from migraine or tension-type headache. When adequately treated, by means of detoxification, it reverts back to the episodic pattern in a large percentage of patients. In this study we describe the clinical phenotype of headache attacks in 525 subjects with MOH who underwent standardized in-patient or outpatient detoxification procedure in five clinical centres in Europe and Latin America. Headache characteristics were monitored and recorded daily for up to 6 months after detoxification on an electronic diary which provided assisted diagnosis for each headache attack.

According to the ICHD-II criteria, the primary headache was migraine without aura in 414 subjects, episodic or chronic tension-type headache in 83, mixed in the remaining subjects.

The analysis of attacks in the subjects cured from overuse showed that patients originally diagnosed as suffering from chronic tension-type headache also presented migraine attacks following detoxification. Conversely, patients originally suffering from migraine without aura also suffered from tension-type attacks following detoxification.

Interestingly, we found that patients with migraine without aura showed a greater reduction in headache frequency in the 6 months following detoxification. Furthermore, MOH patients with migraine as primary headache showed in the post-detoxification follow-up a monthly headache index significantly lower than patients suffering from tension-type headache as primary headache.

Electronic tools in the management of headaches may facilitate continuous and sustained monitoring of patients' conditions, and also provide important clinical information for a better diagnostic definition, especially in the chronic and most disabling forms of headache.

Our study, conducted in a large population of MOH patients, suggests that certain clinical characteristics of primary headaches are associated with the outcome of the disease after the detoxification phase. As a matter of fact, the study calls in particular for further investigation of possible clinical factors that should be considered in strategies leading to improve MOH management.

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Pilot study for spreading knowledge on migraine diagnosis and therapy in Calabria

R. Iannacchero¹, M.A. Galimi², F. Corasaniti¹

¹Headache Research Centre, Regional Hospital Pugliese-Ciaccio, Catanzaro, Italy; ²Almirall-Prodesfarma, Project Manager, Milan, Italy; e-mail: rosarioiann@tiscali.it

Introduction Statistical data on the incidence of migraine syndromes in Calabria are similar to data reported in the international literature; however, the lack of an informative, trained, diagnostic and clinical network certainly does not allow researchers to identify “treatment protocols” to tackle the problem globally, thereby being an hindrance to more qualified medical care and to a more comprehensive approach in the management of migraine patients.

Aims In this perspective, and within a limited time-span of activity (about 3 months), the aims of the initiative were the following: to develop a communication campaign in order to establish several new contacts; to increase patients' access to the “territorial outpatient nursing management system”; and to foster the application of a “managerial” medical model within the public healthcare system.

Materials and methods Several approaches were developed, such as, the use of media communication instruments, through which the concept was widely divulged, i.e., campaigns with the use of “posters”; newsletters sent through e-mail marketing; organisation of events with CME credits; development and administration of an ad hoc questionnaire specifically for patients with a section dedicated to the assessment of the communication campaign; and a tailor-made questionnaire for the “stakeholders working in the territorial outpatients nursing management network”.

Conclusions Outlining the differences between marketing and social communication campaigns is useless in the planning of an awareness campaign, since communication strategies and techniques often overlap; moreover, it is fundamental to divulge correct information and foster the application of decision making algorithms aiming for the best clinical practice.

Reasons for under-diagnosis of migraine in primary care

A. Panconesi¹, M.L. Bartolozzi¹, P. Salvadori², N. Mennuti², S. Mugnai¹, L. Guidi¹

¹Headache Centre, Department of Neurology, Empoli, Italy;

²Primary Care, Empoli, Italy; e-mail: a.panconesi@virgilio.it

Migraine diagnosis registered in the databases of general practitioners (GPs) in Italy is rather low (1.6–1.8%), that is, about 15% of migraine prevalence. Another 2–4% of patients have an aspecific diagnosis of headache [1]. A similar percentage (3.1% of migraine or headache) was found in 1.5 million subjects covered by 252 GPs in the UK [2]. Only 15% of subjects presenting for the first time to a Headache Centre in Italy arrive with a previous migraine diagnosis, and only 26% of migraine patients had a previous diagnosis. Therefore, there was an enormous discrepancy between the migraine prevalence in the general population and migraine actually diagnosed and registered in the GP database.

We discuss the reasons for migraine under-diagnosis by the GPs. The main barriers, apart from the lack of consultation (30–50% of cases) and the lack of time and awareness, are:

1. The complexity of diagnostic criteria of the IHS classification. Probable migraine and probable tension-type headache (TTH)

both fulfil all criteria of each respective disorder except one. Probable migraine was 40–50% of total migraine prevalence. In some surveys the prevalent missing feature was the headache duration, but in this case the differential diagnosis with TTH is sufficiently easy. In others, the associated symptoms were missing and so the differential diagnosis was more blurred. The self-awareness, the attack severity and disability of probable migraine are less than strict migraine and therefore probable migraine, as a milder form of migraine, could be one cause of the lack of consultation. However, this does not explain the lack of diagnosis in 80% of patients with chronic migraine.

2. The variability in the clinical picture of the disease in the same patient. In migraine patients 25–30% of attacks are non migraine headaches (Spectrum and Pamina studies). The initial headache diagnosis based on the medical history does not accurately predict the headache type treated in randomized trials. Even the recent indication to treat migraine early when it is mild, can lead to a misdiagnosis of TTH instead of migraine. Another observation is that a percentage of headache subjects did not retain the initial diagnosis over time (GAZEL study). The previous series of findings are compatible with the continuum model of headache.

In conclusion, migraine must be treated in the great majority of cases at the primary care level, but major barriers are the complexity of the IHS classification and the variability of the clinical picture of headache in the same patient. We propose a new organization of headache services.

References

1. Panconesi A, Pavone E, Coletta D (2009) A picture of migraine management in Italy. *J Headache Pain* 10:S32–S33
2. Latinovic R, Gulliford M, Ridsdale L (2006) Headache and migraine in primary care: consultation, prescription, and referral rates in a large population. *J Neurol Neurosurg Psychiatry* 77:385–387

A survey of participants in an internet support group for headache

P. Rossi^{1,2}, C. Tassorelli², F. Antonaci², M. Allena², G. Nappi²

¹INI, Grottaferrata, Italy; ²IRCCS Neurological National Institute C. Mondino, Pavia, Italy; e-mail: paolo.rossi90@alice.it

Background and objective A substantial number of patients suffering for chronic disorders is turning to internet support groups for help. The aim of this study was to evaluate the perceived effectiveness of a virtual support group for headache.

Methods A questionnaire was published in February 2011 in a reserved area of the website <http://www.cefalea.it>. All the subscribers of the support group operating in the same website were invited via e-mail to fill anonymously the questionnaire. The questionnaire addressed the possible benefits and problems associated with belonging to a headache virtual support group.

Results One hundred and eight questionnaires were completed (95 females, 13 males) with a participation rate of 34%. The great majority of the responders were in the age range 35–49 years (61%). Almost 68% of respondents declared to suffer from migraine and 29% declared to suffer from tension-type headache (TTH). Most of the responders (70%) were receiving professional help. Participants in a support group found it helpful in reducing the feeling of loneliness (85%), in receiving psychological support (78%), in improving their knowledge about headache (74%), in improving self-care (69%), in better tolerating the symptoms (69%), in reducing the headache-

related burden (61.5%), whereas only a limited number of patients judged the support group helpful in reducing the severity of headache (24%) or limiting drug intake (42%). Eighty-five percent of patients believed they were not misled by information provided in the support groups.

Conclusions Internet support groups are perceived as effective in terms of feeling supported and increasing awareness about headache and may have a place in the management of headache sufferers.

What Italians say about headache

M.P. Prudeniano¹, L. Merico¹, P. Livrea¹, D. Modica², F. Lanaia², M. D'Ippolito³, L.M. Cupini⁴, M.G. Buzzi³, F. Maggioni⁵, G. Zanchin⁵, E. Guaschino⁶, G. Sances⁶, I. Corbelli⁷, P. Sarchielli⁷, L.A. Pini⁸

Headache Centres: ¹Neurological Clinic L. Amaducci, University of Bari, Bari, Italy; ²Neurological Clinic, University of Catania, Catania, Italy; ³IRCSS S. Lucia Foundation, Rome, Italy; ⁴S. Eugenio Hospital, Rome, Italy; ⁵Neurological Clinic, University of Padua, Padua, Italy; ⁶National Neurological Institute C. Mondino Foundation, Pavia, Italy; ⁷Neurological Clinic, University of Perugia, Perugia, Italy; ⁸University of Modena and Reggio Emilia, Modena, Italy; e-mail: m.p.prudeniano@neurol.uniba.it

Introduction The National Headache Day is an educational event and is organized every year by the Italian Society for the Study of Headache (SISC). The aim of the event is to spread knowledge about headache in the general population by handing out leaflets and giving information on diagnosis and care facilities. In May 2009, during the National Headache Day, a questionnaire was distributed among the public with the aim of receiving information on their feelings about headache.

Methods A questionnaire was proposed to each bystander stopping near a booth that had been set-up in the main square of six Italian cities: Bari, Catania, Rome, Padua, Pavia and Perugia. The questionnaire covered information about age, sex, the reason of interest in the event, one's health condition and possible headache, headache clinical features, the person's feelings about headache and possible therapy. The data were collected and analysed by means of SPSS.

Results Three hundred and two subjects out of the 499 that filled in the questionnaire answered yes to the question if they were affected by recurrent headache episodes. The subsequent evaluations were limited to the group of headache sufferers and about 20% answered that they had never heard of any Headache Centre before. More than 20% of the subjects declared to manage headache by themselves. About 30% were managed by a Headache Centre. Specific headache therapies were taken by about 35% of patients. More than 10% of headache sufferers had referred to the Emergency Room (ER) one or more times in the previous year. When asked about the way they perceived their headache people described it as a problem or very difficult problem in most of the cases. At the request to give a definition of one's headache, the most original answers were: "a trap", "a curse", "a nightmare", "a fog", "a persecution", "a time bomb".

Discussion The findings of this survey show that Italians need more information about headache and territorial health care resources. In particular the existence of Headache Centres is ignored by a considerable part of the general population. Information about the possible consequence of self-management in terms of headache chronification, symptomatic overuse and recurrent access to ER is lacking. Further SISC educational programmes are needed to continue spreading headache knowledge and information about headache care facilities.

Alteration of iron parameters in primary headache patients

V. Rebecchi¹, E. Giudici², E. Crespi², G. Veneziano¹, C. Zandrini¹

¹Section of Neurology, Department of Clinical Medicine, University of Insubria, Hospital of Circolo, Varese, Italy; ²General Medicine, Cittiglio Hospital, Varese, Italy; e-mail: valentina.rebecchi@libero.it

Introduction Coincidence or causality regarding the relationship between iron overload and migraine-headache is still under discussion. Several studies have reported that iron metabolism may be involved in the pathogenesis of migraine: iron overload, in particular, has been suggested to alter neuronal excitability by lowering the threshold for headache attacks due to iron deposition in the periaqueductal grey matter [1, 2].

Objective Aim of the present study was to evaluate the biochemical iron parameters in a group of primary headache patients and to detect an eventual association between different headache forms and iron overload.

Material We investigated 150 consecutive patients (males 28, females 122, mean age 36.8 years, range 21–62) presenting with primary headaches (diagnosis according to the ICHD-II criteria) and we compared them to a control group of healthy subjects, homogeneous for age and sex. Each headache patient underwent neurological examination, standard laboratory analysis plus biochemical iron-related parameters and conventional neuroradiological studies (brain MRI or CT). The frequency of attacks and the ongoing treatments were obtained by headache diaries; severity and disability of attacks were scored by Tfelt-Hansen and MIDAS scales. Patients carrying alterations of iron parameters suggesting for Hereditary Hemochromatosis (HFE) were investigated for the three main HFE mutations.

Results In 43/150 headache patients (F 37, M 6, mean age 35.8 years, range 28–56) iron indices were found altered as follows: 22/43 with iron overload and 7/43 also with elevated ferritin; 12/43 elevated ferritin alone; 2/43 transferrin over-saturation alone. In the control group only 27/150 showed some alterations of iron parameters ($p < 0.05$). The headache diagnosis of these patients was as follows: episodic migraine without aura 6/43 (14.2%) and with aura 4/43 (9.5%); chronic headaches (migraine/tension-type headaches and association), 21/43 (48.8%) and chronic headaches with analgesic overuse 12/43 (28.5%). In the above group, the mean frequency of attacks among episodic migraine patients (10/43) was nine per month, severity was moderate to severe and the disability index scored 3–4 in all patients. Brain MRI did not reveal altered signal intensity in T2 sequency. Genetic testing was required in 3/43 patients: 1/3 of the subjects presented the mutation C282Y of the HFE gene in heterozygosis state.

Conclusions Our data confirm that iron overload may be frequently found among primary headache patients and that there is a significant difference versus healthy controls. A trend versus a significant relationship also between severity/disability of migraine attacks and iron overload may be suggested.

References

1. Rainero I, Rubino E, Rivoiro C et al (2007) Haemochromatosis gene (HFE) polymorphism and migraine: an association study. *Cephalalgia* 27(1):9–13
2. Kruit MC, Launer LJ, Overbosch J et al (2009) Iron accumulation in deep brain nuclei in migraine: a population-based magnetic resonance imaging study. *Cephalalgia* 29(3):283–285

Case reports

A case of migraine without aura at risk for cerebrovascular events

R.L. Trinchi¹, M.P. Prudeniano²

¹Ambulatorio Cefalee, P.O. G. Chidichimo, U.O. Anestesia, Rianimazione e Terapia del Dolore, Trebisacce, Italy; ²Centro Cefalee, Clinica Neurologica L. Amatucci, Azienda Ospedaliera Universitaria Policlinico, Bari, Italy; e-mail: ritatrinchi@gmail.com

Introduction The cerebral autosomal dominant arteriopathy with subcortical infarcts and leukocephalopathy (CADASIL) is classified according to the ICHD-II classification (2004) at point 6.7.1 as migraine caused by cerebrovascular intracranial pathology. It is a rare vascular encephalopathy of autosomal type correlated to the mutation of receptors of the NOTCH3 gene, of chromosome 19 p13.2 and p13.1 adhesion molecule involved in the intracellular signaling and fundamental for the maturation and maintenance of microcirculation. The arterial smooth muscles meet progressive destruction with repairing fibrosis and obliteration.

Diagnosis search for specific mutation in peripheral blood leukocytes; cutaneous biopsy in search of NOTCH3 antigen by means of monoclonal antibodies. RM is able to detect both infarctions in a strict sense, hyperintensity in the T2 sequences and hypointensity in a T1 sequences, and lesions only visible in T2, as hyperintensity of the white substance [1, 2].

Clinical case A 30-year-old woman, married, housewife, had been suffering for 1 year from medium-severe migraine soon after awakening, lasting 2–3 days, about 3–4 times a month. Pulsating pain was located in the left monolateral, orbital, temporoparietal area. The syndrome was associated to nausea, and photophobia. It worsened with physical effort. Triggering factors: cold, fasting, prolonged sleep; smoking: 13–14 cigarettes a day, no alcohol. Neurologic examination was negative.

Remote Pathological History Tonsillectomy, depressive disorder treated with escitalopram. Two suicide attempts, nasal vasoconstrictor for 20 years.

Family History:

Maternal line: nothing relevant.

Paternal line: Father: ischaemic stroke at 47, migraine without aura (MO), CADASIL; Uncle: deceased at 63 of ischaemic brain stroke; Uncle: CADASIL, 3 strokes, depressive disorder, MO; Aunt: deceased at 74 of ischaemic brain stroke; Cousin: deceased at 52 after 3–4 strokes; Cousin: CADASIL at 20 strokes with outcomes; Cousin: Oligophrenic, CADASIL.

Vascular Risk factors Oral contraceptives intake for over 10 years, cigarette smoke, nasal vasoconstrictors.

Discussions and conclusions The headache of this patient can be diagnosed as migraine without aura. She showed 3 risk factors in her personal history that might anticipate or worsen possible ischaemic events. Given the clinical familiarity in some of the family members and the diagnosis of CADASIL in others, the patient should undergo instrumental and genetic examinations, and clinical follow-up.

References

1. Di Piero V, Mercurio A, Bruti G et al (2010) Neuroimaging. In: Pini LA, Sarchielli P, Zanchin G (eds) Trattato Italiano delle Cefalee. Centro Scientifico Editore, Torino, pp 100–101
2. Sacco S, Di Dionisio L, Carolei A (2010) Cefalea e patologia cerebrovascolare. In: Pini LA, Sarchielli P, Zanchin G (eds) Trattato Italiano delle Cefalee. Centro Scientifico Editore, Torino, pp 350–351

Recurrent palatal ulcerations in a patient with a complex chronic headache syndrome

S. Benemei¹, B. Giomi², M. Bonciani³, P. Geppetti¹

¹SOD Centro Cefalee, Farmacologia Clinica, AOU Careggi, Florence, Italy; ²Dipartimento di Area Critica Medico-Chirurgica, Università di Firenze, Florence, Italy; ³Maria Teresa Hospital, Florence, Italy;
e-mail: silvia.benemei@unifi.it

Introduction No information on cluster headache (CH) and palatal ulceration occurring together has ever been reported in past or current research. A search for CH and oral lesion resulted in only two reports [1, 2], describing HSV reactivation after or before CH attacks, respectively. **Case report** We report the case of a 60-year-old patient affected by a complex chronic headache syndrome characterised by the coexistence of three different types of headache, which, according to the IHS diagnostic criteria, could be diagnosed as migraine, CH and paroxysmal hemicrania. Five years ago, after several days of severe and frequent CH attacks, the patient noticed a mucosal lesion in her oral cavity. The neither painful nor bloody lesion was: ipsilateral to the pain side, localized in the anterior palatal region, and appeared as a multilobular erosion with rounded margins. The lesion vanished in 4–5 days without scarring. The lesion invariably appeared every time the patient experienced severe and frequent (at least 4–5 attacks per day for 2 consecutive days) CH attacks, for a total of 10 times in 5 years. Except for the concomitant headache, the patient did not complain of fever, gastrointestinal symptoms, ocular disturbance, otalgia or arthralgia. Routine blood examination and urinalysis were within normal limits. HIV test, VDRL, TPHA and the serological markers for viral hepatitis were negative. Screening for autoimmunity and anti-transglutaminase antibodies did not reveal any abnormality. A swab for microbial agents resulted negative, as did PCR analysis for HSV1, HSV2 and VZV DNA, performed the day after the appearance of the lesion. Herpes virus serology, performed at the same time, demonstrated negative IgM anti-HSV1–2 and IgG anti-HSV2 values, but positive IgG anti-HSV1 levels (30 UM), according to a positive history for herpes labialis. No significant levels of VZV IgM antibodies were detected.

Discussion and conclusions Because of the clinical presentation and the two reports published, we first hypothesized that the patient showed HSV reactivation during the CH exacerbations. However, the herpetic nature of the oral lesion was excluded by negative PCR and serology. Thus, we propose the alternative diagnosis of aphthous-like ulcers. Psychological and emotional stress have always been reported as a primal mechanism of aphthosis and could not be excluded in our case. However, the consistently ipsilateral lesion observed in our patient suggests the activation of peripheral endings of peptidergic trigeminal neurons with their pro-inflammatory potential as the underlying mechanism of the palatal lesions during the exacerbation of CH attacks.

References

1. Rajiv E (1985) Cluster headache and herpes simplex. *Br Med J (Clin Res Ed)* 291(6490):284
2. Hardebo JE (1986) An association between cluster headache and herpes simplex. *N Engl J Med* 314(5):316

Headache in acute cerebral ischaemia and intracranial artery stenosis

F. Viaro, C. Baracchini, C. Disco, F. Maggioni, G. Zanchin

Headache Centre of the Veneto Region, Department of Neurosciences, University of Padua, Padua, Italy;
e-mail: federica.viaro@unipd.it

Background Headache is a common symptom in transitory ischaemic attacks (TIA) and acute ischaemic stroke (AIS), but many aspects of its association with other clinical causative conditions are controversial [1]. Stenosis of intracranial arteries is reported to be responsible for 30–50% of strokes in Orientals, 11% in Hispanics, 6% in Blacks, and only 1% in Caucasians. However, the clinical importance of intracranial stenosis in Caucasians may have been underestimated [2]. Moreover, to the best of our knowledge, data on the occurrence of headache in TIA/AIS attributed to intracranial arterial stenosis are not reported in the literature.

Methods We examined our database registry of all AIS occurred in Caucasian patients over a 2-year period, from January 1, 2009 to December 31, 2010. All patients underwent a complete extra- and transcranial Echo-color Doppler sonography (ECDS) and neuroradiological confirmation (magnetic resonance angiography or ct angiography or digital subtraction angiography) at onset and after 3 months. We excluded patients with hemorrhagic stroke, cerebral venous thrombosis, cervical vessel dissection, vasculitides, receiving thrombolytic treatment, having signs of vessel recanalization, who constituted our control group.

Results Among 110 patients included in this study, 30 (27.3%) harboured at least one intracranial stenosis responsible for the symptoms; 10 (33.3%) of these patients reported a severe headache at stroke onset: 6 had a middle cerebral artery stenosis, 3 had a vertebral artery stenosis and 1 had a basilar artery stenosis. None of them had a history of headache. In our control group, 15% (51/340) had a headache at onset.

Conclusions These preliminary results of our study on Caucasian patients with AIS show a much higher prevalence of intracranial stenosis than previously reported. Headache is a relevant symptom at the onset of AIS in a third of patients with a causative intracranial arterial stenosis.

References

1. Tentschert S, Wimmer R, Greisenegger S (2005) Headache at stroke onset in 2,196 patients with ischemic stroke or transient ischemic attack. *Stroke* 36:e1–e3
2. Arenillas JF (2011) Intracranial atherosclerosis: current concepts. *Stroke* 42(Suppl 1):S20–S23

A case of reversible cerebral vasoconstriction syndrome (RCVS): clinical and instrumental features supporting the diagnosis in the acute phase of the disease

S. Gori¹, F. Giorgi¹, C. Lucchesi¹, A. Chiti¹, M. Puglioli², G. Orlandi, L. Murri¹

¹Department of Neuroscience, Institute of Neurology, University of Pisa, Pisa, Italy; ²Department of Neuroscience, Unit of Neuroradiology, University of Pisa, Pisa, Italy;
e-mail: s.gori@med.unipi.it

Introduction Reversible cerebral vasoconstriction syndrome (RCVS) is a condition characterised by sudden, severe headache at onset (thunderclap headache), vascular narrowing involving the circle of Willis and its immediate branches and angiographic evidence of vasoconstriction reversibility within minutes to weeks of onset. RCVS is a condition under recognized and often misdiagnosed. The diagnosis of reversible cerebral vasoconstriction syndrome (RCVS) is challenging because it can mimic other neurologic diseases, such as primary angiitis of the central system (PACNS), which warrant specific and potentially dangerous therapeutic regimens, raising safety and efficacy concerns. We report the case of a woman with a probable RCVS, underlining clinical and instrumental data which support the diagnosis in the acute phase of the disease.

Case report A 55-year-old woman with a pre-menopausal history of migraine without aura presented with recurrent episodes of severe “thunderclap” headache not responsive to non-steroids anti-inflammatory drugs. Cranial CT showed mild signs of subarachnoid haemorrhage (SAH) in the sulci of the frontal convexity; MRI/MRA confirmed SAH, in absence of parenchymal lesions or large vessels abnormalities. Digital subtraction angiography (DSA) revealed narrowing of some middle-sized arteries (left pericallosal artery and occipito-parietal branches of cerebral posterior artery bilaterally), likely not due to the slight frontal SAH; rheumatologic blood screening was unremarkable. Cerebrospinal fluid examination was consistent with SAH. During hospital stay the patient subacutely developed a bilateral visual field disturbance; further CT/MRI showed bilateral occipital lesions suggestive of vasogenic oedema with slight contrast enhancement and a mild haemorrhagic component. Transcranial Doppler findings were normal on large intracranial vessels; notably, eyes opening did not affect velocimetric values on posterior cerebral arteries. Intravenous methylprednisolone was administered, but only oral nimodipine provided headache improvement. The patient was discharged with her medical therapy and a control DSA, performed 3 months later resulted normalized, while MRI showed reduction of the previously detected lesions. In the meantime, no further episodes of “thunderclap” headache were reported and visual impairment improved.

Conclusions In our case clinical, neuroradiological and transcranial Doppler features were already suggestive of RCVS rather than PACNS in the acute phase of the disease. While awaiting for follow-up DSA, we suggest that it might be useful to rely on such data to choose the proper treatment, warranting therapy with calcium channel blockers instead of cytostatic drugs (which are recommended in case of PACNS but could worsen RCVS) on top of corticosteroid.

Migraine and valsartan: a case report

C. Disco¹, F. Viaro¹, M. Bellamio¹, M. Margoni¹, F. Maggioni¹, G. Zanchin¹

¹Headache Centre, Department of Neurosciences, University of Padua, Padua, Italy; e-mail: caterina.disco@studenti.unipd.it

Introduction Among antihypertensive drugs administered for migraine prophylaxis, a role for angiotensin II receptor blockers (ARBs) has been proposed [1], particularly for candesartan [2]. We present a case of chronic migraine (CM) which showed an excellent, persistent improvement with valsartan administration.

Case report A 70-year-old woman presented since childhood about four attacks/month of migraine without aura (MO, ICHD-II criteria). A former employee, her family history was positive for MO. Her personal history was unremarkable. When she was 20 years old, MO progressively shifted to CM (more than 20 days/month). NSAIDs and triptans were ineffective; only suppositories with an association of ergotamine tartrate 2 mg, caffeine 100 mg and aminofenazone 250 mg (15–20 doses/month) gave partial relief. During the years, no satisfying effect was obtained with the preventative drugs amitriptyline, flunarizine, metisergide, propranolol, topiramate, pizotifen. Sodium valproate had to be discontinued after a few weeks because of an increase of hepatic enzymes.

In the last 3 years the patient was prescribed atenolol 50 mg/die for a mild essential hypertension. Antihypertensive therapy improved blood pressure but did not modify CM. General and neurological examinations as well as brain MR, ECG and echocardiogram were unremarkable.

In March 2010, because of an incomplete blood pressure control, the association valsartan 160 mg/hydrochlorothiazide 12.5/day was added.

After 2 weeks, the patient reported the disappearance of CM, documented in her headache diary, with complete discontinuation of the association of drugs used during attacks.

One month later, the patient had to discontinue her antihypertensive therapy because of an excessive reduction of blood pressure. After a week, CM attacks returned to the same frequency as before. Two weeks later, she took again valsartan 160 mg/day, no longer in association with hydrochlorothiazide. She began to rapidly improve and in 2 weeks the headache frequency was reduced to three attacks/month. After 13 months her headache diary still documents three MO attacks/month lasting about 6 h, among which only one attack presents with a severe intensity and is effectively treated with a suppository of ergotamine tartrate, caffeine and aminofenazone (1–2 doses/month). The patient has not reported any undesired effect by valsartan.

Conclusions This case report documents an excellent improvement with valsartan of a patient suffering from CM for 50 years unresponsive to other preventative drugs. If confirmed by further observations, this case would suggest a possible role for the ARB valsartan in CM prophylaxis.

References

1. Gales BJ, Bailey EK, Reed AN et al (2010) Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for the prevention of migraines. *Ann Pharmacother* 44:360–366
2. Tronvik E, Stovner LJ, Helde G et al (2003) Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA* 289:65–69

A “painful tic convulsif” (trigeminal neuralgia and ipsilateral facial spasm) due to double neurovascular impingement: a case report

G. Giglia¹, M. Romano², V. Virzi³, F. Narese³, A. Palermo¹, B. Fierro¹, F. Brighina¹

¹Dipartimento di Biomedicine Sperimentali e Neuroscienze Cliniche (BioNeC), Università di Palermo, Palermo, Italy; ²Dipartimento di Neurologia, Ospedale Villa Sofia, Palermo, Italy; ³Unità Operativa di Radiologia, Casa di Cura Regina Pacis, San Cataldo, Italy; e-mail: fbrighina@unipa.it

Introduction “Painful tic convulsif” is a rare condition characterised by paroxysmal irritative dysfunction of the V and VII ipsilateral cranial nerves [1]. Most of them were caused by masses or by a singular vascular loop in the posterior fossa, involving both the facial and trigeminal nerves.

Case report Here we present the case of a 50-year-old man suffering from “painful tic convulsif”, on the left side of the face, i.e., left trigeminal neuralgia associated with ipsilateral hemifacial spasm. An angio-MRI scan showed a neurovascular conflict of the left superior cerebellar artery with the ipsilateral V cranial nerve and of the left inferior cerebellar artery with the ipsilateral VII cranial nerve. Neurophysiological evaluation through exteroceptive blink reflex showed the involvement of the left facial nerve (reduced area and increased latency of RII component recorded on the left side). An initial carbamazepine treatment (600 mg/daily) was ineffective, so the patient was shifted to lamotrigine 50 b.i.d., that showed good efficacy reducing attacks from 4–6 times per day to 1–2 per week. Considering the good response to drugs, the neurosurgeon decided to delay surgical treatment.

Conclusions To our knowledge this is the first “painful tic convulsif” case due to two separate neurovascular conflicts underlying trigeminal and facial nerve impairment. Even if this condition is considered

rare, we think that a considerable number of cases might escape notice unless careful history, and neuroimaging and neurophysiological tests are performed.

References

1. Tsuyumu M, Kohmo Y (1991) Painful tic convulsif: case report. *Surg Neurol* 4:310–313

Ictal epileptic headache: headache as first ictal symptom in focal epilepsy

F. Dainese¹, R. Mai², F. Mainardi³, S. Francione², G. Zanchin⁴, F. Paladin¹

¹Epilepsy Centre, Neurologic Division, Hospital of Venice, Venice, Italy; ²Epilepsy Surgery Centre C. Munari, Milan, Italy; ³Headache Centre, Neurologic Division, Hospital of Venice, Venice, Italy; ⁴Headache Centre, Department of Neurosciences, University of Padua, Padua, Italy; e-mail: fdainese@gmail.com

Introduction Headache is commonly associated with seizures as a preictal, ictal, or postictal phenomenon, but it is often neglected because of the dramatic neurologic manifestations of the seizure. Headache can also be the sole or most predominant clinical manifestation of epileptic seizures, although this is relatively rare. We report two cases of focal symptomatic drug-resistant epilepsy with headache as first ictal symptom.

Cases The first case is an 11-year-old, left-handed boy, with seizure onset at the age of 4 years. His initial symptom consisted of sudden pain on the left side of the head and vertex, tightening in quality and severe intensity; in case of seizure progression he had visual hallucination and ocular deviation with secondary loss of contact. Cerebral MRI showed cortical dysplasia in the right lingual gyrus. He underwent a stereo-EEG recording with evidence of ictal EEG discharges contralateral to the pain. The ictal headache was also triggered by the electrical stimulation. The second case is a 47-year-old woman with focal symptomatic epilepsy in tuberous sclerosis with almost one seizure daily. The seizure started with pain in the right frontal side of the head, eye movement sensation and tonic posture of the right arm; she usually suffered from only ictal headache lasting a few seconds three or four times per day with seizure progression once a day. Two typical seizures were recorded during video EEG registration, in one case with only headache, with EEG discharge started in the central left derivation with spreading to the anterior derivation; we suppose an anatomical correlation with tuberous in the left inferior parietal cortex.

Discussion and conclusions In both cases the headache lasting a few seconds, was contralateral to the ictal discharge, and did not have clinical features of migraine. Ictal headache is a rare epileptic symptom that can help to localize ictal EEG discharge [1]. Recently, the term “ictal epileptic headache” has been proposed in cases in which headache is the sole ictal epileptic manifestation [2]. Diagnosis requires the simultaneous onset of headache with EEG-demonstrated ictal discharge. Further reports are required to propose new criteria for migraine and epilepsy comorbidity.

References

1. Siegel AM, Williamson PD, Roberts DW et al (1999) Localized pain associated with seizures originating in the parietal lobe. *Epilepsia* 40:845–855
2. Belcastro V, Striano P, Kasteleijn-Nolst Trenité DG et al (2011) Migraine, hemispheric epileptic, post-ictal headache and “ictal epileptic headache”: a proposal for terminology and classification revision. *J Headache Pain* (Epub Mar 1)

Coexisting form of trigeminal autonomic cephalalgias in the same patient: case report

F. Sovani, C. Lepre, F. Pauri

Dipartimento di Scienze e Biotechnologie Medico-Chirurgiche, Sapienza Università di Roma, Rome, Italy; e-mail: flavia.pauri@uniroma1.it

Introduction The trigeminal autonomic cephalalgias (TACs) are short-lasting unilateral headaches associated with autonomic features. The coexistence of different ipsilateral TACs in the same patient has been previously reported in male patients. We describe the coexistence of two different contralateral TACs.

Case report A 50-year-old man complained of recurrent attacks of headache. From the age of 16 he suffered two attacks/day of unilateral right orbital/supraorbital severe pain, without radiation, lasting 30–120 min. The pain was throbbing, associated with ipsilateral tearing, conjunctival injection, ptosis, nasal stuffiness, photophobia, and phonophobia. The attacks were concentrated in a cluster lasting about a month, usually during the summer, when he was young, and preferentially during the winter in adult life. He remembered having had a cluster period every year in the last decade. He was treated with ergot and flunarizine.

During headache periods alcohol intake triggered the beginning of the headaches. He had suffered of gastric ulceration treated with omeprazole and he was taking antihypertensive drugs.

When he came to our clinic the cluster period was ending, but he was complaining of a new kind of headache, pulsating in quality, located on the left side, left temple, eye, and forehead, with radiation to the nostril associated with lacrimation, nasal congestion, photophobia, and phonophobia. These headaches lasted 90 min, starting at 11 pm, almost every night. Rarely did he have an attack at 4 pm. He experienced these new headaches for 2 months and the drugs he used for cluster headache (CH) gave no relief. Indomethacin, 100 mg taken at night, before sleeping, dramatically stopped the crisis.

Discussion The right-sided headache complained by the patient fulfilled the criteria for CH, according to the latest International Classification of the Headache Society criteria (ICHD-II). Some doubts arise regarding the left-sided headache: it was actually a strictly unilateral headache with autonomic features fulfilling the criteria for paroxysmal headache (PH); only the duration was a little unusual, about 90 min, and the frequency, one or sometimes two attacks/day. Conversely, the sudden response to indomethacin, and the inefficacy of drugs used for CH, suggest the diagnosis of PH. Furthermore, the patient clearly distinguished the two headaches and entered our clinic for the left-sided headache, because he was able to recognize and treat the right-sided headache he had suffered from his youth, but all the drugs he had used for CH were unsuccessful for the other kind of headache.

Case report: Eagle syndrome or glossopharyngeal neuralgia?

A. Tarsitano¹, P. Scarpelli¹, U. Cannistra², E. Pisani³

¹SOC Centre of Medicine Pain, INRCA-IRCSS, Cosenza, Italy; ²SOC Neurology, Regional Hospital Pugliese-Ciaccio, Catanzaro, Italy; ³SOC Neurology, Regional Hospital Annunziata, Cosenza, Italy; e-mail: a.tarsitano@inrca.it

Case report A 38-year-old woman from April 2004 after a vaccine therapy against the flu started abruptly to suffer from spinning vertigo,

nausea, vomiting and pain in the left ear defined like a “shake”. She had several relapses diagnosed as BPPV and in 2006 these symptoms become continuous and the rocking boat sensation was particularly aggravated when there were other symptoms such as a flu or a cold. She was also treated with duloxetine in 2006 for panic attacks and depression with duloxetine. She also reported a sensation of paresthesia in her left ear and a headache on the left side, from time to time associated with nausea. She often got neck pain radiating to the occiput and bi-parietal areas. She was treated with propranolol for “migraine” prophylaxis without solution. She came to our observation with persistent pain in her left ear defined like a “shake”. The paroxysms of pain are triggered by swallowing, yawning and cold food. The clinical exam revealed pain on palpation of left tonsillar pillar. She started therapy with pregabalin and celecoxib: pain was reduced about 60% but she discontinued the therapy because it made her very sleepy. So we tested the glossopharyngeal nerve through injection of lidocaine 2% into the anterior tonsillar pillar that provided relief of symptoms within minutes. MR and MR angiography of the brain and the brain stem were normal. X-rays of the skull, both in AP and lateral views, reveal the elongated left styloid process >3 cm. In agreement with an otolaryngologist, we diagnosed Eagle syndrome. She underwent a tonsillectomy. After this she had a reduction of vertigo and rocking boat sensation, but ear and headache pain were still present. At present she is waiting for surgical shortening of the styloid process.

Discussion Eagle syndrome is a rare, secondary cause of glossopharyngeal neuralgia and comprises a constellation of symptoms, which in the classic type, may include facial pain, ear pain, dysphagia, voice changes and a globus sensation in the throat that prompts frequent swallowing, that occurs secondary to an elongation of the styloid process [1]. The first may be confused with GF neuropathy. In this case the syndrome is probably caused by a reactive ossifying hyperplasia of the styloid process followed by chronic tonsillitis. In conclusion, the differential diagnosis of glossopharyngeal neuralgia is broad and should include Eagle syndrome.

References

- Kim E, Hansen K, Frizzi J (2008) Eagle syndrome: case report and review of the literature. *Ear Nose Throat J* 87(11):631–633. Review

Headache, neurological deficit with cerebrospinal fluid lymphocytosis (HaNDL): a case report

C. Lucchesi, A.N. Sassi, A. Amidei, S. Gori, L. Murri

Department of Neuroscience, Institute of Neurology,
University of Pisa, Pisa, Italy; e-mail: cinzia.lucchesi@gmail.com

Introduction The headache, neurological deficit with cerebrospinal fluid lymphocytosis syndrome (HaNDL) is a benign, self-limiting, rare disease, characterised by episodes of moderate or severe headache, transient neurological deficits and lymphocytic pleocytosis. Patients are asymptomatic in the interictal phase, most of the episodes last hours and can recur over <3 months. Cerebrospinal fluid (CSF) analysis shows pleocytosis, with lymphocytic predominance, elevation of CSF total proteins (90% of cases) and increased CSF opening pressure (50% of cases). Neuroimaging and microbiological examinations are typically normal. The etiopathogenesis is unknown.

Case report We report the case of a healthy 38-year-old patient, presenting a first episode, characterised by mild right-sided numbness, mild hemiparesis, speech disturbance and frontal moderate headache; the episode lasted 1 h and a half and symptoms were fully reversible.

Two days later, the patient presented an episode characterised by vomiting, soporous state, left-sided paresthesias and severe frontal headache; he was conducted to the Emergency Department.

A brain CT scan was immediately performed and resulted normal. A lumbar puncture showed lymphocytic pleocytosis, in agreement with the diagnosis of “serous meningitis with normal glucose levels” and an EEG showed “diffuse severe abnormalities”; according to these exams, the patient was admitted to hospital with the suspicious of meningitis. Three to four hours later, the symptoms completely disappeared.

A brain MRI was performed and a non specific frontal subcortical white matter hyperintensities was reported; second EEG resulted normal. The patient was discharged with the diagnosis of “atypical meningoencephalitis”.

The day after the hospital discharge, the patient presented an episode of spatio-temporal disorientation and headache, lasting about 1 h and a half; at hospital admission, a second lumbar puncture was performed and cerebrospinal fluid analysis showed raised CSF opening pressure, lymphocytic pleocytosis and elevation of CSF total proteins. CSF microbiological examinations, immunological blood tests were normal; a second brain MRI was unchanged.

The presence of three episodes of headache, transient neurological deficits and lymphocytic pleocytosis, fully reversible, not recurrent after 3 months from the first episode, supported the diagnosis of HaNDL. The patient performs regular neurological follow-up visits and after 2 years he is still asymptomatic.

Discussion This case is in agreement with the diagnosis of HaNDL, a rare benign, self-limiting pathology; a differential diagnosis is however mandatory, in particular vascular, inflammatory and infectious etiologies must be ruled out.

Headache due to Vogt-Koyanagi-Harada syndrome

C. Mostardini¹, G. Nola², L. Marchione¹

¹U.O.C. of Neurology, G.B. Grassi Hospital, Rome, Italy;

²U.O.C. of Otorhinolaryngology, G.B. Grassi Hospital, Rome, Italy;
e-mail: cmostardini@gmail.com

We describe the case of a 23-year-old woman, who came to the attention of an ophthalmologist for the acute onset of binocular vision disorders associated with severe throbbing headache which started 2–3 days before and hearing loss in the right ear with tinnitus.

The patient had a history of episodic migraine without aura, and rare crises of migraine with visual aura characterised by scintillating scotomas (1–2 episodes/year) were also present.

The initial clinical characteristics of the headache were similar to a migraine, even if the pain was less defined, but the onset of visual disturbance and meningeal symptoms like a slight positive Brudzinski and Lasègue signs led to an alternative diagnosis.

The visual disturbance was characterised by rapid reduction of binocular visual acuity, in particular in the central vision, intense photophobia, eye pain, with residual vision of 2/10 in the right eye and 4/10 in the left, starting from a normal vision. Eye examinations showed bilateral severe posterior uveitis with a moderate retinal exudation, and initial iridocyclitis.

The patient also had tinnitus, mainly in the right ear and hearing tests revealed a high frequency hearing loss in the right ear. The vestibular component was affected with vertigo, nystagmus and in videonystagmography abnormal ocular saccades test was observed. The vestibular evoked myogenic potential (VEMP) altered in initial phases resolved after 1 month of treatment. No central vestibular and auditory processing disorder was seen.

The patient was immediately treated with a high dosage of methylprednisolone for a month. Clinical improvement occurred rapidly with full recovery within 30–45 days, no cutaneous findings were discovered.

Vogt-Koyanagi-Harada (VKH) syndrome is a rare systemic disease involving various melanocyte-containing organs. Bilateral panuveitis associated with cutaneous, neurologic, and auditory abnormalities are manifestations of this inflammatory granulomatous disorder. The etiologic and pathogenic factors in VKH syndrome suggest a non infective inflammatory headache included in chapter 7.3.3 of the ICHD-II classification.

Crowned dens syndrome presenting with a throbbing unilateral daily headache aggravated by valsalva and postural changes

M. Viana^{1,2}, P.P. Sainaghi³, A. Stecco⁴, F. Mortara², F. Monaco², P.J. Goadsby¹

¹Headache Group, Department of Neurology, University of California, San Francisco, CA, USA; ²Department of Neurology, University of Eastern Piedmont A. Avogadro, Novara, Italy; ³Immuno-Rheumatology Outpatient Unit, University of Eastern Piedmont A. Avogadro, Novara, Italy; ⁴Department of Radiology, University of Eastern Piedmont A. Avogadro, Novara, Italy; e-mail: michele.viana@headache.ucsf.edu; michele.viana@ymail.com

Introduction Crowned Dens syndrome (CDS) is a clinical-radiological entity characterised by calcification of the peri-odontoid articular structures and by acute attacks of neck pain with fever, rigidity, and general sign of inflammation. The crystal deposit can be frequently due to pseudogout, but also to rheumatoid arthritis and osteoarthritis [1].

Methods This is a case report with 10 months follow-up, of a patient with an atypical presentation of CDS.

Case description An 81-year-old man, who had never suffered from headache before July 2010, developed progressively a strictly left-sided headache that after a couple of weeks became daily. The pain was localized on the whole left scalp but it was felt more intense on the frontal area, the intensity was moderate to high and the quality of the pain was throbbing. There were no associated symptoms. The headache intensity was constant during the day but the pain was aggravated by gaining the orthostatic position and by Valsalva. We saw him 15 days after the headache onset. The neurological and general examinations were normal except for a reduced range of motion in the neck. A brain MRI with Gd and cervical MRI were ordered and the patient was prescribed indomethacin. He partially responded to indomethacin orally 25 mg t.i.d and after a week he was given a dosage of 50 mg t.i.d. with a complete regression of the pain. The brain MRI was normal while a MRI of the cervical spine showed a non homogeneous 12 mm mass behind the odontoid process of C2, narrowing the subarachnoid space in C1, stretching the posterior longitudinal ligament and touching the left vertebral artery. A CT scan focused on C1–C2 showed calcification in the soft tissue around odontoid process and an inflammation thickening of C2 left root. The patient was referred to a Rheumatologist who concluded there was spinal osteoarthritis with involvement of the atlanto-axial joint.

Discussion This is a case with typical radiological findings for CDS. Indeed the clinical picture was not at all typical for CDS for some features such as the unilaterality and localization of the head pain, the aggravation by Valsalva and gaining orthostatic position, and the lack of either fever or inflammatory sign.

Conclusions This case widens the spectrum of the clinical presentation of CDS, a condition that we should keep in mind as it can be a source of secondary headache, which usually response well to medical treatment.

References

1. Scutellari PN, Galeotti R, Leprotti S et al (2007) The crowned dens syndrome. Evaluation with CT imaging. *Radiol Med* 112(2):195–207

Coexistence of “headache attributed to airplane travel” and “mountain ascending headache”

F. Mainardi¹, C. Lisotto², F. Maggioni³, G. Zanchin³

Headache Centres: ¹Neurological Division, SS Giovanni e Paolo Hospital, Venice, Italy; ²San Vito al Tagliamento Hospital, San Vito al Tagliamento, Italy; ³Department of Neurosciences, Padua University, Padua, Italy; e-mail: federico.mainardi@ulss12.ve.it

Introduction The term “Airplane headache” (AH) refers to a form of a recently described headache disorder, whose attacks are strictly related to airplane travel, mostly to the landing phase. We have been studying AH features in a large series of patients fulfilling the diagnostic criteria that we have previously proposed [1].

Materials and methods Through a detailed questionnaire we identified, in our total population of 60 AH cases, 3 patients suffering from headache attacks also occurring during the rapid ascent of a mountain by car.

Results These patients (2 males, 1 female, mean age 36 years), who have complained of AH attacks during landing in more than 50% of their flights, referred the occasional onset of jabbing, severe, unilateral headaches in the fronto-temporal region when ascending a mountain by car. They described the headaches as quite similar, with exactly the same features, as compared with those experienced during landing. No accompanying symptoms were reported. They reached the altitude of 2,000 m in <30 min; the pain began shortly afterwards, the maximum peak of intensity developing in a few minutes. They were forced to stop their ascent; all of them reported the pain subsidence within 20 min from the rapid descent. No concomitant airways disturbance was reported during the travel. Two of them experienced this pain in three different occasions; one patient had only one attack. General and neurological examination, brain MRI, angio-MRI, and cranial CT-scan for sinuses were normal.

Conclusions The coexistence of headache attacks with peculiar features triggered by these different situations, landing by airplane and ascent of high altitude by car, strengthens the hypothesis of a possibly shared pathophysiological mechanism, i.e., the rapid change of air pressure, which occurs in both conditions.

References

1. Mainardi F, Lisotto C, Palestini C et al (2007) Headache attributed to airplane travel (“airplane headache”): first Italian case. *J Headache Pain* 8:196–199

Migraine with aura and typical aura without headache secondary to colloid cyst

F. Mainardi¹, C. Lisotto², M. Disaro³, F. Maggioni⁴, G. Zanchin⁴

Headache Centres: ¹SS Giovanni e Paolo Hospital, Venice, Italy; ²San Vito al Tagliamento Hospital, San Vito al Tagliamento, Italy;

³Radiological Department, SS Giovanni e Paolo Hospital, Venice, Italy; ⁴Headache Centre, Department of Neurosciences, Padua University, Padua, Italy; e-mail: fmainardi@iol.it

Colloid cyst is a congenital rare benign tumor, most frequently located in the antero-superior side of the third ventricle; its growth is generally slow, explaining the symptoms' late onset. A 52-year-old woman presented to our Headache Centre complaining of recurrent episodes of visual disturbances lasting up to 30 min, described as the appearance of a scotoma in her left visual hemifield, which slowly increased in size, reaching the maximum in about 15 min and then gradually disappearing; it was surrounded by brilliant zigzagging lines resembling "fortification spectra". A moderate throbbing fronto-temporal unilateral headache with side shift, accompanied by nausea, lasting several hours and exacerbated by routine physical activity, incessantly followed the visual symptoms. These episodes started about 15 days prior to our observation, occurring once or twice daily. Physical and neurological examinations were unremarkable. The patient underwent a CT scan which revealed the presence of a third ventricle colloid cyst associated with obstructive hydrocephalus. A subsequent cerebral MRI with contrast confirmed this finding. The lesion was removed by a frontal transcortical approach. In the post-operative period the neurological examination did not reveal sensory or motor deficiencies; she only complained of a slight memory impairment, confirmed by neuropsychological testing. This disturbance improved spontaneously, and neuropsychological evaluation performed 2 months later was normal. After the lesion removal, the migraine with aura-like (MA-like) and the typical aura without headache-like episodes did not recur during the 15-month follow-up. The histological study of the lesion was consistent with the radiological diagnosis. In clinical practice it is known that some clinical presentations, which at first observation seem to be completely suggestive of a primary headache, may later turn out to be related to a secondary cause, as we already reported in a paper including a large case series of TACs-like headaches [1, 2]. Structural disorders, such as intracranial arteriovenous malformations and brain tumors, have been reported as possible causes of MA-like attacks. In the literature, the abnormalities associated with symptomatic migraine with visual aura were found to involve the cortex, either directly or indirectly. However, since the thalamus can be a site for spreading depression in experimental animal models, in our patient the third ventricle colloid cyst might have triggered spreading depression, possibly by an intermittent increase of intraventricular pressure.

References

1. Mainardi F, Trucco M, Palestini C et al (2010) Clusterlike headache. A comprehensive reappraisal. *Cephalalgia* 30:399–412
2. Trucco M, Mainardi F, Maggioni F et al (2004) Chronic paroxysmal hemicrania, hemicrania continua and SUNCT syndrome in association with other pathologies: a systematic review. *Cephalalgia* 24:173–184

The headache of Giacomo Girolamo Casanova

G. Cristofori, A. Granato, G. Relja

Department of Medical, Technological and Translational Sciences, Headache Centre, University of Trieste, Trieste, Italy; e-mail: antonio_granato@hotmail.com

Objective Recurrent headache is described in biographies of many famous politicians, scientists, literary men, and artists of the past. Aim of the present study was to analyse the headache described by Giacomo Girolamo Casanova (1725–1798), a famous Venetian writer,

traveller, adventurer and womanizer, in his autobiography "Histoire de ma vie" [1].

Clinical case G.G. Casanova took a degree in law, was a hedonist, followed a varied diet, consumed a moderate amount of alcohol and did not smoke. He suffered from recurrent epistaxis, smallpox, a not well defined herpes, rectal fistula, gonorrhoea, lues, duel slashes, kinetosis while on a journey by gondola or stagecoach. When he was 18 years old, he experienced a visual disturbance described as "a right tall pyramidal flame or uncommon lamp", with duration "from the dawn to daylight", which was not followed by headache. He began complaining of episodic headache at the age of twenty. The attacks were triggered by "anxiety, rages, journeys", the intensity was severe, and he was forced to "stay in room or in bed" for one to 3 days. He had "nausea, vomiting, and osmophobia to perfumes". Alleviating factors were fasting and sleeping. Bloodlettings and drugs were not effective.

Discussion Casanova described many attacks of recurrent, severe, 4–72 h duration, headache worsened by stress and routine physical activity. Data on localization and quality of pain are not available. The headache described meets the ICHD-II criteria for migraine without aura [2]. Additional factors suggesting a diagnosis of migraine are kinetosis, aggravating and alleviating factors, and osmophobia. The visual disturbance reported may be classified as a single episode of typical visual aura without headache. The diagnostic exclusion criteria for other pathologies can not be verified.

Conclusions The analysis of the autobiography of Giacomo Casanova revealed that he suffered from migraine without aura and from typical visual aura without headache. He extensively described his headache. After two centuries, the clinical characteristics of migraine remain unchanged.

References

1. Casanova de Seingalt J (1961) Histoire de ma vie. Traduzione italiana: Storia della mia vita di Giacomo Casanova. Ed. Casini, 1, Roma
2. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd edn. *Cephalalgia* 24(Suppl 1):1–160

Developmental age

Headache and migraine equivalents: analysis of 916 children and adolescents referring to a paediatric headache centre

M. Citti, S. Tarantino, C. Vollono, A. Capuano, F. Vigeveno, M. Valeriani

Headache Centre, Division of Neurology, Paediatric Hospital Bambino Gesù, IRCCS, Rome, Italy; e-mail: monica.citti@opbg.net

Introduction Several clinical conditions including recurrent abdominal pain (RAP), cyclic vomiting (CV), lower limb pain (LLP), periodic torticollis (PT), motion sickness (MS), and benign paroxysmal vertigo (BPV), are currently reported as migraine equivalents (ME), probably sharing common pathophysiological mechanisms with primary headaches. The aims of this study were: (1) to assess the prevalence of migraine equivalents in children referring to our Headache Centre, and (2) to evaluate its possible correlation with some headache characteristics (attack frequency and pain intensity) and gender.

Materials and methods Nine hundred and sixteen consecutive patients with primary headache, referring to our Headache Centre from June 2007 to April 2011, were included. Their age ranged from 2 to 18 years (mean age 9.9 ± 3.1). The patients were divided into

three groups according to the frequency of attacks, gender and pain intensity.

Results ME were encountered in 631 patients (68.8%). Among them, 574 patients had migraine without aura, 37 patients had migraine with aura, 18 patients had tension-type headache, and 2 children had migraine without aura and tension-type headache. RAP was the most frequent ME (36%), followed by LLP (34%) and MS (30%). A significant relationship between high frequency of headache attacks and presence of ME was found ($\chi^2 = 5.04$; $p < 0.01$). Females showed ME more frequently than males ($\chi^2 = 1.34$; $p < 0.04$).

Discussion and conclusions Our results show that ME, in particular RAP, LLP and MS, are very frequent among children with headache, thus suggesting common pathophysiological mechanisms with primary headaches. The statistically significant correlation between high frequency of headache attacks and presence of ME may suggest that an augmented susceptibility to pain could represent a background for both conditions (primary headache and ME).

Paediatric chronic headaches: a retrospective descriptive study in a headache centre population

C. Vollono¹, A. Capuano¹, S. Tarantino¹, R. Torriero^{1,2},
R. Mariani^{1,3}, F. Vigevaro¹, M. Valeriani¹

¹Headache Centre, Neurology Division, Paediatric Hospital Bambino Gesù, IRCCS, Rome, Italy; ²Department of Paediatrics, University of Rome Tor Vergata, Rome, Italy; ³Department of Paediatrics, Sapienza University of Rome, Rome, Italy; e-mail: lvoll@libero.it

Introduction Headaches are common neurologic conditions in children and adolescents causing a significant impact on quality of life. Chronic headaches, conversely, occur rarely in paediatric age. Aim of this study was to evaluate the prevalence and the characteristics of chronic headaches in a paediatric population referred to a Headache Centre.

Materials and methods A retrospective chart review was conducted on all headache patients referred to our Headache outpatient Division over a period of 10 years. Records were reviewed for pertinent data including patient history, diagnosis, frequency of attacks, treatment regimens and follow-up.

Results We studied 132 patients with chronic daily headache recruited from our 4,000 headache outpatients over a period of 10 years. Ninety-six girls and 36 boys were identified. The mean age of the patients was 11.20 ± 2.81 years, the youngest being 7.2 years and the oldest 16.3 years. In our sample the mean duration of chronic headache was 5.92 ± 9.35 months. Most patients had chronic migraine (42.4%) and chronic tension-type headache (36.3%). The percentage of patients fulfilling criteria for new daily persistent headache was 18.2% and only 3.03% had a medication-overuse headache. The reported occurrence of throbbing character was 33.3%, aching 9.1%, stabbing 3%, and pressure 54.5%. The pain was predominantly bilateral in 60.6% of patients, unilateral in 18.1%. Fifteen percent of patients reported both sided/generalized pain attacks. Nausea was the most consistently reported autonomic feature (30.3%), followed by both photophobia and phonophobia (24.2%), only phonophobia (21.2%) and only photophobia (18.1%). Twelve percent of patients reported dizziness during the headache attack. Headache was aggravated by activity in 30.3% of patients. At follow-up, on the basis of data from the diaries, about 60% of patients were classifiable in high frequency episodic form of primary headache.

Discussion and conclusions Our data confirm that chronic headaches have lower prevalence in children and adolescents, when compared with data in the adult populations. Symptomatic abuse, the main cause

of chronic headache in adulthood, is extremely rare within paediatric chronic headaches. In our study, the most common type of chronic headache was chronic migraine and there was a higher prevalence of new daily persistent headache, when compared with data in adults. Often there was a spontaneous remission of daily frequency of attacks, probably due to a natural fluctuation of frequency. The use of diaries is the most important tool not only for the therapeutic approach but also to follow the natural history of the disease.

Clinical presentation of headache in children younger than age 6: preliminary results of a retrospective study

R. Torriero^{1,2}, A. Capuano², R. Mariani^{2,3}, S. Tarantino²,
C. Vollono², F. Vigevaro², M. Valeriani²

¹Department of Paediatrics, University of Rome Tor Vergata, Rome, Italy; ²Headache Centre, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; ³Department of Paediatrics, Sapienza University of Rome, Rome, Italy; e-mail: roberto.torriero@hotmail.it

Objective To investigate clinical characteristics of headache at onset in a retrospective cohort of children aged <6 years.

Methods Charts of outpatients referring to our Headache Centre were retrospectively analysed. Only children with primary headache were included. Clinical characteristics of headache included: characteristics of the referred pain, frequency of headache, and duration of headache. Accompanying symptoms were also investigated, in particular, nausea, vomiting, photo- and phonophobia. In the history, occurrence of childhood periodic syndromes and familial history of any primary headache were analysed.

Results Seventy-five patients ranging from 1 to 6 years of age (mean age: 4.4 ± 1.27 SD) were eligible for our study (males: 46.67%, females: 53.33%). The major findings of our study were: (1) the site of headache was without lateralization in most cases; (2) the frequency of headache at onset ranged between 2 and 4 episodes per month, however, episodes were more than 4 per month in 20% of cases and in 13.3% they occurred in cluster, daily for 1 week; (3) the mean duration of attacks was <1 h (mean: 25.8 ± 22.3 SD minutes); (4) photophobia and phonophobia occurred in 57.33% and were highly associated with nausea; (5) at least one childhood periodic syndrome was found in the medical history of more than 50% of children.

Conclusions Our study may be useful to improve our current knowledge in the diagnosis of primary headache in very young children.

Migraine: 3 case reports

E. Tozzi¹, D. Maiorani², N. Fiorentini¹

¹Child Neuropsychiatric Clinic, University Hospital, L'Aquila, Italy;
²Paediatric Clinic, University Hospital, L'Aquila, Italy;
e-mail: elisabetta.tozzialleva@univaq.it

Introduction ICHD-II defines migraine at point 1.5.5 as a “migraine triggered seizure” in which a seizure occurs during migraine aura and is included among the complications of migraine. In the ILAE classification this entity is not recognized. In the literature there is an ongoing debate about pertinence of this diagnosis and the majority of the Authors [1] suggest that this term should be deleted until unequivocal evidence of the existence of this condition emerges. Conversely, the term “hemispheric epilepsy” should be

maintained and the term of “ictal epileptic headache” should be introduced [2].

We report three clinical cases observed at the Child Neuropsychiatric Department, University Hospital, L’Aquila.

P.R., a 4-year-old, came to our attention for crises characterised by frontal headache of high intensity, fixity of the look, sialorrhoea and tonic-clonic seizures, lasting 2 min and followed by a protracted confused state of mind and dejection. We introduced valproic acid treatment and obtained a gradual improvement of motor symptoms, even though the headache crises associated with objective dizziness, photophobia, vomiting and occasionally generalized tremor were still present.

D.Z., a 10-year-old, presented to our Centre because of fronto-orbital throbbing headache crises, followed by crying and loss of consciousness. We introduced valproic acid treatment. The child no longer lost consciousness, even though he still reported sporadic headaches, triggered by visual stimulus and associated with dizziness.

E.E., a 7-year-old, came to our attention for a crisis, which occurred in sleep and was characterised by head and mouth deviation on the right, fixity of the look, ipotony and loss of consciousness. The child also reported trafactive headache, which arised recently and she referred being afraid of thunderstorms. She began valproic acid treatment. Currently the child no longer loses consciousness and has partial seizures. She still reports frontal throbbing headache associated with phosphene, subjective dizziness and vomiting. Crises are always triggered by emotional stress and it was possible to record a crisis during a thunderstorm with EEG.

In all the cases the EEG reports at the onset showed electrical discharges as spike and spike-waves in the T-C-O district, that were widespread or alternating, and accentuated by hyperventilation and intermitted light stimulation. In the last case, EEG abnormalities were predominant in sleep records. In all the cases, they improved after valproic acid treatment, during a period of almost 2 years.

Conclusions It is interesting to note that in the three cases considered above, valproic acid treatment was more effective in the resolution of the motor symptoms rather than in the sensory ones. In case 3 an electro-clinical crisis during a thunderstorm was recorded. In the other cases crises were triggered by visual stimulus.

References

1. Verrotti A, Coppola G, Tozzi E et al (2011) Should “migralepsy” be considered an obsolete concept? A multicenter retrospective clinical/EEG study and review of the literature. *Epilepsy Behav* 21(1):52–59
2. Verrotti A, Coppola G, Tozzi E et al (2011) Peri-ictal and inter-ictal headache in children and adolescents with idiopathic epilepsy: a multicenter cross-sectional study. *Childs Nerv Syst* Mar 29 [Epub ahead of print]

Cluster headache in childhood: case series from a paediatric headache centre

R. Mariani^{1,2}, A. Capuano¹, R. Torriero^{1,3}, S. Tarantino¹, C. Vollono¹, F. Vigevaro¹, M. Valeriani¹

¹Headache Centre, Bambino Gesù Children’s Hospital, IRCCS, Rome; ²Department of Paediatrics, Sapienza University of Rome, Rome, Italy; ³Department of Paediatrics, University of Rome Tor Vergata, Rome, Italy; e-mail: rosanna.mariani@tiscali.it

Background Cluster headache (CH) is a rare primary headache disorder in childhood. CH is frequent in the second and third decade of life, however few cases of CH are reported in childhood. On the basis of the International Headache Society classification cluster headache

can be divided into episodic and chronic CH. The attacks are characterised by unilateral and severe pain, lasting 15–180 min, cranial autonomic features and periodicity. However, in childhood the clinical picture and therapeutic approach of CH may be different. We report our experience in a Childhood Headache Centre.

Methods A retrospective study of the medical charts of all patients from 2002 to 2010 with a diagnosis of primary headache was conducted. Patients diagnosed as CH sufferers were selected. We evaluated clinical features of the headache, familial history for primary headache, neuroimaging and therapeutic management.

Results We identified ten children (6 males and 4 females) among 4,000 records. The mean age of CH onset was 10.5 years (range 5–16 years). All children had episodic CH, unilateral orbital pain; seven patients showed throbbing pain, and three patients had stabbing pain. The mean duration of the attack was 86 min (ranging from 30 to 180 min). The frequency of episodes was more than one per day. All children had the typical autonomic features of CH such as lacrimation, conjunctival injection, ptosis and rhinorrhoea. Furthermore, five patients also showed photophobia, four phonophobia and in one case diplopia was recorded. We observed that clinical and neuroradiological examinations were normal. Six patients had familial history of migraine; in one case familial history of CH was observed. In regards to therapeutic management of CH, steroids showed a good clinical response in interrupting CH recurrence, whereas symptomatic drugs, acetaminophen as well as ibuprofen were ineffective; indomethacin was effective in only one case. Oxygen therapy was not reported in our cases.

Conclusions In summary, onset of cluster headache in childhood is a rare excruciatingly painful and distressing condition. Knowing about the typical clinical pictures of this headache helps to differentiate it from other headaches, especially migraine. This can be very important since CH requires a peculiar pharmacological treatment.

Alexithymia and attachment in adolescence headache

T. Carigi¹, F. Ferro¹, F. Maraschi¹, A. Mita¹, S. Molteni¹, G. Spada¹, F. Piazza¹, C. Termine^{1,2,3}, U. Balottin^{1,3}

¹Department of Child and Adolescent Neuropsychiatry, IRCCS C. Mondino National Institute of Neurology Foundation, Pavia, Italy; ²Child Neuropsychiatry Unit, Department of Experimental Medicine, University of Insubria, Varese, Italy; ³University Consortium for Adaptive Disorders and Headache (UCADH), University of Pavia, Pavia, Italy; e-mail: tiziana.carigi@unipv.it

Introduction Headache presents with high prevalence also in childhood and adolescence. Its etiopathogenesis is still unknown. According to the psychosomatic hypothesis (Kresleire, Lanzi), it can be interpreted as a neurobiological dysregulation in which a deficit of the emotion elaboration process and the poor fantasmatic abilities play an important role. This concept appears related to the construct of alexithymia and its core characteristics: difficulty identifying and describing feelings and externally oriented thinking (operative thinking). It also recalls the role played by attachment in reflective function onset. Our study aim was to verify the presence of alexithymia and attachment styles in adolescents suffering from primary headache, compared with healthy controls, matched for age and sex.

Materials and methods We recruited 18 adolescents (13 F, 5 M), referred to our Department of Child and Adolescent Neuropsychiatry (IRCCS Mondino, Pavia), for headache, and 18 healthy controls, matched for age and sex. According to the ICHD-II criteria and on the basis of clinical history and neurological examination, diagnosis was of migraine without aura in ten adolescents and of tension-type headache in eight. Both cases and controls filled in TAS-20 [1], a

questionnaire for the identification of the degree of alexithymia, and RQ and ARSQ [2], questionnaires for the assessment of attachment style. Comparison between cases and controls was made through Mackintosh PASW (SPSS) Statistics 18.0.2 (statistical significance if $p < 0.05$).

Results We recruited 18 adolescents (13 F and 5 M; mean age 14.72 ± 1.13), 10 suffering from migraine without aura and 8 from tension-type headache. Data collected from the patients regarding alexithymia and attachment style were compared with data collected from 18 healthy controls, matched for age and sex (respectively, $p = 0.271$ and 0.128).

Cases showed higher rates of alexithymia than controls, with significant difference in operative thinking sub-scale ($p = 0.020$), confirming a more concrete psychological functioning and a difficulty in mentalization.

According to RQ, the comparison of attachment style profiles highlighted a major prevalence of secure attachment in controls than in cases ($p = 0.019$). The same result emerged from ARSQ ($p = 0.203$) which also highlighted a major prevalence of avoiding style in cases than in controls ($p = 0.268$).

Discussion and conclusions Our study results confirm the role played by deficit in keeping in touch with the internal world in headache adolescents whose psychological functioning is characterised by operative thinking, when compared with healthy controls. They also underline the potential involvement in headache onset of attachment styles, considering their role in favouring or avoiding reflective function and mentalization.

References

1. Bagby RM, Parker JDA, Taylor GJ (1994) The twenty-item Toronto Alexithymia Scale-I. Item selection and cross-validation of the factor structure. *J Psychosom Res* 38:23–32
2. Bartholomew K, Horowitz LM (1991) Attachment styles among young adults: A test of a four-category model. *J Pers Soc Psychol* 61:226–244

Migraine history and management of frustration in children: a possible correlation

S. Tarantino¹, M. Citti¹, C. Dionisi², C. De Ranieri³, C. Vollono¹, A. Capuano¹, F. Galli⁴, F. Vigevaro¹, V. Guidetti⁴, G. Biondi³, M. Valeriani¹

¹Headache Centre, Division of Neurology, Paediatric Hospital Bambino Gesù, IRCCS, Rome, Italy; ²Faculty of Psychology 1, Sapienza University of Rome, Rome, Italy; ³Unit of Paediatric Psychology, Paediatric Hospital Bambino Gesù, IRCCS, Rome, Italy; ⁴Department of Child and Adolescent Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy; e-mail: gone.st@libero.it

Introduction Although psychological factors are known to increase the severity and intensity of headaches in children, very few studies have analysed the management of frustration. Aim of this study was to analyse the possible correlation between the headache's natural history and the psychological profile, with particular attention to the management of frustration.

Materials and methods We studied 43 migraineur children (mean age 11.7 ± 2 years; 22 M and 21 F). The patients were divided into two groups according to the frequency of attacks at the first consultation (low and high frequency). The headache's natural history was assessed by comparing the number of attacks between the first and the second consultation (mean interval 2.8 months). No prophylactic treatment was assumed by any patient. The psychological profile was assessed by the picture-frustration study (PFS) test for the analysis of the management of stress and frustration.

Results Attack frequency changed between the first and the second consultation in 22 patients (11 worsened and 11 improved), while it remained unmodified in the remaining 21 patients. Analyzing the psychological profile, we found a significantly higher IA/OD score (feeling embarrassed to be involved in causing frustration to someone else) in patients with high attack frequency at the first consultation ($p = 0.01$). The attack frequency improvement showed: (1) a positive correlation with the E index (extraggression) ($p = 0.01$), and (2) a negative correlations with both I index (assuming blame or guilt) ($p = 0.03$) and M index (minimize the frustration provoked by others) ($p < 0.01$). Moreover, the improvement in headache history was negatively correlated with the N–P index (trying to achieve the goal) ($p = 0.01$).

Discussion Our results showed that the difficulty in expressing anger was related to a higher frequency of headache attacks at the first consultation. Confirming this finding, in our children the exhibition of aggression toward the source of the frustration (E index) was related to an improvement in the frequency of attacks. Conversely, the feelings of guilt as the cause of the frustration (I index) or the minimization of the frustration provoked by others (M index) were related to worsening the headache.

Conclusions This is the first study showing that the management of frustration, in particular the direction of the aggression (extraggression, im aggression, and intraggression), plays a role in the natural course of migraine.

Blood pressure as an instrumental parameter of the effectiveness of pet therapy

D. Moscato, B. Calabrese, F.R. Moscato

Childhood Headache Centre, IDI Sanita, Rome, Italy; e-mail: dmoscat@tin.it.

Introduction Pet therapy can be an intervention of choice for the treatment of headache in children. The effectiveness of this intervention, and the stability of the results has already been documented by our group [1]. This study seeks to contribute to delineate the mechanisms of action on what will make pet therapy an effective method of intervention in the treatment of childhood headaches.

The literature has already documented that pet therapy can change the vital functions (pa, fc, EEG), and even contribute to increased life expectancy in adult cardiac patients [2, 3]. This is one of the first studies to evaluate the variations of blood pressure in children who underwent pet therapy.

Materials and methods Changes in blood pressure (systolic, diastolic) were assessed in headache children and adolescents who underwent only pet therapy, before and after the session. Blood pressure was measured in 45 patients (18 F, 27 M, aged 6/13), 36 patients with a diagnosis of migraine without aura (MO) and 9 with migraine with aura (MA), before and after the session. Three paediatric bracelets were used, which corresponded to 1/3 of the arm in the patients examined; the measurements took place 5 min before and after the session with at least two measurements 2 min apart to control the possible effects of anxiety for ten sessions. The measurements were compared also to the parameters of the headache (fxd) at the first and tenth session.

Results The results showed that there was a statistically significant reduction in blood pressure (systolic $119.2 > 107.3$, diastolic $77.6 > 63.8$) between the beginning and the end of the session. Both age and sex were independent variables that influenced the amount of the reduction, while it was independent of the number of sessions conducted.

Conclusions The simultaneous reduction of blood pressure with the concomitant reduction in headache ($97.3 > 53.7$) leads to hypothesise that the effectiveness of pet therapy is to frame issues through variables which affect the autonomic nervous system, not necessarily modulated by cognitive and symbolic that the patient attributes to the condition relationships.

References

1. Moscato D, Calabrese B, Moscato FR et al (2008) A global intervention for migraine children and adolescents: the pet therapy. *Cephalalgia* 4:439–440
2. Allen K, Shykoff B E, Izzo JL (2001) Pet Ownership, but Not ACE inhibitor therapy, blunts home blood pressure responses to mental stress. *Hypertension* 38:815–820
3. Friedmann E, Thomas SA (1995) Pet ownership, social support, and 1-year survival after acute myocardial infarction in the cardiac arrhythmia suppression trial (CAST). *Am J Cardiol* 76:1213–1217

Psychological, audiological and vestibular assessment in primary paediatric headache

A. Ciriaco, E. Caffo, E. Genovese, D. Monzani, P. Benincasa, L.A. Pini

Headache and Drug Abuse Inter-Department Research Centre,
University of Modena and Reggio Emilia, Modena, Italy;
e-mail: pinila@unimore.it

Introduction Primary paediatric headache (PPH) could be associated with psychiatric disorders or precipitated by psychological difficulties or may be unrelated to the patient's emotional problems. Many investigators found higher levels of somatization and internalizing disorders in headache sufferers using the Achenbach Child Behaviour Checklist (CBCL) [1].

Sometimes patients with migraine (M) or tension-type headache (TTH) refer some attentional deficits. A tendency to be easily distracted and fidgety, have poor concentration and poor school achievements are characteristics of children with an auditory processing deficit, because of difficulty in understanding conversation amid background noise. Auditory processing deficit resides primarily in the processing of non-speech sound, rather a deficit in speech perception that is a characteristic of language impairments. Currently there is no trial that investigates the auditory processing in PPH.

Patients with M or TTH often complain of non-specific unsteadiness, moreover they rarely show a clinical significance in the objective examinations regarding their equilibrium. At times, balance disorders can be evaluated using diagnostic procedures such as static stabilometry.

Methods We enrolled 30 subjects (aged 6–12) suffering from primary headache according to the ICDH-II criteria and 24 age- and sex-matched controls seen at our University Hospital. All subjects underwent the following protocol: psychological assessment (CBCL), audiological and vestibular assessment (Pure tone audiometry, Speech perception test in quiet and noise, Static stabilometry), headache examination (Paediatric Migraine Disability Assessment questionnaire and Migraine Index).

Results Children with headache showed in CBCL scales significant differences in Somatic Complaints ($p < 0.001$), Thought Problem ($p = 0.002$), Internalizing ($p = 0.006$) and Total Problem Scale ($p = 0.018$) than healthy controls.

In PPH subjects the audiological assessment showed reduced speech discrimination with noise compared to the controls ($p < 0.001$ in almost Speech perception tests).

Considering static stabilometry, Surface was greater in the headache group with closed eyes than in controls ($p = 0.049$) and Romberg quotient of surface in closed eyes/open eyes showed difference between M and TTH and controls ($p = 0.036$). The statistical analysis was performed with non-parametric tests.

Conclusions Primary headache children have higher internalizing scores than healthy subjects (in particular somatisation) without any differences between M and TTH. Children with primary headache, especially M, often have more difficulty in speech discrimination with noise and these results could be correlated to attention and memory deficits or auditory processing disorder. Moreover, in PPH there is incomplete control over visual-spatial integration due to a disorder in involuntary eye movement, whereas patients with TTH in the stabilometric study did not show significant differences compared with M.

References

1. Just U, Oelkers R, Bender S et al (2003) Emotional and behavioural problems in children and adolescents with primary headache. *Cephalalgia* 23(3):206–213

My son suffers from headache: analysis of parental stress

E. Tozzi, A.A. Perrone, E. Aloisi, N. Fiorentini

Centro Cefalee, Ambulatorio Età Evolutiva, U.O.C. di
Neuropsichiatria Infantile, Università L'Aquila, L'Aquila, Italy;
e-mail: elisabetta.tozzialleva@univaq.it

Introduction Clinical experience shows that psychological factors influence the course of the headache, but until now there were no differences that allowed you to clearly discriminate between the different forms of primary headache [1]. This research had three main objectives: (1) To assess whether the parents of patients with headache were more stressed than parents of healthy children; (2) To assess whether there were significant differences in the stress levels among two groups of patients with tension-type headache and those of children suffering from migraine; (3) To verify if the comorbidity with other disorders could influence the parents' stress.

Materials and methods The following instruments were administered: (1) the Parenting Stress Index/Short Form (Abidin 1995) to assess the impact of specific temperamental characteristics of the child on the parent (the child domain) and the function as a competent caregiver (parent domain). The combined perception of the two domains could affect the overall evaluation of the experience of stress; and (2) The Child Behaviour Checklist (CBCL).

The sample consisted of 24 mothers and 22 fathers, 40 children, aged 5–14 years admitted to the UOC of Child Neuropsychiatry, University of L'Aquila (Headache Clinic) suffering from headache and 20 parents of healthy children, interviewed in a kindergarten, an elementary school and a middle school. The diagnosis of headache was made according to the criteria of the ICHD-II, 2004. Parents of healthy children were 17 mothers and 3 fathers.

Results Twenty-two children suffered from migraine without aura and 18 with frequent episodic tension-type headache. The index of total stress was pathological in 36.6% of the parents of the headache patients compared with 15% of parents in the control group. In particular, we found that 77.8% were parents of children with migraine and 22.2% parents of children with TTH. In fact, only 53.8% of migraine patients had higher scores over 80°, compared with 16.6% of subjects with frequent episodic tension-type headache and controls ($p = 0.10$). In particular, the highest scores in the headache sample could be found within the P-CDI subscale (parent-child dysfunctional

interaction), followed by sub DC (problem child) of the PSI-SF. Analysing the results of the CBCL headache patients, we found that 28% of children showed a positive risk for internalizing disorders, 12% presented a risk for externalizing disorders and 10% have both disorders.

Using the Child Behaviour Checklist (CBCL), we found a subset of parents of children who had, besides the headache, associated psychopathology, indicating that 42% were particularly stressed.

Conclusions A screening instrument such as the Parenting Stress Index, could help in the management of the family of the children with headache, because the parental stress that may be symptomatic of an approach which is not suitable for the child's headache which could create a sort of vicious circle.

References

1. Galli F, Canzano L, Scalisi T et al (2009) Psychiatric disorders and headache familial recurrence: a study on 200 children and their parents. *J Headache Pain* 10:187–197
2. Mazzone, Vitiello B, Incorpora G et al (2006) Behavioural and temperamental characteristics of children and adolescents suffering from primary headache. *Cephalalgia* 26:194–201

Headache in children with Chiari type I malformation: a case series

I. Toldo, M. Tangari, R. Mardari, M. Calderone, E. Perissinotto, S. Sartori, P.A. Battistella

Department of Paediatrics, University of Padua, Padua, Italy;
e-mail: irene.toldo@unipd.it

Introduction Headache is the most common symptom of Chiari type I malformation (CM1), the herniation of cerebellar tonsils through the foramen magnum [1]. The headache pattern in cases with CM1 is not well defined in the literature and has never been classified according to the diagnostic criteria of the International Classification of Headache Disorders (ICHD-II, 2004).

Materials and methods Among 10,000 children under 18 years of age who underwent neuroimaging at the Padua Hospital in the years 2002–2010, 45 cases were selected. Inclusion criteria were: (1) cerebellar tonsils ectopia; (2) no malformations of the central nervous system; and (3) no secondary causes of CM1. A semi-structured clinical interview (mean follow-up of 2.5 years) was conducted. Headache was classified according to the ICHD-II criteria.

Results Patients were divided into 3 groups according to the herniation of cerebellar tonsils: (1) under 5 mm (12 cases), (2) 5–9 mm (27 cases), (3) ≥ 10 mm (6 cases). Patients of groups 2 and 3 (33 cases) were diagnosed as having CM1. Twenty-nine (64%) patients complained of headache: 5 (42%) of group 1, 19 (70%) of group 2 and 5 (83%) of group 3, with an age at headache onset, respectively, of 9.4 ± 2.8 years, 7.9 ± 4.3 years, and 5.2 ± 2 years. Among the 33 patients with CM1, 24 (73%) presented headache: 14 (42%) cases had a primary headache (PH) (7 migraine, 4 tension-type headache, 3 other), 10 (30%) cases had a secondary headache (SH) [9 headache attributed to CM1 (CMH), 1 Moyamoya]. Nine (27%) patients with CM1 had a CMH. Headache type in the three groups was: (1) 5 PH (4 migraine, 1 tension-type headache); (2) 13 (68%) PH (6 migraine, 4 tension-type headache, 3 other primary headaches), 6 (32%) SH (5 CMH, 1 headache attributed to cranial vascular disorder); (3) 1 (20%) migraine, 4 (80%) CMH. Other neurologic symptoms attributed to CM1 ($N = 33$) were neck pain (24%), paresthesias (15%), dizziness (8%), sleep apnea (6%) and ataxia (3%). Three patients (group 3), with CMH and other neurological symptoms, were surgically treated with benefit.

Discussion and conclusions Headache is the main symptom of CM1. We found a relevant correlation between the headache patterns and the extent of cerebellar tonsils herniation. PH prevailed in cases with CM1 under 10 mm, while CMH was the most common type of headache in patients with CM1 above 10 mm.

References

1. Aitken LA, Lindan CE, Sidney S et al (2009) Chiari type I malformation in a pediatric population. *Pediatr Neurol* 40(6):449–454

Acute cerebellitis and headache: a case report in a child

D. De Carlo, I. Toldo, R. Manara, S. Sartori, M. Gatta, P.A. Battistella

Juvenile Headache Centre, University of Padua, Padua, Italy;
e-mail: pierantonio.battistella@unipd.it

Introduction Acute cerebellitis (AC) is a rare inflammatory syndrome, which often manifests with ataxia, dysarthria and nystagmus. Diagnosis is aided by neuroimaging studies, in the first place magnetic resonance imaging (MRI). Although usually self-limiting, pulsed high-dose methylprednisolone is the first choice of treatment.

Case report We describe the case of an 11-year-old boy with previously unremarkable family and personal history. He presented in the last year sporadic, short-lasting, throbbing, mild attacks of headache on the left frontal region, sometimes associated with nausea and with spontaneous remission.

In February 2011, during a febrile episode associated with rhinitis and cough, the boy presented a new type of headache attack, exacerbated by physical activity, associated with vomiting and resistant to analgesics. At the first neurological examination, the fundus oculi and a cerebral computed tomography scan were normal. Brain MRI on T2-weighted images showed a high signal lesion in the cerebellar cortex with mild effacement of cerebellar sulci and with normal diffusion-weighted images.

The biological blood investigations were all negative. Neurological examination, including fundus oculi, by our Juvenile Headache Centre were negative; rather in the last 2 weeks, there was a rapid improvement of the general conditions with almost complete remission of headache without any treatment. A second cerebral MRI, 6 weeks later, demonstrated a significant decrease of the areas of hyperintensity on T2-weighted images with mild focal cortical atrophy.

Two months later, the neurological condition remained normal with only mild and rare headaches, without accompanying symptoms.

Discussion AC is a rare disease in childhood which can occur as a primary infectious or a postinfectious or postvaccination disorder. The clinical presentation is truncal and/or gait ataxia, nystagmus, tremor and myoclonic jerks and/or dysarthria. MRI plays an important role in the diagnostic assessment, showing parenchymal hyperintensities on T2-weighted and swelling of the cerebellar cortex with compression of the fourth ventricle [1]; a patient affected by AC with only abnormal diffusion-weighted imaging on MRI findings was described by Donmez et al. [2].

In our case, characterised by headache with vomiting and fever, the clinical pattern of AC was atypical for the absence of neurological deficits.

In conclusion, an acute “new” onset headache may be the only symptom of a AC and only by means of an MRI a correct diagnosis may be performed.

References

1. Shkalim V, Amir J, Kornreich L et al (2009) Acute cerebellitis presenting as tonsillar herniation and hydrocephalus. *Pediatr Neurol* 41:200–203
2. Donmez FY, Agildere AM, Tore HG et al (2008) Abnormal diffusion-weighted imaging findings in an adult patient with acute cerebellitis presenting with a normal magnetic resonance imaging. *J Comput Assist Tomogr* 32:156–158

Treatment of primary headaches in children: preliminary results of a multicentre Italian study

I. Toldo¹, D. De Carlo¹, B. Bolzonella¹, E. Perissinotto¹, S. Sartori¹, L.N. Rossi², A. Vecchio³, A. Simonati⁴, M. Carotenuto⁵, C. Scalas⁶, V. Scirucchio⁷, V. Raieli⁸, G. Mazzotta⁹, U. Balottin¹⁰, E. Tozzi¹¹, V. Guidetti¹², P.A. Battistella¹

¹Juvenile Headache Centre, Department of Paediatrics, University of Padua; ²Second Paediatric Department, University of Milan; ³Child Neuropsychiatry Division, University of Palermo; ⁴Department of Neurological and Visual Sciences, University of Verona; ⁵Clinic of Child and Adolescent Neuropsychiatry, Second University of Naples; ⁶Child Neurology Clinic, Meyer Children's Hospital of Florence; ⁷Paediatric Neurology, Hospital Giovanni XXIII of Bari; ⁸Child Neuropsychiatry Department, Hospital Ingrassia of Palermo; ⁹Child Neuropsychiatry Division, University of Perugia; ¹⁰Child Neuropsychiatry Unit, University of Pavia; ¹¹Department of Experimental Medicine, University of L'Aquila; ¹²Department of Child and Adolescent Neurology, Psychiatry and Rehabilitation, University of Rome, Italy; e-mail: irene.toldo@unipd.it

Introduction There are few data in the literature about the use of pharmacological and non-pharmacological therapies for primary headaches (migraine: M; tension-type headache: TTH) in children [1]. **Materials and methods** A retrospective study was conducted by twelve Juvenile Headache Centres; inclusion criteria: (1) diagnosis of primary headache (ICHD-II, 2004); (2) stable headache pattern (>6 months).

Results Three hundred and twenty cases (163 M, 157 F) with mean age at interview of 11.1 ± 3.2 years (1–19 years). Headache types: M 71% (MO 62%, MA 6%, chronic M 3%), TTH 20% (ETTH 17%, CTTH 3%), and M + TTH 7%, other 2%.

(A) **Symptomatic treatment** used in 92% of cases (1 drug 57%, 2 drugs 26%, 3 drugs 9%); M 95% versus TTH 82% ($p < 0.0002$); type of drug: paracetamol (P) (M 84%, TTH 73%), NSAIDs (M 46%, TTH 24%), triptans (T) (M 5%, TTH 0%); good–excellent efficacy 53%, good–excellent tolerability 86%. Prescriber: paediatrician (47%), child neuropsychiatry (41%), self-prescription (10%).

(B) **Prophylaxis therapy** used in 46% of cases (1 drug 31%, 2 drugs 11%, 3 drugs 4%); M 53% versus CT 29% ($p < 0.01$); type of drug: flunarizine (M 22% vs. TTH 2%, $p < 0.0002$), pizotifen (M 7%, TTH 0%), propranolol (M 3%, TTH 0%), amitriptyline (M 1%, TTH 2%), anticonvulsants (M 7%, TTH 0%), supplements (M 25%, TTH 19%), melatonin (M 4%, TTH 6%); good–excellent efficacy 65%, good–excellent tolerability 80%. Prescriber: paediatrician (14%), child neuropsychiatrist (84%), no self-prescription.

(C) **Non-pharmacological treatments** (N = 27, 8%): relaxation/biofeedback (30%), cognitive-behavioural therapy (22%), homeopathy (15%), treatment of malocclusion (15%), acupuncture (7%), psychotherapy (7%) and biofeedback (4%).

(D) **Rating** more effective therapy: pharmacological symptomatic (57%) than prophylaxis combined with symptomatic (25%) or alone (16%); better tolerated therapy: pharmacological symptomatic (57%),

than prophylaxis combined with symptomatic (22%) or alone (18%). Main expectations of the patient: effect on pain (62%), speed of action (30%) and lack of side effects (21%).

Discussion and conclusions The study population consists predominantly of migraineurs (71%). The therapy most widely used was symptomatic (92%), especially P or NSAIDs, with limited use of T (E 5%) with good efficacy and tolerability. The prophylactic drugs most used were supplements (25%) and flunarizine (22%), while AEDs were rarely used (7%). The prophylaxis was ineffective in a third of migraineurs (28–34%), although often well tolerated (43–60%). The non-pharmacological therapy was not widely used (7%) and rarely preferred by patients (2–3%).

References

1. Cuvellier JC, Donnet A, Guégan-Massardier E et al (2009) Treatment of primary headache in children: a multicenter hospital-based study in France. *J Headache Pain* 10(6):447–453

Open label clinical study on the efficacy, tolerability, effect on disabilities of L-tryptophan + 5-hydroxytryptophan (*Griffonia simplicifolia*) plus vit. B6 and vitamin pp, in the prophylactic treatment of headache in children and adolescents

F. Consolo¹, V. Raieli¹, G. Santangelo¹, C. Spitaleri², G. Giordano², F. Vanadia¹

¹Child Neuropsychiatry Unit, Di Cristina Hospital, ARNAS Civico, Palermo, Italy; ²Neuropsychiatry Department, University of Palermo, Palermo, Italy; e-mail: flavia.consolo@ospedalecivicopa.org

Introduction Serotonin plays a key role in the pathophysiology of migraine that is considered just as a condition characterised by reduced availability of serotonin. Studies in laboratory animals also show that a deprivation of serotonin facilitates the activation of the mechanisms that underlie the headache, respectively (trigeminal vascular system) and aura (cortical spreading depression) migraine. Brioplus is a compound that can promote the synthesis of serotonin, with documented efficacy in mood disorder, which explains why it was included in the treatment group since in the sample tension-type headache suffers were also present.

Objectives To evaluate the efficacy and tolerability of open Brioplus in the prophylactic treatment of headache (both migraine and tension-type headache).

Materials and methods From 1/11/10 to 30/04/11 a population of individuals with primary headache between the ages of 7 and 18 years was recruited. Inclusion criteria: at least four crises per month of migraine and at least eight crises/month of tension-type headache. Exclusion criteria: diseases that internists had diagnosed, and other prophylactic therapies. We recruited 34 cases of tension-type headache with 14 attacks per month on average and 66 cases of migraine with 10 attacks per month on average. Each group of patients underwent Migraine Disability Assessment (MIDAS): 18 (To) patients had tension-type headache and 45 migraine.

Results Thirty-five patients concluded the study: 20 patients with migraine and 15 patients with tension-type headache, MIDAS (T2) performed at 3 months was, respectively, 16 and 7. The frequency of attacks in the group of tension-type headache was reduced by 5 attacks per month on average and 3 per month in the migraine group. Five patients abandoned the study and three patients suspended treatment due to minor adverse events.

Conclusions The preliminary study shows that the drug is well tolerated and is effective on both the frequency and disability in both samples. Controlled randomized studies in a larger sample are needed to confirm the data.

Effectiveness of prophylactic treatment in the short-and long-term follow-up in migraine children: preliminary data

A. Vecchio¹, G. Giordano², L. Paziente², C. Spitaleri², C. Termine¹, I. Camarda², F. Consolo², V. Raieli², M. Saladino², G. Santangelo², E. Vanadia², F. Vanadia²

¹Paediatric Headache Centre, Aiuto Materno ASP 6, Palermo, Italy;

²Child Neuropsychiatry Unit, Di Gristina Hospital, ARNAS CIVICO, Palermo, Italy; e-mail: vraieli@libero.it

Introduction Different studies demonstrated that prophylactic treatment for migraine reduce the number and the severity of the migraine attacks. The aim of our study was to evaluate the efficacy of the migraine therapy after 12 and 24 months of therapy withdrawal and to compare the results with an untreated population in order to determine whether cycles (with lengths from 3 to 6 months) of prophylaxis facilitate remission in migraine patients after discontinuation of treatment. To the best of our knowledge this topic has never been explored by other authors.

Methods We recruited retrospectively, from 1/1/2009 to 30/06/2009 and from 1/1/2010 to 30/06/2010, a population of ten patients with migraine (age range 5–18 years). The therapy was prescribed for at least four attacks of severe headache in the last few months preceding the start of prophylaxis therapy. We excluded from the study those patients who continued prophylaxis treatment. After 12 and 24 months, respectively, through a standardised telephone interview we acquired information about the number of episodes and the number of symptomatic drugs used in the last 3 months. An untreated migraine population (n = 10) was recruited, age-matched with the previous population, suffering from four or more attacks of severe headache a month.

Results The data revealed that during prophylactic treatment (T0) the frequency of migraine attacks was reduced by 65%. After 12 months of having terminated the treatment (T1) the reduced percentage of attacks was 40% and after 24 months from the end of treatment (T2) 38%, and a 50% reduction in symptomatic drug use in the last 2 months was also observed.

Discussion The preliminary study shows that prophylactic treatment for a period between 3 and 6 months after its withdrawal continues to reduce the frequency of headache attacks in both short- (12 months) and long-term (24 months) periods. Further studies on a larger population and randomized controlled studies are required to confirm our results.

Pathophysiology

Evidence of visual cortical hyperexcitability by sound-induced flash illusions in migraine: preliminary results in 47 patients

F. Brighina¹, N. Bolognini², G. Cosentino¹, P. Paladino¹, S. Talamanca¹, A. Puma¹, B. Fierro¹, G. Vallar²

¹Dipartimento di Biomedicine Sperimentali e Neuroscienze Cliniche (BioNeC), Università di Palermo, Palermo, Italy; ²Dipartimento di Psicologia, Università di Milano-Bicocca, Milan, Italy; e-mail: fbrighina@unipa.it

Introduction Clear evidence of relevant modulation and interaction between sensory modalities in multisensorial perceptions is given by the phenomenon of cross-modal illusions.

One of the most powerful examples of such illusions is the sound-induced flash illusion described by Shams et al. [1]: when a single flash is accompanied by two auditory beeps, the single flash is perceived as two flashes (fission illusion), conversely a “fusion” illusion occurs when a single beep causes the fusion of a double flash stimulus. The neural mechanisms underlying generation of such illusory perception are not yet known, but it has been shown, through the technique of transcranial direct current stimulation (tDCS), that it critically depends on the excitability level of visual or temporal cortex. Indeed, application of anodal activating currents over occipital cortex and of cathodal inhibitory stimulation over temporal cortex could disrupt the illusion [2]. In the present study we explored if “fission” or “fusion” flash illusions can be differently perceived in migraine where a condition of cortical hyperexcitability (especially of visual cortex) has been hypothesised.

Methods We have studied until now 47 migraine patients: 32 of them without aura (MO) and 15 with aura (MA); 13 from the MO group and 6 from the MA group were examined during the attack and the remaining patients in the interictal phase. The experimental paradigm consisted of 1–4 or white filled circles presented in the centre of a black screen isolated or preceded by 1–4 beeps in different combinations. Results in patients were compared with those obtained with the same stimulation paradigm in a group of healthy age- and sex-matched controls.

Results MO in the interictal phase presented fusion and fission illusion in a similar manner to what was observed in healthy controls. Whereas, significantly less illusions, both of fission and fusion type, were observed in MO patients examined during the attacks and in MA patients in the interictal as well as ictal phases.

Conclusions In patients with MA and in those with MO during attacks, results (less illusions) are similar with those observed by Bolognini et al. [2] after increasing visual cortical excitability (through anodal tDCS) in healthy controls, thus pointing to a condition of hyperexcitability of the visual cortex during migraine attacks and also in the interictal phase in MA patients.

References

1. Shams L, Kamitani Y, Shimojo S (2000) Illusions. What you see is what you hear. *Nature* 408(6814):788
2. Bolognini N, Rossetti A, Casati C et al (2011) Neuromodulation of multisensory perception: a tDCS study of the sound-induced flash illusion. *Neuropsychologia* 49(2):231–237 (Epub 2010 Nov 19)

Comparison between migraineurs and healthy subjects of trigeminal evoked potentials (TEPs) elicited by transcutaneous electrical nociceptive stimulation

C. Di Lorenzo¹, G. Coppola², G. Di Lorenzo³, A. Daverio³, A. Curra⁴, A. Siracusano³, F. Pierelli^{5,6}

¹Don Carlo Gnocchi Onlus Foundation, Italy; ²G.B. Bietti Eye Foundation, IRCCS, Department of Neurophysiology of Vision and Neuro-ophthalmology, Rome, Italy; ³Laboratory of Psychophysiology, Chair of Psychiatry, Department of Neurosciences, University of Rome Tor Vergata, Rome, Italy; ⁴Department of Medical and Surgical Sciences and Biotechnologies and A. Fiorini Hospital, Terracina, Sapienza University of Rome, Polo Pontino, Latina, Italy; ⁵Department of Medical and Surgical Sciences and Biotechnologies and ICOT, Sapienza University of Rome, Polo Pontino, Latina, Italy; ⁶INM Neuromed, IRCCS, Pozzilli, Italy; e-mail: cherub@inwind.it

Introduction Laser evoked pain-potentials (LEPs) are studied in migraine to better understand its pathophysiological bases. Among

these, trigeminal evoked-potentials (TEPs) were broadly examined. The electrical nociceptive stimulation is an alternative method of TEPs elicitation: an electrode with a concentric design and small anode–cathode distance produces a high current density at low intensities that depolarizes only the superficial layer of the dermis containing nociceptive A-delta fibres, but not the A-beta. These characteristics account for some differences in stimulation and TEPs elicitation from LEPs. Aim of this study was to examine the N2-P2 amplitude of TEPs in a group of migraineurs and compare them with healthy volunteers (HV).

Methods Trigeminal stimulation was performed with an electrode placed on the right side, 10 mm above the entry zone of the supra-orbital nerve. Recordings were performed with an electrode placed at Cz and referenced to bilateral ear lobes. The N2 and P2 components of the TEP were identified as, respectively, the most negative and the most positive peaks occurring between 90 and 260 ms.

A one-way ANOVA was performed to identify differences among groups.

Results Fifty-two subjects were enrolled in the study: 32 HV and 20 migraineurs. Eleven migraineurs reported to having had an attack within 24 h of stimulation participated in a second recording session during an interictal phase of migraine (not before 2 weeks from the first session).

The N2-P2 amplitude was, respectively, 29.12 ± 8.27 in HV, 22.90 ± 6.08 in migraineurs during the interictal phase, and 54.73 ± 10.10 in ictal migraineurs. Differences were significant among the three groups ($F_{2,60} = 41.146$; $p < 0.0001$; Bonferroni post hoc test: HV vs interictal migraineurs, $p < 0.009$; HV vs ictal migraineurs $p < 0.0001$; interictal vs ictal migraineurs $p < 0.0001$).

Discussion Unlike observations performed by LEPs, we found reduced amplitude of N2-P2 in interictal migraineurs that increased during the crisis. The P2 component is thought to be generated in the cingulate gyrus [1] that is activated during a migraine attack [2]. Possibly, the cingulate gyrus may become hypoactive in the interictal phase and it could favour desynchronisation of the evoked response resulting in a decrease of amplitude: just this peculiar characteristic of migraineurs cingulate gyrus could account for our observations.

Conclusions Transcutaneous electrical nociceptive stimulation has further shown to be a valid tool in the study of migraine pathophysiology, being able to elicit TEPs with peculiar characteristics, different from the LEPs.

References

1. Bentley DE, Derbyshire SW, Youell PD et al (2003) Caudal cingulate cortex involvement in pain processing: an inter-individual laser evoked potential source localisation study using realistic head models. *Pain* 102:265–271
2. May A (2004) The contribution of functional neuroimaging to primary headaches. *Neurol Sci* 25(Suppl 3):S85–S88

Effects of repetitive transcranial magnetic stimulation on low- and high-frequency somatosensory activity in migraine

G. Coppola¹, F. Pierelli², J. Schoenen³

¹G.B. Bietti Eye Foundation, IRCCS, Department of Neurophysiology of Vision and Neuro-ophthalmology, Rome, Italy; ²Department of Medical and Surgical Sciences and Biotechnologies, Sapienza University of Rome, Polo Pontino, Latina, Italy; ³Headache Research Unit, University Department of Neurology and GIGA-Neurosciences, Liège University, Liège, Belgium; e-mail: gianluca.coppola@gmail.com

Background Migraine patients are characterised interictally by a lack of habituation during stimulus repetition for a number of different sensory modalities, somatosensory comprises. Whether it is due to increased cortical excitability or reduced thalamocortical activation is still under debate. We found evidence for decreased interictal thalamocortical activation in migraine in a study of high-frequency somatosensory oscillations (HFOs). We report here the effects of excitatory (10 Hz) and inhibitory (1 Hz) repetitive transcranial magnetic stimulation (rTMS) on the HFOs and on conventional low-frequency (LF) SSEPs.

Materials and methods rTMS was performed on the motor cortex of healthy volunteers ($n = 13$; HV) and migraine without aura patients ($n = 13$; MO). We measured LF N20-P25 SSEP amplitude and habituation, and maximal peak-to-peak amplitude of early (reflecting thalamocortical activity) and late (reflecting cortical activation) HFOs (band-pass filter 450–750 Hz) before and after rTMS.

Results In HV, low frequency rTMS significantly reduced the 1st N20-P25 amplitude block and its habituation, whereas high frequency rTMS left all unchanged. In MO, high frequency rTMS increased 1st N20-P25 amplitude block and induced habituation, whereas low slow rTMS had negligible effects. Low frequency rTMS had no significant influence on HFOs neither in HV nor in MO. High frequency rTMS instead produced an increase of late HFOs in both groups of subjects. Regarding early HFOs, 10 Hz rTMS had no effect in HV, but induced a significant increase of the early HFOs in MO, which were reduced at baseline compared to HV.

Discussion Our data suggest lack of habituation in migraine can be reverted to response normalization by increasing thalamocortical activity with excitatory rTMS. This may not be possible in HV because their thalamocortical activity is already maximal before the rTMS. Taken together with similar effects we observed for visual evoked potentials, supports the hypothesis that reduced cortical pre-activation due to dysfunctioning thalamocortical loops could be responsible for the abnormal information processing (i.e., habituation deficit) found interictally in migraine.

Anomalous response to visual stimuli in migraine with aura patients

C. Serpino¹, S. Stramaglia², M. Pellicoro², E. Vecchio¹, V. De Vito Francesco¹, K. Ricci¹, G. Franco¹, M. de Tommaso¹

¹Dipartimento di Scienze Neurologiche e Psichiatriche, Università di Bari Aldo Moro, Bari, Italy; ²Dipartimento di Fisica, Università di Bari Aldo Moro, Bari, Italy; e-mail: claudia.serpino@gmail.com

Introduction The study of phase synchronization in EEG rhythms, showed in migraine without aura patients a pattern of alpha rhythm (8–12.5 Hz) hyper-synchronization under repetitive flash stimulation. Approximately one-third of people who suffer migraine headaches perceive an aura (visual abnormality lasting 10–30 min) as a sign that the migraine will soon occur. There is evidence of relationships between migraine aura and the spreading depression (SD) (a wave of electrophysiological hyperactivity followed by a wave of inhibition).

Objectives The aim of the study was to evaluate the effects of repetitive flash stimuli on EEG rhythm in migraine with aura patients.

Methods EEG was recorded in 19 patients (7 males, aged 20–44 years) affected by migraine with aura, 19 (4 males, aged 21–45 years) patients affected by migraine without aura, and in 11 healthy subjects (3 males, aged 20–46 years). During the acquisition,

flash stimuli were presented at a rate of 9, 18, 21, 24, 27 Hz; also EEG in the absence of stimuli (base) was recorded. Each frequency of stimulation was delivered by a flash with 0.2 J luminance for about 20 s. EEG data were recorded by six scalp electrodes: two occipital channels (O1 and O2), two parietal ones (P3 and P4), a central electrode (Cz) and a frontal one (Fz); the sampling rate was 256 Hz, and the EEG was digitally filtered off-line by a filter with a band-pass 0.3–30 Hz. The synchronization pattern and effective connectivity were evaluated by means of Hilbert transform and Granger causality.

Results The pattern of alpha band hyper-synchronization in presence of flash stimuli was confirmed for migraineurs without aura, while patients with aura did not show alpha band hyper-synchronization in presence of light stimuli. Moving to the beta band (12.5–30 Hz), migraine patients with aura showed a peculiar pattern of visual reactivity compared with migraine patients without aura and healthy subjects, consisting of an increased effective connectivity and reduced functional connectivity among EEG channels in the beta band.

Conclusions The phenomenon of increased effective connectivity and reduced functional connectivity among EEG channels diffused over the cortex may be a facilitating factor for SD progression and aura symptoms perception.

Visual evoked potentials in subgroups of migraine with aura

G. Coppola¹, C. Di Lorenzo², F. Pierelli²

¹G.B. Bietti Eye Foundation, IRCCS, Department of Neurophysiology of Vision and Neuro-ophthalmology, Rome, Italy; ²Department of Medical and Surgical Sciences and Biotechnologies, Sapienza University of Rome, Polo Pontino, Latina, Italy; e-mail: gianluca.coppola@gmail.com

Background Migraine patients are characterised between attacks by an abnormal visual cortical reactivity. In fact, lack of visual evoked potentials (VEPs) amplitude habituation was disclosed equally in migraine with and without aura, i.e., the two forms of migraine that are traditionally differentiated from each other. Patients suffering from migraine with aura could experience pure visual symptoms, and/or complex aura with sensory disturbances and dysphasia. The pathophysiology of these subgroups of common forms of migraine with aura has rarely been studied.

Method Thirty-two migraine with aura patients were subgrouped in migraine with pure visual aura (MA, N = 17) and migraine with complex aura (MA+, N = 15), i.e., those who had visual aura associated with paraesthesia and/or dysphasia. We recorded VEPs (15 min of arc cheques, 3.1 reversal rate, 600 sweeps) amplitude and habituation (slope of the linear regression line for N1-P1 amplitude from the 1st to 6th block of 100 sweeps) in patients and in 23 healthy volunteers (HV) of comparable age and gender distribution.

Results In MA VEP N1-P1 amplitude block started well below that of HV ($p = 0.04$) and increased across the successive blocks (mean slope + 0.05, $p = 0.04$), although never exceeding 1st amplitude block of HV. In MA + VEP amplitudes started in the same range of HV and increased in the subsequent blocks, remaining well above 1st amplitude block of HV during the whole time of visual stimulation (slope + 0.19, $p = 0.01$).

Conclusions We found different patterns of visual responses in the subgroups of MA patients. We hypothesise that a different genetic load and energetic metabolism may characterise migraine with aura patients with more severe focal symptoms.

Habituation deficit to nociceptive trigeminal stimuli in migraine patients is frequency dependent

M. Bolla¹, A. Perrotta², A. Ambrosini², C. Tassorelli¹, G. Coppola³, F. Pierelli⁴, G. Sandrini¹

¹IRCCS Neurological National Institute C. Mondino, Pavia, Italy; ²Headache Clinic, IRCCS INM Neuromed, Pozzilli, Italy; ³G.B. Bietti Eye Foundation, IRCCS, Department of Neurophysiology of Vision and Neuro-ophthalmology, Rome, Italy; ⁴Department of Medical and Surgical Sciences and Biotechnologies, Sapienza University of Rome, Polo Pontino, Latina, Italy; e-mail: monica.bolla@mondino.it

Introduction The habituation phenomena, a response decrement as a result of repeated stimulation, represents a fundamental form of central nervous system plasticity mediated by a complex interaction of segmental and suprasegmental mechanisms. The nociceptive specific blink reflex (nBR) is considered a sensitive mean to explore both pain processing and habituation at the trigeminal level. In migraine patients the habituation deficit is considered a trait marker of the disease related to its pathophysiology.

Since the habituation is a complex process that depends also on the nature and frequency of stimulation, the aim of our study was to better characterise the nBR habituation deficit in migraine patients applying different frequencies of stimulation.

Subjects and methods Eighteen migraine without aura (MO) and eight migraine with aura (MA) patients were enrolled in the study and compared with ten healthy volunteers. Each subject underwent six different nBR recording sessions where a series of 26 electrical stimuli were delivered at different, randomly chosen, stimulation frequencies (1, 0.5, 0.3, 0.2, 0.1 and 0.05 Hz). Rectified electromyographical sweeps were averaged off-line to obtain five consecutive blocks of five sweeps (first sweep was excluded to avoid startle response) for habituation investigation.

Results Habituation rate decreased progressively from high to low frequency stimulation in healthy volunteers and patient groups. Habituation trend was found significantly lower in patient groups than in healthy volunteers from 0.5 to 0.05 Hz frequency stimulation. No significant differences were found between forms of migraine.

Discussion and conclusions We demonstrated that nBR habituation profile is frequency dependent in both patients and controls. We confirmed a marked nBR habituation deficit in migraineurs when compared to healthy volunteers. It is inversely related to the stimulation frequency both at highest and lower frequencies. We failed to detect any significant difference between migraine with and without aura patients, even if the data need further investigations to be confirmed.

Abnormal sensorimotor long-term plasticity in migraine without aura patients

G. Coppola¹, E. Iacovelli², M. Bracaglia², E. Porretta², C. Di Lorenzo², F. Pierelli²

¹G.B. Bietti Eye Foundation, IRCCS, Department of Neurophysiology of Vision and Neuro-ophthalmology, Rome, Italy; ²Department of Medical and Surgical Sciences and Biotechnologies, Sapienza University of Rome Polo Pontino, Latina, Italy; e-mail: gianluca.coppola@gmail.com

Background Lack of habituation and abnormal responses to repetitive transcranial magnetic stimulation (rTMS) characterise migraine

between attacks. Since these immediate and longer-lasting cortical changes presumably both reflect CNS plasticity mechanisms that alter synaptic effectiveness in the stimulated cortex through short- and long-term depression (LTD) phenomena, altered functional plasticity of sensory cortices in migraine was hypothesized. In healthy subjects (HS), paired associative stimulation (PAS), in which peripheral nerve stimuli are followed by TMS of the motor cortex, may produce a long-lasting depression in the excitability of corticospinal output neurons. We report the effects of PAS in migraine without aura (MO) patients.

Method Changes in motor evoked potential (MEP) amplitudes were recorded in 9 MO patients and 10 HS before and after PAS, which consisted of 90 peripheral electrical right ulnar nerve stimulation and subsequent TMS pulse over optimal site for activation of the first dorsal interosseus (FDI) muscle with a delay of 10 ms (excitability depressing).

Results MEP amplitudes significantly decreased after PAS 10 ms in HS (−4%), whereas it increased in MO patients (+41%, $p = 0.04$).

Conclusions These results suggest interictal impairment of LTD mechanisms in migraine. Knowing that somatosensory information, such as that induced by ulnar nerve stimulation, reaches the motor cortex via corticocortical fibres from the somatosensory cortex after a relay in the ventrolateral thalamus, or via thalamocortical fibres from the thalamus, we postulate that the impaired LTD mechanisms in migraine could be due to a deficient thalamocortical activation, as already documented in somatosensory evoked high-frequency oscillations studies.

Habituation deficit to nociceptive trigeminal stimuli is frequency dependent in trigeminal autonomic cephalalgias

A. Perrotta¹, M. Bolla², A. Ambrosini¹, C. Tassorelli², G. Coppola³, G. Sandrini², F. Pierelli⁴

¹Headache Clinic, IRCCS INM Neuromed, Pozzilli, Italy; ²IRCCS Neurological National Institute C. Mondino, Pavia, Italy; ³G.B. Bietti Eye Foundation, IRCCS, Department of Neurophysiology of Vision and Neuro-ophthalmology, Rome, Italy; ⁴Department of Medical and Surgical Sciences and Biotechnologies, Sapienza University of Rome, Polo Pontino, Latina, Italy; e-mail: armando.perrotta@uniroma1.it

Introduction A growing body of evidence supports the pivotal role of the hypothalamus in the pathophysiology of cluster headache (CH) and other trigeminal-autonomic cephalalgias, as paroxysmal hemi-crania (PH). On the basis of animal studies, it has been suggested that a hypothalamic dysfunction can lead to an habituation deficit of brainstem reflex responses, as a result of a stress-like condition. In a previous study [1] we demonstrated that CH patients are characterised by an habituation deficit of blink reflex responses during cluster period higher than migraine patients suggesting abnormal modulation of suprasegmental structures.

The nociceptive specific blink reflex (nBR) is a more sensitive mean to explore pain processing at the trigeminal level as evoked by a concentric planar electrode able to stimulate only nociceptive fibres. Taking into account these considerations, we aimed to investigate nBR habituation process in CH and PH patients during attack periods. **Subjects and methods** Five CH and 5 PH patients were enrolled in the study and compared with 10 healthy volunteers and 10 migraine without aura (MO) patients. Each subject underwent, during periods of attack, six different nBR recording sessions where a series of 26 electrical stimuli were delivered at different, randomly chosen, stimulation frequencies (1, 0.5, 0.3, 0.2, 0.1 and 0.05 Hz). Each

frequency series was acquired from the affected and non-affected side for each patient. Rectified electromyographical sweeps were averaged off-line to obtain five consecutive blocks of five sweeps (first sweep was excluded to avoid startle response) for habituation investigation.

Results Habituation rate decreased progressively from high to low frequency stimulations in healthy volunteers and the patient groups. Habituation trend was found significantly lower in CH and PH patients compared to healthy volunteers at every frequency of stimulation; comparing CH and PH to MO patients we found a significant difference at 1, 0.5, 0.3 and 0.2 Hz stimulation frequencies. No significant differences were found between CH and PH patients and comparing affected and non-affected side.

Discussion and conclusions We demonstrated that nBR habituation profile is frequency dependent in both patients and controls. We confirmed in CH, and for the first time, in PH patients, a marked nBR habituation deficit, even more pronounced than MO patients. We failed to detect any significant difference between affected and non-affected side, even if this data needs further investigations to be confirmed.

References

1. Perrotta A, Serrao M, Sandrini G et al (2008) Reduced habituation of trigeminal reflexes in patients with episodic cluster headache during cluster period. *Cephalalgia* 28(9):950–959 (Epub 2008 Jul 8)

The habituation of blink reflex through biofeedback training in migraine patients

M. Delussi¹, A. Federici², M.F. De Caro¹, M. de Tommaso¹

¹Neurofisiopatologia del Dolore, Dipartimento di Scienze Neurologiche e Psichiatriche, Università di Bari Aldo Moro, Bari, Italy; ²Dipartimento di Fisiologia e Farmacologia, Università di Bari Aldo Moro, Bari, Italy; e-mail: m.delussi@gmail.com; m.detommaso@neurol.uniba.it

Introduction Recent studies with regard to the pathogenesis have emphasized the trigeminal system role (Moskowitz 1997). The reduced habit of nociceptive blink reflex is a migraine phenotypic pattern (Diclemente et al. 2007). The electromyographic biofeedback is a psychophysiological clinical technique successfully applied in tensive migraine and headaches, by measuring various muscular groups, in order to provide the patients with continuous and real time information on their muscular state of tension to aid conditioning (target behaviour).

Objective The aim of this study was to induce the habit and the control of the nociceptive blink reflex by electromyographic biofeedback training in groups of patients with migraine without aura.

Materials and methods The sample was made up of 35 patients (25 F, 10 M) suffering from migraine without aura presenting to the Neurological and Psychiatric Department, Neurophysiopathology of Pain Ambulatory. Criterion of inclusion: migraine crisis frequency greater or equal to 3 crises per month. The patients were randomly assigned to 3 different groups: *Group A*: therapy with antiepileptic drugs (topiramate 50 mg bid); *Group B*: therapy with antiepileptic drugs (topiramate 50 mg bid) + biofeedback training; *Group C*: biofeedback training. The Biofeedback sitting took place during a pain absence phase. The target behaviour of each sitting, lasting 40 min, was to induce the control and the habit of blink reflex through electrical stimulation with concentric electrode and electromyographic monitoring of the magnitude of orbicular muscular response. The clinical evaluation of the patients was carried out over a period between 0 and 2 months for the biofeedback training and/or

pharmacological therapy, correlating the neurophysiological results with clinical effectiveness, evaluated by the frequency of migraines, the MIDAS scale, the SF36 total tenderness score, and allodynia.

Results In every patient of Groups B and C the electromyographic biofeedback training involved a steady control and a greater habit to nociceptive reflex. Furthermore, in the three groups a significant reduction of the frequency of the crisis and disability linked to migraine, which was more evident in Group C, was noted. Group C showed significant correlation among cranial nerves tensing reduction and gravity of allodynia and entity pattern variation of unaccustomed blink reflex nociceptive.

Conclusions From the correlation of neurophysiological exhibits with clinical effectiveness we are able to conclude that a steady reduction of ability learning and muscular reaction control reflected in nociceptive trigeminal activation could rank as a specific technique for migraine patients with the purpose of reducing the central sensitization phenomenon.

Lack of association between *HCRT1* gene and migraine with aura

I. Rainero¹, E. Rubino¹, S. Gallone¹, D. Carli², P. Fenoglio¹, F. Govone¹, A. Vacca¹, L. Pinessi¹, G. Dalla Volta²

¹Neurology II, Headache Centre, Department of Neuroscience, University of Turin, Turin, Italy; ²Operative Unit of Neurologia, Clinical Institute, Brescia, Italy; e-mail: irainero@molinete.piemonte.it

Introduction Genetic factors play a major role in migraine but, at present, the type and the number of genes involved in pathogenesis of the disease are still unclear. Hypocretin-1 and -2 (also called orexin-A and -B) are recently discovered neuropeptides processed from a common precursor, preprohypocretin. Two known G(q)-coupled receptors, Hcrtr1 and Hcrtr2, have been identified. The peptides of the hypocretin system influence a wide range of physiological and behavioural processes in mammals [1]. Several of these, such as sleep regulation, pain modulation, reward processing and addiction, may be of relevance for the pathogenesis of migraine. In a previous study, we found a significant association between a non-synonymous polymorphism (rs2271933) within the *HCRT1* gene and migraine without aura (MO) [2]. To further investigate this issue, we genotyped a large cohort of migraine with aura (MA) patients in order to test the hypothesis that the same polymorphism would modify the occurrence or the clinical features of MA.

Materials and methods A total of 243 consecutive unrelated MA patients (73 men, 170 women, mean age \pm SD = 38.4 \pm 13.4 years) were involved in the study. The diagnosis of migraine with aura was made according to the ICHD-II criteria. A group of 372 healthy age, sex and ethnicity-matched subjects were used as controls (143 men, 229 women, mean age \pm SD = 45.8 \pm 17.0 years). Cases and controls were genotyped for the bi-allelic non-synonymous polymorphism (rs2271933, 1222 G > A, Ile408Val) of the *HCRT1* gene. Statistical analyses were performed using SVS—version 7 and SPSS—version 18. The level of statistical significance was taken at $p < 0.01$.

Results The Hardy–Weinberg equilibrium was verified for all tested populations. Allelic and genotypic frequencies of the examined polymorphism resulted similarly distributed between cases and controls. The clinical features of migraine were not significantly modified by different genotypes.

Discussion In this study of an Italian population we found no evidence of genetic association between *HCRT1* gene and migraine with aura. Furthermore, the examined polymorphism did not

significantly modify the clinical characteristics of the disease. Thus, it is unlikely that genetic variations within the *HCRT1* gene greatly contribute to migraine susceptibility.

Conclusions The results of this study do not support our research hypothesis that the *HCRT1* gene may be a major genetic risk factor for migraine with aura.

References

1. Nishino S (2003) The hypocretin/orexin system in health and disease. *Biol Psychiatry* 54:87–95
2. Rainero I, Rubino E, Gallone S et al (2011) Evidence for an association between migraine and the hypocretin receptor 1 gene. *J Headache Pain* 12:193–199

Pharmacological and non pharmacological treatment

Analysis on the use of migraine attack drugs in current clinical practice

M. Margoni, M. Bellamio, C. Disco, F. Mainardi, F. Maggioni, G. Zanchin

Headache Centre of the Veneto Region, Department of Neurosciences, University of Padua, Padua, Italy; e-mail: giorgio.zanchin@unipd.it

Introduction In 2002 the Italian Society for the Study of Headaches (SISC) introduced a second version of guidelines (GL) aimed to determine the most appropriate choice of drugs for the therapy of migraine. The impact of attack therapy GL in the general practice had been assessed in 1995 [1] when drug use was evaluated before (1989–1992, n 200) and in 1998 [2], after (1995–1998, n 206) the introduction of the 1993 GL.

Materials and methods Our aim was to establish the impact in migraine patients of the present SISC GL in view of the forthcoming publication of a revised version. We assessed the attack drugs taken, before coming to our observation, by a consecutive series of patients suffering from migraine without aura (ICHD II criteria, 2004), seen in the period 2009–2011, and compared them with those taken in the periods '89–'92 and '95–'98.

Results Our preliminary data showed that among 130 patients studied so far, the most frequently used drugs were NSAIDs, 76% of patients (vs. 80% in '89–'92, 87% in '95–'98), followed by triptans 30% (vs. 17% sumatriptan, the only triptan available in '95–'98), and combination drugs 22.3% (vs. 79.5% in '89–'92, 51% in '95–'98). Ergotamine and dihydroergotamine were no longer in use (27.5 and 9.5% in '89–'92, 6 and 3% in '95–'98). Among NSAIDs, the most commonly used drugs were ibuprofen 45.5% (vs. 37.5% in '95–'98) and nimesulide 39.4% (vs. 15.6% in '95–'98); among triptans, sumatriptan 30.8% (vs. 17% in '95–'98); among association drugs, caffeine + indomethacin + prochlorperazine 41% (vs. 27% in '89–'92, 19% in '95–'98) and paracetamol + codeine 46% (vs. 5% in '95–'98).

Conclusions These preliminary results underline the fact that in current clinical practice the utilization of attack drugs for migraine differs in many aspects from the SISC GL. A more adequate diffusion of the forthcoming GL should be planned in order to impact more effectively current practice.

References

1. Maggioni F, De Boni A, Rossi P et al (1995) A study of symptomatic drug use in migraine without aura. *Ital J Neurol Sci* 16:459–465

2. Zanchin G, Mainardi F, Moscardo P et al (1998) The impact of the migraine therapy guidelines on the patient. 4th EHF Congress. Functional Neurology 13:BC2

Analysis on the use of migraine preventative drugs in current clinical practice

M. Bellamio¹, M. Margoni¹, C. Disco¹, L.A. Pini², F. Maggioni¹, G. Zanchin¹

¹Headache Centre of the Veneto Region, Department of Neurosciences, University of Padua, Padua, Italy;

²Headache Centre, Department of Clinical Toxicology and Pharmacology, University of Modena and Reggio Emilia, Modena, Italy; e-mail: giorgio.zanchin@unipd.it

Introduction In 2002 the Italian Society for the Study of Headaches (SISC) introduced a second version of guidelines (GL) aimed to determine the most appropriate choice of drugs for the therapy of migraine. The impact of preventative GL in the general practice had been assessed in 1999, when drug use was evaluated, respectively, before (1989–1992, n 351) and after (1995–1998, n 204) the introduction of the 1993 GL [1].

Materials and methods Our aim was to establish the impact in migraine patients of the present SISC GL in view of the forthcoming publication of a revised version. We assessed the preventative drugs taken, before coming to our observation, by a consecutive series of patients suffering from migraine without aura according to the ICHD-II criteria (2004), seen in the period 2009–2011, and compared them with those taken in the periods '89–'92 and '95–'98.

Results Our preliminary data showed that among 104 patients studied so far, 31 (30%) had experienced preventative therapy (vs. 38% in '89–'92, 41% in '95–'98) [1]. They suffered high (>5/month), intermediate (3–5), low (≤3) attack frequency in 48.4, 32.2, 19.4%, respectively (vs. 17, 54, 29%, respectively, in '89–'92). In the remaining 73 patients (70%) without preventative therapy, attack frequency was high in 34.7% (vs. 11%), intermediate 29.2% (vs. 46%), low 36.1% (vs. 43%) [2]. Therefore, according to the current SISC GL, in the 2009–2011 group of patients taking preventative drugs this treatment was not indicated only in 3% of the cases (vs. 29% in '89–'92); whereas in the group not taking preventative drugs more than 55% of patients should have received a prophylactic therapy (vs. >50%) [2]. The most prescribed drugs were amitriptyline (29.4% of the patients vs. 27% in '95–'98, 6% in '89–'92), followed by flunarizine (17.6 vs. 48% and 54%); propranolol (7.8 vs. 18% and 7%). Pizotifen figures were 5.9 versus 18%, and 27%; whereas topiramate was used by 7.8% of patients [1]. Dihydroergotamine and lisuride are no longer prescribed (31% and 13%, respectively, in '89–'92) [2].

Conclusions These preliminary results underline the fact that the common use of migraine preventative drugs in current clinical practice differs in many aspects from the SISC GL.

A more adequate diffusion of the forthcoming GL should be planned in order to impact more effectively current practice.

References

1. Zanchin G, Mainardi F, Occhipinti C et al (1999) Impatto delle linee guida SISC nella terapia dell'Emicrania. Workshop "Migraine Day". Saint Vincent
2. Zanchin G, Rossi P, Fortunato M et al (1996) Preventative drug use in migraine without aura. Cephalalgia 16:383–384

Open label efficacy and tolerability of pregabalin in prophylaxis treatment in patients with migraine caused by anxiety disorders and fibromyalgia

R. Iannacchero^{1,2}, F. Migliazza^{1,2}, F. Corasaniti^{1,2}, U. Cannistrà¹, E. De Caro^{1,2}

¹Headache Centre, Regional Department of Neurosciences, A.O. Pugliese-Ciaccio, Catanzaro, Italy; ²Pain Clinic Neurology, S.O.C. Neurology, A.O. Pugliese-Ciaccio, Catanzaro, Italy; e-mail: rosarioiann@tiscali.it

Objective In recent years, antiepileptic drugs have been effectively employed in the prevention of migraine (topiramate, valproate sodium). Pregabalin is a new antiepileptic drug that has shown efficacy also in the treatment of neuropathic pain syndromes. We evaluated efficacy and tolerability of pregabalin for prophylaxis treatment in patients with migraine caused by anxiety disorders and fibromyalgia.

Materials and methods Twenty-six patients (18 females/8 males), mean age 38 ± 6 years) with migraine and fibromyalgia due to anxiety were selected. Patients were treated for 6 months with pregabalin that was slowly titrated (after 30 days) to final doses of at least 450 mg/daily; primary endpoint efficacy was migraine attack frequency/month, secondary endpoints were attack duration and intensity, number of symptomatic drugs/month, percentage of responders assessed with the State Trait Anxiety Inventory for scores on pain VAS (scale analogic) at the beginning of the study and every 3 months. Patients were evaluated at the beginning of the study and every month thereafter.

Results Pregabalin was well tolerated and no relevant side effects were reported. No patient dropped out of the study. Three patients complained of somnolence. Pregabalin also showed good efficacy significantly reducing attacks, frequency after 1 month ($p < 0.1$); the frequency of the attacks was further reduced at 3- and 6 month follow-up. Secondary endpoints were all significantly reduced at the third and the sixth month of treatment with responder rate at 65–75%, respectively, VAS scale was 45–55% (STAI).

Discussion and conclusions If confirmed by studies in larger patient series, pregabalin may represent a new option for prophylactic treatment in migraine caused by anxiety and fibromyalgia. Patients suffering from fibromyalgia show a reduced decline of pain sensitivity. Fibromyalgia and migraine may share a common mechanism of altered sensitive modulation of pain. The majority of migraine patients showed one or more psychopathological disturbances, including psychiatric disorders of DSM IV generalised anxiety disorders (GAD).

Observational study about role of diet in overweight migraineurs: comparison between ketogenic diet and traditional low-calorie diet

C. Di Lorenzo¹, A. Currà², G. Sirianni³, G. Coppola⁴, F. Pierelli^{5,6}

¹Don Carlo Gnocchi Onlus Foundation, Italy; ²Department of Medical and Surgical Sciences and Biotechnologies and A. Fiorini Hospital, Terracina, Sapienza University of Rome, Polo Pontino, Latina, Italy; ³Wellness and Aesthetics Medicine, Krom Genetics Institute, Rome, Italy; ⁴G.B. Bietti Eye Foundation, IRCCS, Department of Neurophysiology of Vision and Neuro-ophthalmology, Rome, Italy; ⁵Department of Medical and Surgical Sciences and Biotechnologies and ICOT, Sapienza University of Rome, Polo Pontino, Latina, Italy; ⁶INM Neuromed IRCCS, Pozzilli, Italy; e-mail: cherub@inwind.it

Introduction Ketogenic diet is used since ancient times to treat epileptic seizures; more recently it was adopted also in weight-loss strategy. Anecdotal reports stated its effectiveness also in migraine. Aim of this study was to verify this observation in an ample population of overweight migraineurs, comparing the effect with another population that followed a traditional low-calorie diet.

Methods Migraine anamnesis of overweight subjects self referred to a nutritionist for weight lose was collected, then we selected 100 migraineurs (50 underwent a ketogenic-diet, 50 a traditional low-calorie diet) and recorded clinical data and psychometric measures of depressive symptoms and aggressivity. A paired sample *t* test was adopted to compare continues measure.

Results Before the diet, the first group (ketogenic diet) of patients reported 3.76 migraine attacks per month (SD = 2.491) and 7.12 migraine days per month (SD = 5.995); they assumed analgesics for 6.22 (SD = 5.828) days per month, with a total amount of 7.64 doses (SD = 7.594). S.T.A.S.-T score (adopted to measure aggressivity) was 28.90 (SD = 7.565), and BDI score (depressive symptoms) was 12.22 (SD = 8.503). During the period of observation (30 days during the ketogenic phase), the mean attack frequency was 0.76 (SD = 1.318; *t* = 9.305; *p* < 0.0001) and migraine days were 0.98 (SD = 1.708; *t* = 7.821; *p* < 0.0001); analgesics were consumed for 0.54 (SD = 1.199; *t* = 7.443; *p* < 0.0001) days, for a total amount of 0.6 doses (SD = 1.370; *t* = 6.876; *p* < 0.0001). S.T.A.S.-T score 26.18 (SD = 6.05; *t* = 3.495; *p* = 0.001), and BDI score was 7.44 (SD = 5.059; *t* = 5.327; *p* < 0.001). Before the diet, the second group (traditional low-calorie diet) reported 3.36 (SD = 1.747) attacks and 6.98 (SD = 4.918) migraine days per month; analgesics were consumed for 6.58 (SD = 4.739) days per month, for a total amount of 7.06 (SD = 6.644) doses. The mean S.T.A.S.-T score was 29 (SD = 7.229) and BDI Score was 12.86 (SD = 7.913). During the observed first month of diet, patients reported 3.6 migraine attacks (SD = 1.884; *t* = -1.218; *p* = 0.229) and migraine days were 6.66 (SD = 4.461; *t* = 1.354; *p* = 0.182); analgesics were consumed for 6.22 (SD = 4.739; *t* = 1.477; *p* = 0.146) days, for a total amount of 6.26 doses (SD = 4.793; *t* = 1.519; *p* = 0.135). S.T.A.S.-T score 32.78 (SD = 5.596; *t* = -4.472; *p* < 0.0001), and BDI score was 14.88 (SD = 6.775; *t* = -4.019; *p* < 0.001).

Discussion During ketogenesis, all measured clinical parameters of migraine, and psychiatric symptoms, were improved. Conversely, the traditional low-calorie diet did not improve migraine, and psychometric scores were worsened.

Conclusions Our observation confirms the effectiveness of ketogenic diet in migraine improvement.

Advice alone vs structured detoxification programmes for complicated medication-overuse headache: a prospective, randomized, open-label trial

P. Rossi^{1,2}, J.V. Faroni¹, G. Nappi²

¹INI, Grottaferrata, Italy; ²IRCCS Neurological National Institute C. Mondino, Pavia, Italy; e-mail: paolo.rossi90@alice.it

The aim of this study was to compare the effectiveness of advice on how to withdraw the overused medication with the effectiveness of two structured detoxification strategies in a cohort of patients diagnosed with complicated medication-overuse headache (MOH) plus migraine.

One hundred and thirty-seven complicated MOH patients participated in the study. MOH was defined as complicated in patients fulfilling at least one of the following criteria: (a) a diagnosis of coexistent, significant and complicating medical illnesses; (b) a current diagnosis of

mood disorder, anxiety disorder, eating disorder or substance addiction disorder; (c) a relapse after previous detoxification treatment; social and environmental problems; (e) daily use of multiple doses of symptomatic medications.

Group A (46 patients) received only intensive advice on how to withdraw the overused medication. Group B (46 patients) underwent a standard detoxification programme (advice + steroids + preventive treatment). Group C (45 patients) underwent a standard in-patient withdrawal programme (as in group B + fluid replacement and antiemetics). Withdrawal therapy was considered successful if, after 2 months, the patient had had reverted to an intake of NSAIDs lower than 15 days/month or to an intake of other symptomatic medication lower than 10 days/month.

Twenty-two patients failed to attend follow-up visits (11 in group A, 9 in group B, 2 in group C, *p* = 0.03). Overall, we were able to detoxify 70% of the whole cohort, 60.1% of patients in group A and group B, and 88.8% of those in group C (*p* < 0.05).

In-patient withdrawal strategy is significantly more effective than advice alone and outpatient strategy for complicated MOH patient.

An alternative approach to migraine prophylaxis: osteopathic treatment

C. Lepre¹, V. Rosati², F. Tango¹, F. Sovani¹, G. Fiermonte¹, F. Pauri¹

¹Dipartimento di Scienze e Biotechnologie Medico-Chirurgiche, Sapienza Università di Roma, Rome, Italy; ²Dipartimento Organi di Senso, Sapienza Università di Roma, Rome, Italy; e-mail: flavia.pauri@uniroma1.it

Introduction Worldwide a considerable amount of drugs are used to treat headache; the use is often followed by collateral effects and sometimes by medication-overuse headache. Thus, some efforts are devoted to find alternative ways to treat headache. Aim of the study was to verify the effectiveness of an osteopathic treatment in subjects affected by migraine with or without aura. The target of the osteopathic treatments was to reduce the frequency, length and pain intensity of crises through techniques that re-establish the physiological circulatory conditions of the patients.

Patients and method Fifteen subjects, both male and female, with migraine with or without aura, with attack frequency equal to or higher than 5 per month were selected using the IHS criteria. Patients gave their informed consent to participate in this study. Each patient was evaluated by an “ad hoc form” and they were instructed to complete a diary for at least 2 months in order to evaluate the frequency of the attacks, the pain intensity and the length of each attack. The values of these three parameters led to define the headache index. An osteopathic test was prepared to select subjects which included evaluation of the hinge occipital-atlanto-axis (OAA), decrease of occipital flexion mobility movements, mobility limitation in ipsilateral or bilateral temporal bone, “primary breathing mechanism” alteration. The subjects were treated in order to release the OAA complex; release the nuchal basis; correction of low mobility suture, sphenopalatine ganglion technique, and pressure of the IV ventricle. Patients underwent treatment twice a month for at least 2 months: in subjects showing positive responses the treatment was extended for two more months. We considered a positive response if the headache index decreased at least by 50%.

Results and conclusions All subjects included in the study were satisfied by this alternative approach to headache and did not complain of any side effects. All patients treated reported a reduction (more than 50%) of the headache index. Osteopathic treatment seems to be a possible alternative approach to headache and it should be considered, for example, in subjects who are reluctant to use drugs.

Potential toxicity of oxycodone overuse in chronic headaches

S. Guerzoni, I. Tiraferri, A. Bazzocchi, L. Neri, L.A. Pini

Headache and Drug Abuse Inter-Department Research Centre,
University of Modena and Reggio Emilia, Modena, Italy;
e-mail: pinila@unimore.it

Opioid analgesics are commonly used in chronic pain treatment. These drugs are increasingly prescribed also in headache treatment as rescue medication in some non-responders to migraine-specific medications. The pain appears to be best controlled with an opioid analgesic like oxycodone for a brief period.

In this report, we refer two cases of male patients, aged between 30 and 50 years, with a previous diagnosis of medication-overuse headache (ICHD-II, 8.2.3) and a recent history of opioid abuse [1]. Opioid medication (oxycodone 20 mg/day) was prescribed to each patient by their physician for a chronic pathology not related to the headache. Over time they noticed that oxycodone was effective also as rescue medication in migraine attack. Therefore, the patients begun to replace the usual migraine therapy with the opioids progressively increasing the daily dose without being monitored by their physician. Patients were seen in our Headache Centre with a clinical strong opioid dependence. Oxycodone daily dose was about 400 mg. They were hospitalized for a rehabilitation programme, and a withdrawal therapy with oral methadone, a commonly used drug for the treatment of heroin addiction, was decided. The dosage was set following the equianalgesic transformation tables.

Oxycodone (dihydrohydroxycodone) is a full μ and κ opioid agonist, metabolized by the P450 2D6 enzyme to at least one active metabolite, oxycodone. It has pharmacological actions just like strong opioids but with a better pharmacokinetic profile and greater analgesic potency than morphine. Oxycodone has proven to be an effective analgesic in acute postoperative pain, cancer pain, visceral pain and chronic nonmalignant pain. Historically, oxycodone was considered to be associated with a lower abuse liability, similar to that of codeine, therefore it was initially introduced in combination with over-the-counter non-opioid analgesics [2].

Oxycodone, a sustained release formulation of oxycodone, has been identified as an especially problematic and dangerous drug of abuse because it is available in higher dosages than other oxycodone formulations.

In the last 20 years there has been a dramatic increase in opioid prescriptions with increased evidence of adverse effects, including migraine chronification.

We stress the importance of a careful indepth discussion with the patient and family about the potential abuse of this drug and about carefully monitoring the adherence of the appropriate dosage and maintenance of the prescription by a single physician. It is possible that patients with a prior opioid history had a more aggressive disorder and therefore became more easily non-responders to the common migraine prophylaxis and rescue medications.

References

1. Saper JR, Lake AE 3rd, Bain PA et al (2010) A practice guide for continuous opioid therapy for refractory daily headache: patient selection, physician requirements, and treatment monitoring. *Headache* 50(7):1175–1193
2. Walsh SL, Nuzzo PA, Lofwall MR et al (2008) The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription opioid abusers. *Drug Alcohol Depend* 98(3):191–202 (Epub 2008 Jul 7)

Drug-resistant chronic cluster headache responding to hyperbaric oxygen therapy: a case report

C. Lucchesi¹, G. De Iaco², N. Morelli¹, M.R. Maluccio¹, S. Gori¹, L. Murri¹

¹Department of Neuroscience, Institute of Neurology, University of Pisa, Pisa, Italy; ²Emergency Department, Unit of Anaesthesiology and Reanimation, University of Pisa, Pisa, Italy;
e-mail: cinzia.lucchesi@gmail.com

Introduction It is well known that 100% oxygen inhalation represents a first choice symptomatic treatment for acute cluster headache attacks. The role of hyperbaric oxygen therapy (HBOT), which consists in the therapeutic administration of 100% oxygen at environmental pressures greater than one atmosphere, is still controversial in the treatment of cluster headache (CH). Isolated reports and a limited number of clinical trials, have suggested a potential role of hyperbaric oxygen therapy as a symptomatic and preventive treatment of CH; according to these data, HBOT could be able to interrupt cluster headache attacks and in some patients even to interrupt the cluster period. Since no clinical trials have shown statistically significant efficacy of HBOT as symptomatic or preventive treatment, a recent meta-analysis emphasized the need for further research on the possible role of HBOT in patients unresponsive to standard therapy.

Case report We report the case of a 63-year-old patient, suffering from chronic cluster headache (IHS criteria 2004), resistant to standard treatment, fully responding to hyperbaric oxygen therapy.

Cluster headache started at the age of 36, with an episodic pattern. At the age of 45, CH became chronic, with several attacks a day, resistant to standard symptomatic options (oxygen inhalation at the rate of 7 l/min for 15 min, sumatriptan, zolmitriptan, dihydroergotamine, indomethacin, corticosteroids). Several prophylactic therapies (verapamil, lithium, topiramate, valproic acid, gabapentin, carbamazepine, oxcarbazepine, lamotrigine) administered in monotherapy and in multiple combination therapies, showed no efficacy.

Before considering surgical procedures, we performed a therapeutic attempt with HBOT.

The patient performed ten consecutive daily sessions; then five sessions on alternate days, two sessions a week for 4 weeks and one session every 2 weeks. The patient presented a dramatic improvement of the clinical picture; at first the number of daily attacks significantly decreased and 18 days after beginning the treatment, the attacks stopped. At the moment, follow-up is set at 1 year: our patient is still performing HBOT every 15 days and the cluster period is still in remission.

Discussion This case underlines the importance of considering hyperbaric oxygen therapy as an alternative option in the treatment of cluster headache, especially in drug resistant patients with a chronic pattern. Other studies are necessary in order to assess the exact role of HBOT as a symptomatic or even preventive therapy of cluster headache and to define important parameters, such as duration and frequency of treatment.

Cluster headache during pregnancy: a therapeutical challenge

D. Cassano, A. Amato, G. D'Onofrio, M.R. Porcaro, A.M. Romano

Territorial Headache Centre, Distretto n. 60, ASL SA, Nocera Inferiore, Italy; e-mail: info@domenicocassano.it

Introduction We report a single case of a woman with episodic cluster headache (CH), whose attacks reappeared during the third trimester of an otherwise normal pregnancy. In the absence of definite guidelines for the treatment in such a case, many are the difficulties related to the appropriate choice of therapy.

Case report A 30-year-old woman, primipara, 28 weeks pregnant, was admitted because of severe headache diagnosed as typical CH: intense, repeated, unilateral painful attacks located around and behind the right eye, lasting between 30 and 60 min, from three to four per day, accompanied by ipsilateral autonomic symptoms (rhinorrhoea and lacrimation), at least one of them happening during her sleep. Similar attacks have been reported since the age of 18, happening generally every 2 years, lasting 10 days, always considered and treated as sinusitis. The patient was otherwise healthy and had no significant medical history. The clinical examination showed only a moderate edema of both legs. The brain MR imaging scan performed was normal.

Neither rest nor non-opioid drugs were able to reduce the pain. Opioid drugs were ineffective and caused an apparent reduction in baby motions which induced a stressful situation in the mother. Pure oxygen inhalation (95%, by mask for 3–5 min at the onset of the attack) had no effect on pain. At times we considered inducing early delivery.

Discussion The choice of treatment was based on careful evaluation between maternal benefit and potential risk to the fetus. Verapamil was prescribed in daily 360 mg doses for a short period of time and intranasal lidocaine application was proposed, since the patient refused sumatriptan injections. On the fourth day of verapamil treatment, the pain was considered by the patient as tolerable (reduction in both frequency and intensity) and it stopped on the seventh day. The delivery occurred on the due date without complications for the mother or baby. Clinical controls 3 months later proved normal with no recurrence of attacks.

Conclusions Rules to follow in CH during pregnancy [1]:

- detailed briefing about risks and safety of various treatment options;
- informed consent (most drugs in pregnancy are used off-label);
- regular pregnancy care, detailed fetal ultrasound from week 18;
- both the overall number of medications and the medication dosage kept as low as possible;
- close cooperation between headache centre, gynaecologist and a teratology information centre.

Treatment recommendations [1, 2]

- *For acute pain:* oxygen; sumatriptan subcutaneous or intranasal (first choice); lidocaine (second choice).
- *Prophylactic treatment:* verapamil (first choice); corticosteroids, gabapentin (second choice).

References

1. Juergens TP, Schaefer C, May A (2009) Treatment of cluster headache in pregnancy and lactation. *Cephalalgia* 29(4):391–400 (Epub 2009 Jan 19. Review)
2. Giraud P, Chauvet S (2008) Cluster headache during pregnancy: case report and literature review. *Headache* 49(1):136–139

A multimodal approach to chronic headache with symptomatic drug abuse

C. Piro

Ambulatorio Cefalee e Terapia del Dolore, AUSL/FG, Foggia, Italy;
e-mail: dottorepirocarmine@libero.it

Introduction The patient with chronic headache and symptomatic abuse often shows myofascial trigger points (TP) in the pericranial muscles. The myofascial pain could play a role in the pathogenesis of migraine because 75% of migraine patients have neck and cervical pain starting from C1, C2, C3. Improving the tension of the neck and shoulder muscles, the psycho-physical control and balance is also improved, making eventual pharmacological therapies more efficacious. The chronic headache patient also shows vegetative symptoms during the attack as well as in the inter-critical phase. The vegetative dysfunction contributes to nociceptor sensitiveness, peripheral and central allodynia, which represent the main cause of the insufficient therapeutic response. We present a holistic therapeutic approach based on reflex-therapeutic techniques both direct (T.P. dry needling blockage of neural therapy) and indirect, on the control over the neurovegetative response to nociception (B.G.S.) and on the strengthening of the serotonergic system. The management programme is completed by the control of the main triggering factors (cardiovascular, metabolic, alimentary, endocrine and triggers related to the psychic balance) and by the correction of structural inadequacies (visual, occlusive, podalic).

Case report We present the case of a 40-year-old woman, with a past history of episodic migraine since the age of 14 then spaced out over time with lesser severity, non-throbbing, forehead located headache. She began taking paracetamol daily, alternating it with opioids, with an initial partial improvement followed by a worsening of headache. At the baseline observation, the headache diary showed a chronic headache with symptomatic drug abuse. She also complained of sleep troubles, depression symptoms and memory impairment. The objective examination showed the presence of TP in the cervical muscles with difficulty in neck movements. Neurological examination was negative.

The therapeutic approach based on 8 B.P.T–B.G.S. manipulation sessions resulted in a 70% improvement of the existing headaches in terms of: frequency, severity and duration. Sleep and humour improved. She underwent a monthly recall therapeutic session. The results persisted in over a 1 year time period.

Discussion The evaluation of chronic headache patients with symptomatic overuse should always take into account muscular TP and vegetative dysfunctions. A therapeutic programme should be as holistic as possible to obtain a better and persistent therapeutic response. With this kind of management the therapeutic results in this case have remained stable over a 1 year time period.

Onabotulinumtoxina (BOTOX®) for chronic refractory migraine: preliminary data

L. Ruiz, D. Ferrandi, C. Prevost, M.L. Dell'Acqua, G. Ursino,
E. Ursino

Headache Centre, ASO Santi Antonio e Biagio, Alessandria, Italy;
e-mail: lruiz@ospedale.al.it

Materials and methods Five patients (2 males and 3 females) affected by chronic refractory migraine were treated with BOTOX® in our Headache Centre.

According to the PREEMPT clinical programme we injected 5 U of BOTOX® in 31 fixed sites of head and neck muscles every 12 weeks.

Results One patient underwent three injections, the others received two injections. Treatment was well tolerated: only one patient complained of neck and shoulder pain but its intensity decreased at every injection. No patient had motor side effects. As regards to efficacy the first patient showed an improvement of the headache frequency (–70%) and a higher response to the symptomatic treatment. Another

patient was pain-free for 2 days after several years of daily headache. One patient reported an intensity reduction of daily headache. Headache was unchanged in two patients.

Conclusions Our very preliminary experience with BOTOX® treatment for chronic migraine shows that this approach is safe and well tolerated. Collection of data is still in progress but the first results seem encouraging.

Psychotherapy treatment strategies in chronic daily headache associated to drug abuse

R. Iannacchero¹, F. Corasaniti¹, U. Cannistrà¹, G.B. De Sarro²

¹Headache Research Centre, Regional Hospital Pugliese-Ciaccio, Catanzaro, Italy; ²Clinical Pharmacology, University Magna Grecia, Catanzaro, Italy; e-mail: rosarioiann@tiscali.it

Introduction It is well known that the chronic use of analgesics induces headaches. The abuse of painkiller drugs is a common problem among migraine patients. It is characterised by a reported increase in the frequency and intensity of pain attacks, inducing periodic headache to transform into a chronic daily headache (CDH). Treatment can be carried out in an outpatient setting, but often patients require hospitalization to help them discontinue drug abuse.

Patients and methods We report the results obtained from two groups of CDH patients with drug abuse evolving from atypical migraine. Patients were hospitalized for drug withdrawal and then followed regularly in order to determine clinical improvement after withdrawal. The first groups were studied from September 2009 to February 2011; Group A (15 subjects) was treated by means of pharmacological prophylactic therapy; Group B (7 subjects) was treated by means of pharmacological therapy and assisted psychotherapy training behaviour. A statistically significant improvement was found in both groups, with a reduction in pain total indexes, days of headache/month and decrease in analgesics consumption. This improvement was maintained at 1-year follow-up.

Discussion At present it is impossible to identify differences between the two treatment groups, pharmacological versus pharmacological and behavioural therapy: assisted psychotherapy training does not seem to favour a better resolution of drug abuse. Adequate prevention may be obtained by educating patients and their families on the risk of analgesic drug abuse, by means of suitable prescription and information on the side effects, as well as through close clinical monitoring of changes in headache patterns and drugs used.

Efficacy of combined therapy with LMWH and anti-hypertensive therapy for control of hemorrhagic risk in dural sinus thrombosis. a case report

G. Arosio¹, A. Mandelli¹, D. Rossi¹, A. Russo¹, M. Galbussera², P. Merlo¹

¹U.O. of Neurology, Headache Centre, Humanitas Gavazzeni, Bergamo, Italy; ²Emergency Department, Humanitas Gavazzeni, Bergamo, Italy; e-mail: gianpiero.arosio@gavazzeni.it

Introduction Headache is the most frequent but least specific symptom of venous sinus thrombosis, being present in about 90% of patients. This condition might be a consequence of coagulation disorders, infections and head injuries. The use of anticoagulant therapy

is under discussion, especially when thrombosis is associated with traumatic hemorrhages and hypertension.

Materials and methods We report the case of a 53-year-old man observed in our Emergency Department suffering from hypertension undergoing anti-hypertensive therapy and presenting a very severe headache for more than 12 h. He reported a previous head injury. The neurological examination was normal. The CT brain scan showed an irregular density in the left frontal region, compatible with a haematoma. The brain MNR demonstrated a wide frontal left cortical—subcortical hemorrhage with barrier damage. Moreover, it showed a more limited cortical haematoma in the temporal—polar region due to sub-acute damage. Finally, it showed a millimetric subdural haematoma in the right frontal, temporal and parietal region. The angio-magnetic resonance imaging excluded arteriovenous malformations but showed a partial left venous sinus thrombosis. Low—molecular—weight heparin (LMWH) started to be administered. The patient's headache completely receded with the normalization of pressure values.

Results The presence of venous secondary circles to the angio-magnetic resonance imaging and the uncomplete recanalisation after a 20-day treatment with LMWH demonstrate that venous sinus thrombosis was already present. The complete recovery of symptoms was obtained by normalization of pressure values and by the reduction of right cerebral haematoma.

Conclusions Despite the morphological picture revealed a number of diseases each of which could cause headache, the normalization of blood pressure and association with LMWH therapy ensured the resolution of the headache and a major risk of rebleeding. The patient was not treated with anticoagulant therapy, which would have exposed him to an elevated increased risk of hemorrhage, because we considered the venous thrombosis as not being a certain recent event and probably not the only cause of the headache.

Evaluation of the analgesic effect of nabilone versus acetaminophen plus caffeine in an inflammatory pain model (tail flick test) in rats

M. Ciccarese, V. Ruggeri, M.M. Cainazzo, A. Ferrari, L.A. Pini

Headache and Drug Abuse Inter-Department Research Centre, University of Modena and Reggio Emilia, Modena, Italy; e-mail: cainazzo.michela@policlinico.mo.it

Background Nabilone is a synthetic cannabinoid with a potent agonist effect on CB1 cannabinoid receptors, involved in regulation of nausea, vomiting, appetite, movement and pain. Several clinical trials confirm the effectiveness of nabilone in treating anxiety and pain associated with fibromyalgia or multiple sclerosis. Nabilone, in man, shows its analgesic/anti-inflammatory activity, and its modulation of allodynia without having significant psychotropic effects. Modification of the endogenous cannabinoid system has been found in animal pain models, inflammation and neurological disease. Anandamide and cannabidiol are weak agonists of TPVR1 receptors, normally activated by noxious physical/thermal stimuli or inflammatory hyperalgesia [1].

Objective The aim of our study was to evaluate the effect of nabilone and a combination of acetaminophen plus caffeine in acute and chronic treatment on hyperalgesia induced by glyceryl trinitrate (GTN), using tail flick test in rats. We choose glycerol trinitrate as the nitric oxide (NO) donor; infusion of NO induces delayed headache in migraineurs and activity of neurons in the spinal trigeminal nucleus [2].

Methods Adult male Wistar rats were treated, in acute, with nabilone (2.5 mg/kg p.o.), acetaminophen plus caffeine (400 mg/kg p.o. + 52 mg/kg p.o.); and in chronic (8 days) with nabilone (1 mg/kg p.o.), acetaminophen plus caffeine (200 mg/kg p.o. + 26 mg/kg p.o.), or vehicle, 1 h before the i.p. injection of GTN (10 mg/kg). Tail flick test was performed during acute treatment, 2–4 h after injection of GTN; during chronic treatment after a period of 8 days. The test was conducted with a tail flick device that used a 375-W movie light focused on the rat's tail (2–3 cm from the tip) by means of a condenser lens positioned below the light source. The latency time (s) was evaluated as the time between the beginning of test and the deviation of tail. The highest execution time to avoid tissue damage was 15 s.

Results The treatment with nabilone increased the latency time, during tail flick test vs controls, in fact, the latency time was 15 ± 0.8 and 10 ± 0.5 s, respectively, in acute and chronic treatment; rats treated with acetaminophen, 400 or 200 mg/kg p.o. plus caffeine 52 or 26 mg/kg p.o., respectively, in acute and in chronic administration, did not show changes versus controls (2.7 ± 0.3 s; ANOVA and Bonferroni's test; $p < 0.05$).

Conclusions The data support the efficacy of nabilone in the management of acute and chronic pain. Our main interest is to focalize its use in chronic headaches, providing a novel target for an innovative therapeutic approach.

References

1. Basavarajappa BS (2007) Neuropharmacology of the endocannabinoid signalling system-molecular mechanisms, biological actions and synaptic plasticity. *Curr Neuropharmacol* 5(2):81–97
2. Dieterle A, Fisher MJ, Link AS et al (2011) Increase in CGRP- and n NOS-immunoreactive neurons in the rat trigeminal ganglion after infusion of an NO donor. *Cephalalgia* 31(1):31–42

New drugs for prophylaxis of cluster headache: three cases effectively treated with levetiracetam

A. Palermo¹, V. Raieli², A. Puma¹, G. Cosentino¹, G. Giglia¹, B. Fierro¹, F. Brighina¹

¹Departimento di Biomedicine Sperimentali e Neuroscienze Cliniche (BioNeC), Università di Palermo, Palermo, Italy; ²U.O. di Neuropsichiatria Infantile, P.O. G. Di Cristina, Palermo, Italy; e-mail: fbrighina@unipa.it

Introduction Cluster headache (CH) is one of the most severe and debilitating primary headache syndromes consisting of recurrent attacks of short-lasting excruciating pain accompanied by signs of autonomic dysfunction. The pathophysiology of this condition is not well understood. Current thinking is that the pain and the autonomic symptoms arise, respectively, as a result of the activation of the trigeminal nerve and craniofacial parasympathetic nerve fibres as a consequence of the pathological activation of the trigemino-autonomic brainstem reflex. Here, a relevant role is likely played by neurotransmitters, like glutamate and CGRP, whose action is mediated and regulated by voltage gated calcium channels (VGCCs) [1]. Interestingly, verapamil that affects calcium channels activity is very effective and represents the first choice drug in CH prophylaxis. Levetiracetam (LEV) is an antiepileptic drug that affects activity of calcium channels significantly reducing N- and P/Q-type high-voltage-activated (HVA) Ca^{2+} currents [2].

Case reports We describe three patients with chronic CH refractory to verapamil, lithium and topiramate, effectively treated with LEV. LEV was started at 500 mg daily and increased by 500 mg every 3 days until the maximum dosage of 2,000 mg (1,000 mg bid). In all

patients CH attacks progressively reduced until complete resolution after 30–45 days. LEV was well tolerated (mild somnolence was the only adverse event reported, especially in patients 2 and 3).

Conclusions To our knowledge this is the first report about efficacy of LEV in the prophylaxis of CH. If other studies in a larger patient sample will confirm these results, we will have a new option for the treatment of this severe and sometimes incapacitating condition.

References

1. Xiao Y, Richter JA, Hurley JH (2008) Release of glutamate and CGRP from trigeminal ganglion neurons: role of calcium channels and 5-HT₁ receptor signalling. *Mol Pain* 4:12
2. Madeja M, Margineanu DG, Gorji A et al (2003) Reduction of voltage-operated potassium currents by levetiracetam: a novel antiepileptic mechanism of action? *Neuropharmacology* 45:661–671

Botulin toxin type A for chronic daily headache: a retrospective cohort study

C. Cesaretti¹, S. Lori¹, F. Pinto¹, F. De Cesaris², P. Geppetti², S. Benemei²

¹Centro di Riferimento Regionale di Chemodenervazione (CRRC), SOD Neurofisiopatologia, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; ²SOD Centro Cefalee e Farmacologia Clinica, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; e-mail: pierangelo.geppetti@unifi.it

Introduction Chronic daily headache (CDH), a heterogeneous group of disorders including headaches not related to other illness and occurring more than 15 days per month, is often associated with relevant disability, including, among the most frequent conditions, chronic migraine (CM) and medication-overuse headache (MOH). CDH affects approximately 4% of the general population worldwide. Moreover, up to 0.5% of patients with CDH has severe headaches on a daily basis. For some years botulin toxin type A, a focally administered neurotoxin, has been studied as a prophylactic treatment for migraine and recently, in PREEMPT 1 and 2 trials, onabotulinum-toxinA (BOTOX[®]) was found effective in CM and particularly in MOH. In December, 2009, Allergan Limited applied to the UK Medicines and Healthcare Products Regulatory Agency for an extension of the licence for BOTOX[®] to include an indication for the prophylaxis of headaches in adults with chronic migraine, which was eventually approved in July, 2010. US Food and Drug Administration authorized BOTOX[®] for chronic migraine in October 2010. In Italy BOTOX[®] has not yet been authorized for this condition and its off-label utilization is currently the only possibility in headache patients.

Methods and materials We retrospectively reviewed clinical charts of patients with CDH not satisfactorily responding to pharmacological treatment who, after signing informed consent, were screened to receive the off-label treatment with BOTOX[®] in AOU Careggi between 2009 and May 2011.

Results Twenty-three patients, 85% women, mean age 47 years (95% CI 43–56) were treated as already described by Blumenfeld et al. [1]. At baseline eight patients had tension-type headache (TTH), six patients had migraine without aura, five patients had both TTH and migraine (4 without aura, 1 with aura) and the remaining four patients had not better specified CDH. Furthermore, all patients could be diagnosed with MOH. Five patients underwent only the preliminary visit and were not treated. Eighteen patients were treated. Among them, nine patients reported a persistent good response to BOTOX[®] treatment, with a decrease in the intensity and/or frequency of attack

and/or a decrease in analgesic consumption. Three patients reported a non-persistent response to BOTOX[®] treatment, while six patients reported no change in their headache frequency or intensity.

Discussion Limitations linked to the retrospective nature of our study and the short follow-up period undermine the external validity of our observation. However, the data reported show clinical amelioration in approximately 50% of patients treated, regardless of their headache type.

Conclusions BOTOX[®] could represent a therapeutic useful treatment for a relevant number of patients affected by CDH. However,

prospective well-powered studies are needed to assess its real clinical value and to possibly identify the type of patients who would better benefit from the treatment, in order to maximize BOTOX[®] cost-effectiveness.

Reference

1. Blumenfeld A, Silberstein SD, Dodick DW et al (2010) Method of injection of onabotulinumtoxinA for chronic migraine: a safe, well-tolerated, and effective treatment paradigm based on the PREEMPT clinical program. *Headache* 50(9):1406–1418

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