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ABSTRACT BOOK**

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Outcome of vitamin C supplementation on lead-induced apoptosis in adult rat hippocampus

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Background Lead (Pb), due to its numerous industrial applications has caused widespread pollution of the environment. One principle target for lead in the human body is the central nervous system (CNS). Research has shown however that the toxic effects of lead can be moderated by antioxidant agents such as vitamin C.

Objective To investigate the protective effects of vitamin C supplementation against lead induced apoptosis in the adult male rat hippocampus.

Design, time and setting Animal experiment, including light and electron microscopic staining and western blot analysis, was performed in the College of Medicine, Iran University between December 2007 and April 2009.

Materials Lead (Pb) was used for toxication and Vit C was used as an antioxidant drug and Bax and Bcl-2 were used as primary antibodies.

Methods Animals were divided into three groups; control, Lead treated, Lead + Vit C-treated group) rats. They treated for 7 days.

Main outcome measure At the end of treatment, blood Lead level was measured. Neuronal death was determined using light and electron microscopic staining and western blot analysis

Results Lead + Vit C treatment reduced neuronal apoptosis compared to Lead treated rats. There were decrease of Bax expression in the hippocampus of Lead + Vit C group compared to Lead group in western blotting. Changes in blood Lead level was not significant in three groups.

Conclusion The results suggest that supplementing essential nutrient vitamin C may prevent lead-induced apoptosis.

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Suboccipital neurostimulation in chronic headache: a prospective, randomized with cross over study

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Patients affected by chronic headache experience a significant reduction in quality of life. No effective treatments are today available for this condition. We performed a prospective, randomized study to evaluate safety and efficacy of bilateral suboccipital neurostimulation in patients with chronic migraine (CM) and medication overuse headache (MOH). Patients with CM and MOH were enrolled in a single Hospital headache Center by a neurologist with experience in headache. In a preliminary phase, after signed informed consent, stimulators (Medtronic Synergy Versitrel) were provisionally implanted as an external device. After 30 days, if attack frequency was reduced $\geq 50\%$, neurostimulator was subcutaneously implanted. Patients were randomized into treatment (ON stimulator) or control (OFF stimulator) groups. At week 4 cross-

over between groups was realized. The frequency and the intensity of headache as well as the amount of drug intake were registered on a standardized diary from three months before the implant until the end of follow-up. Quality of life was measured using a dedicated scale (SF_36 e MIDAS) at -3 0-1-3-6-12 months follow-up. 34 patients have been enrolled in this study. After 1 year follow-up our results demonstrate a significant reduction in headache frequency (56%) and intensity (from 7.8 to 5.8 in Visual analogic scale); drugs intake reduced (from 45 to 11 intakes for month) till then MOH changed in original primary headache (100% migraine without aura (1.1 ICHD-II); chronic migraine (1.5.1 ICHD-II) became too migraine without aura (1.1 ICHD-II). Adverse events were light and completely reversible.

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Wolff's extracranial vascular theory of migraine: a great story confirmed by the facts

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Objectives To clarify the role of extracranial vasodilatation in migraine, and to expose the distortions and misrepresentations in the literature concerning this subject.

Background There has over the years been a considerable amount of controversy over whether the vascular component of migraine pain arises from the intracranial or the extracranial vessels, or both. Some have even questioned whether vasodilatation actually plays a significant role in migraine pain, and have described it as an unimportant epiphenomenon. The controversy is an artificial one though, which has been generated as a consequence of misrepresentation of the facts in the headache literature.

Methods The literature on the subject is extensively researched for verifiable hard scientific data on the subject.

Results There have been blatant distortions in the literature with regard to the role of extracranial vasodilatation in migraine. There is a plethora of hard scientific evidence to show that extracranial vasodilatation is important in migraine.

Conclusions There have been significant distortions and misrepresentations in the literature, which have led many headache specialist to believe, erroneously, that extracranial vasodilatation is not important in migraine. The hard scientific evidence shows that

- (i) vasodilatation is indeed a source of pain in migraine,
- (ii) that this dilatation does not involve the intracranial vasculature,
- (iii) that the extracranial terminal branches of the external carotid artery are a source of pain in migraine.

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Endothelium dependent vasodilatation in migraine patients

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Although endothelial dysfunction might be an important feature involved in the pathophysiology of migraine, it has been

investigated only in a few studies. The obtained conflicting results did not provide definitive answer on the presence of endothelial dysfunction in migraine patients. We sought to explore flow-mediated dilatation (FMD) in migraine patients. By employing strict inclusion criteria we avoided the possible changes of FMD by confounding factors, that could produce previously obtained conflicting results. Forty-two patients with migraine (female 34, male 8) and twenty-one healthy subjects matched by gender and age were included. All patients had normal values of intima-media thickness of carotid arteries and did not have diseases known to affect endothelial function. FMD of brachial arteries were measured by using standard procedure. We did not find any difference in FMD between patients with migraine and healthy subjects ($p = 0.78$). Also no differences were found between group of healthy subjects, migraine with aura and migraine without aura ($p = 0.92$) nor between group of migraine with and without aura ($p = 0.76$). We found that FMD is not impaired in migraine patients, neither in those with nor without aura ($p > 0.05$). Thus, it could be convincingly concluded systemic endothelial function are not altered during the interictal period, but migraine could be associated with cerebral endothelial dysfunction.

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Orthostatic headache revealing multiple periradicular cysts

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Spontaneous postural headache was observed in a 49 years old woman. MRI of the brain showed a Chairi I like aspect of the posterior fossa but with a meningeal enhancement. The lumbar puncture pressure was lower than 5 cm of H₂O without cellularity. MRI of the spine cord revealed multiple epidural ectasia without proved CSF leak. The patient had no cutaneous or morphological aspect of Marfan disease or connective tissue disorder. She was successfully treated by an epidural blood patch.

Conclusion Our patient had orthostatic headache secondary to intracranial hypotension. MRI of the spine cord revealed multiple epidural ectasia without CSF leak.

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Prophylactic treatment of chronic tension-type headache with trigger points: comparison of Gabapentin and local injection of Depomedrol

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Introduction Chronic tension- type headache (CTTH) is one of the most common disorders affecting quality of life. Trigger points (TrPs)

play an important role as a causative factor. Gabapentin and Local injection of trigger points with corticosteroids are noted to be effective in prophylactic treatment of (CTTH).

Materials and methods We selected CTTH patients who had active trigger point in the head and divided them in two groups of Depomedrol and Gabapentin. Depomedrol was injected 10 mg per each TrPt up to total dose of 40 mg in each patient. Gabapentin was initiated with 200 mg/day and gradually increased to 300-600 mg daily.

Results Headache *Intensity* \times *Duration* index showed marked decrease in both groups. It was significantly lower in Depomedrol receiving patients at the end of first (368.13 ± 195.75 Vs 467.73 ± 203.09 , $P < 0.05$) and second months (165.44 ± 62.75 Vs 238.68 ± 81.39 $P < 0.05$). similar superiority was detectable for Intensity, Duration and Frequency of headaches.

Conclusion We found trigger point injection more potent in comparison to daily Gabapentin. This superiority was statistically significant after 4 weeks and continued up to 8th week. It should be noted that trigger point injection was more effective to decrease all aspects of headache including intensity, duration and frequency.

Keywords Chronic tension-type headache, Depomedrol, Trigger point, Gabapentin, Prophylactic

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Blood-patch: immediate effective remedy for headaches secondary to dura mater injury

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Objective The aim of this study was to evaluate if bed rest during 2 h in a supine posture is required to improve the efficacy of the blood-patch procedure.

Patients and methods Patients whose postdural puncture headache remained distressing 48 to 72 h after dural tap despite the use of stage II WHO painkillers were included in this prospective single center study lasted for a 2-year period. The patient's own blood injection in the epidural space was performed until discomfort or pain in the lumbar area occurred or was limited to 20 ml if no such sensation was observed. After blood had been injected, the patient was allowed to stand up as soon as desired, under close observation. The patient was then discharged to the ward for a 48 h follow-up.

Results Nine female and 12 male patients (age: 16-35 years) were included. Headache occurred after spinal anaesthesia in 16 cases, epidural analgesia for delivery in two cases and lumbar puncture by during neurological workup in three cases. Autologous blood volume injected was 20 ml in 19 patients and was reduced to 18 and 16 ml, respectively, in two patients due to lumbar pain. All blood-patches were technically uneventful and led to immediate headache relief, associated with a feeling of wellbeing and desire to stand up. The 48 following hours were without any incident and pain killers were no more needed.

Conclusion In this prospective study, blood-patch was mainly performed after spinal anaesthesia and was associated with a high rate success. This encouraging result suggests that recumbent position maintained for 2 h after the blood-patch is performed might not be necessary to obtain full efficacy.

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Complementary and alternative medicine (CAM) therapies for treatment of cervicogenic headache: a systematic review

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Objectives This systematic review is part of a large evidence-based comparative effectiveness report conducted under contract to the Agency for Healthcare Research and Quality (Contract No. 997392062), Rockville, MD, and funded by the National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, MD. The review compared effects of CAM therapies (acupuncture, manipulation, mobilization, and massage) in adults with neck or back pain.

Data sources MEDLINE, Cochrane Central, CINAHL, and EMBASE were searched up to 2009; unpublished literature was also searched.

Study selection For this review, randomized controlled trials (RCTs) reporting benefits/harms of CAM therapies for treatment of cervicogenic headache in adults (age ≥ 18 years) were selected. Trials reporting effects of CAM therapies on other types of headache (tension-type, migraine) were excluded. The selection of studies was not limited to English language.

Results and conclusions Since the final report of the review is expected to be published in July 2010, Results and Discussion sections for this abstract will be available for presentation at the 2nd European Headache and Migraine Trust International Congress in Nice (October 28-31, 2010).

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Alleviation of migraine, taurine and analogues in nutrition: a hope to cope

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Migraine headache is not a sudden happening. It is accumulative effect of deficiency symptom, toxin and its complex nature. Pathogenesis of migraine is not well understood, yet it is believed that neuronal hyper-excitation, cortical spreading depression, platelet activation and sympathetic hyperactivity are part of complexity. Besides neuro-chemical changes, bad life styles, also partial responsible for such happening. Hence migraine headaches are caused by a constellation of causes. It is recorded that chromo-pathological forms of magnesium depletion is involved in physiopathology of migraine. There is increasing evidence that magnesium and taurine are

complement to each other. Taurine, a sulfur amino acid has neurotransmission/ neuromodulatory role. For record in CSF, taurine has been noted to be high in migraine patients. Plasma taurine levels in patients with classic migraine are correlated negatively with severity of headache. The higher taurine level in CSF may be due to accumulation of taurine via transport to site of action and to participate in preventive measure. In mechanistic view such central taurine liberation during migraine crises may be due to spontaneous depolarization or defensive action of cerebral homeostatic processes. Metabolic platelet defect in migraine patient has been observed, with higher taurine platelet concentration during headache. It seems that taurine has a role in prevention of migraine. Another cause of migraine headaches is neurotoxin monosodium glutamates (MSG). It is believed that taurine neutralizes its effect. Dietary supplementation of magnesium and taurine has alleviating effect on migraine. To provide synergetic effect of both together, magnesium taurate has been found to be effective. Through no one can deny the role of pharmaceutical in therapy of migraine, yet nutritional intervention is a right choice for safe and effective solution to cope with bad life style. Hence supplementation of taurine alone or in combination of its derivatives may provide a hope.

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BI 44370 TA, An oral cgrp antagonist for the acute treatment of migraine attacks: results from a phase II study

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Objectives To assess efficacy and tolerability of BI 44370 in adult female and male patients during a migraine attack.

Background BI 44370 is a novel, orally available, calcitonin gene-related peptide (CGRP) antagonist being developed for acute treatment of migraine attacks.

Methods This was a randomized, double-blind, parallel-group, placebo and active-comparator controlled clinical trial. 416 patients aged 18 to 65 years with migraine with or without aura according to IHS criteria were randomised to BI 44370 TA 50 mg, 200 mg, 400 mg, eletriptan 40 mg or placebo, taken orally during a migraine attack with headache of moderate or severe intensity. The primary endpoint was the proportion of patients reporting pain-free at 2 h after dosing.

Results BI 44370 TA was effective and its effect was dose-dependent. The primary endpoint, pain free after 2 hours was reached by significantly more patients for the 400 mg dose of BI 44370 TA (20/73 = 27.4%) compared to placebo (6/70 = 8.6%, $p = 0.0016$). The 200 mg was numerically better than placebo (14/65 = 21.5%, $p < 0.035$) while the effect of 50 mg BI 44370 TA was similar to placebo (5/64 = 7.8%). Eletriptan 40 mg was superior to placebo (pain free rate 34.8%, $p = 0.0001$). Analysis of secondary endpoints supported the conclusion from the primary analysis.

During the treatment period 23 patients (11.4%) in the BI 44370 TA groups, 7 patients in the placebo group (10.0%) and 12 patients in the eletriptan group (17.4%) reported at least one adverse event (AE). Frequency of AEs was independent of the dose of BI 44370 TA.

Conclusion Proof of concept was shown in a dose dependent manner for BI 44370 TA in the acute treatment of migraine attacks. The incidence of AEs was low in all groups (<5%).

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Smell scores of patients with tension type headache

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Objective Smell scores of patients with migraine are different from normal individuals. Our aim was to investigate smell scores of patients with tension type headache (TTH) by applying short smell test battery of GATA Haydarpaşa (SSTB-GH).

Materials and methods In 2008, during a thesis study Neurology Department of Haydarpaşa Hospital of Gülhane Military Medical Academy established SSTB-GH which was composed of five smell samples (bananas, lemon, rose, mint, chocolate). Within the test the patient was ordered to smell each sample randomly with one minute break and to say the name of it. For each correct answer 1 point was given. Mean value of SSTB-GH for the normal individuals was determined as 3.35 ($p < 0.01$).

240 patients with TTH were admitted to the study. 148 female and 92 male patients' mean age was 27.4.

Results In patients with TTH mean SSTB-GH score was determined as 3.42 ($p < 0.01$) revealing that it was similar with the scores of normal individuals.

Conclusion Patients with TTH did not have different smell scores compared to normal individuals. This may help to explain why smell is not a usual triggering factor for TTH patients compared to the ones with migraine.

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Headache presentation and 1-year development in patients with transient ischaemic attacks: results from 'The Aarhus TIA Study'

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Introduction 262 consecutive patients with recent (≤ 31 days) transient ischaemic attack (TIA) were included in a 1-year prospective study, examining pre-existing headache and development of headache-related disability after TIA.

Methods 262 consecutive patients (M:144; F:118; Age; mean \pm SD: 64.1 \pm 14.0, range 19.8–94.0 yrs). Initial examination took place after median 2.5 days (25th, 75th percentiles: 0; 11) with clinical follow-up and questionnaires after 1 week, and telephone interviews after 3, 12 months. Based on questionnaires patients reported previous headache and present VAS headache at first visit (N = 262) and the HIT-6 scale was applied after 1 week (N = 248) and after 1 year (N = 220). Previous medical history was obtained and changes in medication and stroke/disability scales were assessed at each examination point. Patients underwent initial neurological examination, and assessment of BP, height/weight and paraclinical bloodtests,

MRC/CTC, ultrasonography of precerebral arteries/transcranial Doppler were performed (see Weitzel-Mudersbach et al).

Results 80.5% reported less than one week of headache in previous year, 8.6% less than 1 month and 10.9% had more than one month of headache during last year. HIT-6 score (from 36–78) was low after 1 week (38.6 \pm 6.7) and 1 year (38.9 \pm 5.8). After 1 week 92.3% had no or minor impact of headache and 7.7% moderate to severe disability, with similar figures after 1-yr (92.2% and 7.8%). No raised risk of headache disability was encountered during initial treatment with dipyridamol (prescribed to 4.8% or warfarin (3.6%), and no significant change in HIT-6 disability during ASA treatment (prescribed to 29.8%).
Conclusion After TIA there was no development of significant headache. Only 5% of men and 15% of women complained of initial and 1 year significant headache, which is less than expected in an age and gender matched population. It may be speculated whether TIA exposure moderates descending inhibitory/facilitatory nociceptive pathways.

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Psychopathologies in migraine and tension headaches

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Headaches present a persistent and significant clinical challenge, research shows that psychotherapeutic results are not always maintained over time and pain is unrelieved. The aim of the research was to find the underlying psychopathologies which are causing, maintaining and exacerbating headaches. After an initial pilot study on 19 patients this was carried out in two phases, in phase a 100 headache sufferers, age range 15–55 diagnosed with Migraine/ Tension Headaches were recruited. All under-went diagnostic clinical examination by the Psychiatrist, and only those who fulfilled the criteria of the (Ad hoc Committee for the Classification of the headaches (1962) were referred to the Clinical Psychologist for psychological assessment. Crown and Crisp Experiential Index, adapted version, Afaq & Najam (1992) clinically used in hospitals was utilized to assess psychological status, it has six sub scales: Depression, Free floating anxiety, phobia, somatic, obsession and Hysteria. Significantly higher levels of depressive psychopathology were found in headache patients. These subjects also scored higher on free floating anxiety, Hysteria and very high on somatic scales, keeping in view the above findings phase b a longitudinal study of 37 patients with chronic (reported) headaches was carried out using CCEI, the findings in both studies shed light to help headache patients and the clinicians to achieve effective management of headaches.

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Efficacy of effective management techniques

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Objectives To compare the efficacy of various modalities of headache treatment.

Method Headaches sufferers (N = 37) ages range 15–55 diagnosed with Migraine/Tension and Combined headaches recruited from hospitals, underwent diagnostic clinical examination. Those who met

criteria (Ad hoc Committee for the Classification of Headaches 1962) were referred to the clinical psychologist for assessment and treatment. Pre and post assessments using Interview, MPQ, Faces test, Rating scales, medication index and subjective report of pain were carried out. All participants underwent six weeks of intervention in their respective groups a Drugs, Drugs plus Psychotherapy, Acupuncture Relaxation, Training and Placebo. Significant differences were found among treatment groups, findings of the study showed that Drug plus Psychotherapy is superior to other interventions, but other modalities like Acupuncture, Relaxation and Placebo have beneficial results on outcome.

Conclusion These findings have important implications for future interventions. It is highly recommended that different modalities need to be integrated under one umbrella.

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A CK1 delta mutation in familial migraine with aura alters behavior related to migraine and brain physiology

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A mutant allele of the gene that encodes casein kinase 1 δ (CK1 δ T44A) was found to segregate with dominantly inherited migraine with aura and familial advanced sleep phase syndrome. Mice expressing CK1 δ T44A showed alterations in cortical spreading depression (CSD), cerebrovascular response, nociceptive behavior, and astrocyte signaling. CK1 δ T44A mice had a reduced threshold for CSD induction, increased frequency of CSD, and greater arterial dilation associated with CSD as compared with wildtype controls. CK1 δ T44A mice also showed significantly reduced thermal and mechanical nociceptive thresholds following administration of nitroglycerin, a compound known to induce a migraine-like headache and other migraine symptoms. Astrocytes from CK1 δ T44A mice showed increased spontaneous and evoked intra- and intercellular calcium signaling. These data show that a mutation in CK1 δ causes changes in multiple physiological mechanisms involved in migraine. Alterations in the function of CK1 δ may be a novel genetic basis for migraine with aura.

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A valve disorder which is seen more frequently among refractory migraine patients than normal individuals; mitral valve prolapsus

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Objective Our aim was to investigate cardiac disorders among refractory migraine patients and interpret the results.

Materials and methods 30 migraine patients were included to the study who had appealed for neurology polyclinic at Çanakkale Military Hospital. Age range was 26-32 and 17 were female. Within the study refractory migraine patients who had the disease at least for 10 years and were without cardiological symptoms were examined by cardiologist with pulmonary X ray graphy, ECG and transthoracic echocardiography. **Results** Mitral valve prolapsus (MVP) was found within 12 patients. **Conclusion** MVP which has the prevalence of %4-5 has been detected among %40 of our study group. This suggests refractory migraine patients also should be evaluated cardiologically.

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The peculiar diagnostic approach of migraine in patients with histrionic personality disorders

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Introduction Migraine (M) in patients with hysteria was reported by different authors, but their pathogenetic interaction remains unclear. M diagnosis, due to exclusively subjective criteria, is sometimes difficult to establish in histrionic personality disorders (HPD) associated with conversion disorders (CD) and somatoform disorders (SD).

Objectives Analysis of clinical features of M in HPD patients and the settlement of specific additional diagnostic support to increase the diagnostic certainty of M.

Methods The study included 31 female patients, average age - 41.8 years, referred to the Headache Center (HC) with a diagnosis of M. The M clinical diagnosis in the HC was based on the International Classification of Headache Disorders criteria (ICHD-2004). The HPD, CD, SD diagnoses were confirmed according to DSM-IV criteria. Additionally, we have practiced discussions with relatives concerning the patients' verbal and non-verbal behaviour, repeated discussions with patients about M history in different psychological context, and a detailed analysis of medical documentation.

Results All the patients met the criteria of HPD: 12 associated with CD, 19 - with SD. M was present in 25 patients (80.6%), 6 (19.4%) had tension-type headache. Four patients had episodic probable M, 7 - episodic M (3 with aura) and 14 - chronic M (4 with medication overuse). In 6 patients M attacks coincided with CD and SD exacerbation, usually within a psychogenic context.

Conclusions Headache, including migraine, in patients with HPD and other hysterical phenomena, raise diagnostic problems. The use of a larger diagnostic approach, parallel to ICHD-2004, considerably enhances the M diagnostic certainty.

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Ethno medicinal flora of North Western TARAI forests of Uttar Pradesh, India for headache and migraine

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India represents one of the mega biodiversity centers of the world. In India the North Tarai belt is next only to Eastern and Western ghats

due to its prosperous and distinctive flora including many species of medicinal plants, which may be a source for gainful exploitation of natural resources and ethnic culture. Geographically it covers the area from district Bahraich to Pilibhit. During the survey of study area fourteen plant species viz., *Abrus precatorious* L. (Ghoomachi, Fabaceae); *Acacia catechu* (L.) Willd (Khair, Leguminosae); *Allium sativum* L. (Lehsun, Liliaceae); *Amaranthus spinosus* L., *A. viridis* L. (Chauli, Amaranthaceae); *Citrus medica* L. (Nimbu, Rutaceae); *Clitoria ternatea* L. (Aparajita, Fabaceae); *Ipomea carnera* ssp *fistulosa* Mart ex choisy (Behaya, Convolvulaceae); *Leucas aspera* L. (Guma, Lamiaceae); *Mucuna pruriens* (L.) DC (Kewanch, Fabaceae); *Nyctanthes arbor-tristis* L. (Harshingar, Oleaceae); *Swertia chirayita* (Roxb ex Flem) Karsten (Chirayita, Gentianaceae); *Vanda tasselera* (Roxb.) Hook ex G. Don (Harjodi & Tarwari, Orchidaceae) and *Withania somnifera* L. Dural (Ashgandh, Solanaceae) were recorded by interviewing traditional herbalist, local healers, elderly men and women of the tribal society which were used as herbal medicines for the treatment of headache, sciatica, rheumatism, joint pain, dislocation and body pain .

Use of *Citrus medica* L., *Clitoria ternatea* L. and *Leucas aspera* L. were recorded to be the common plants used in severe headache. Leaf juice of *Citrus medica* is used as nasal drop in migraine and permanent headache. The root paste of *Clitoria ternatea* is applied on forehead to relieve headache. The root juice of *Leucas aspera* is put in to the nostril for relief in headache. The magical effect of these plants has been personally observed by the author. The phytochemical and clinical investigations of these plants are desirable for more uses and interesting results.

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Comorbidity of migraine with somatic diseases in a large population based study

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Context Migraine affects 11% of the adult population in the world and is a common complaint in all specialties and general practice. It is known to be comorbid with depression, anxiety and a small number of somatic diseases. Comorbidity with a variety of other somatic disorders is unknown. Comorbidity in migraine with aura (MA) and migraine without aura (MO) separately and its relation to sex are also largely unknown.

Objective To determine sex specific comorbidity of migraine and its subtypes MA and MO with a number of common somatic diseases.

Design Questionnaire sent to all Danish twins containing previously validated questions to diagnose migraine and its subtypes as well as questions regarding a number of somatic diseases. The twins are representative of the whole Danish population and were used as such in the present study.

Setting and participants Twins residing in Denmark and born between 1931 and 1982. Of 46,418 possible participants, 34,944

(75%) responded but only 31,865 were eligible due to missing data.

Main outcome measure Odds ratio for somatic disease in migraine and its subtypes.

Results A total of 21, 23 and 12 conditions were comorbid with migraine, MA and MO, respectively at $p < 0.001$. Comorbid diseases included previously documented diseases: asthma, epilepsy and stroke as well as new conditions: kidney stone, psoriasis, rheumatoid arthritis, osteoarthritis and fibromyalgia. Twelve conditions were significantly more comorbid with MA than MO. The difference between MA and MO was primarily seen in females. Significantly more women than men had comorbidities with regard to 11 of the diseases.

Conclusion A number of medical diseases were comorbid with self-reported migraine. MA had more comorbidities than MO and females more than males. Migraine occurs in 20-30% of several medical conditions. It should be diagnosed and treated along with the primary disease.

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Association between migraine, lifestyle and socioeconomic factors: population-based cross sectional study

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Objective To investigate whether sex-specific associations exist between migraine and lifestyle or socio-economic factors. We distinguished between the subtypes migraine with aura (MA) and migraine without aura (MO).

Setting and participants In 2002 a questionnaire containing validated questions to diagnose migraine and questions on lifestyle and socio-economic factors was sent to 46,418 twin individuals residing in Denmark. The twins are representative of the Danish population with regard to migraine and other somatic diseases and were used as such in the present study. 31,865 twin individuals aged 20 to 71 were included.

Results An increased risk of migraine was associated with lower level of schooling and education, retirement, unemployment, and smoking. A decreased risk of migraine was associated with hard physical exertion and regular intake of alcohol. Direct comparison between the subtypes showed that the risk of MA was lower than MO in subjects with lower education and weekly intake of alcohol whereas the risk of MA was higher than MO in unemployed or retired subjects. Direct comparison between sexes showed that the risk of migraine was lower for men than women in subjects who were lower educated, unemployed, or retired. However, the risk was higher for men than women in subjects with hard physical exertion, regular intake of alcohol, and body mass index greater than 25. Migraine subjects had lower self-rated health.

Conclusion Migraine was associated with several factors. Most associations such as lower education and job status were probably due to migraine while others such as smoking were risk factors for migraine. More targeted research is needed to evaluate these relations.

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Magnetic resonance imaging of craniovertebral structures: clinical significance in cervicogenic headaches

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Objective To investigate the relevance of morphological changes in the main stabilizing structures of the craniocervical junction in persons with cervicogenic headache (CEH).

Material and methods A case control study of 46 consecutive persons with CEH, 22 consecutive with headache attributed to whiplash associated headache (WLaH) and 19 consecutive persons with migraine. The criteria of the Cervicogenic Headache International Study Group (CHISG) were used for diagnosing CEH; otherwise the criteria of the International Classification of Headache Disorders (ICHD II) were applied. All participants had a clinical interview, and a physical and neurological examination. Proton weighted magnetic resonance imaging (MRI) of the craniovertebral junction, and the alar and transverse ligaments were evaluated blinded to clinical information.

Results The MRI of the craniovertebral and the cervical junctions, the alar and transverse ligaments disclosed no significant differences between those with CEH, WLaH or migraine. The site of CEH pain was not correlated with the site of signal intensity changes of the alar and transverse ligaments. In fact very few had moderate or severe signal intensity changes in their ligaments.

Conclusion MRI shows no specific changes of cervical discs or craniovertebral ligaments in CEH.

Keywords Cervicogenic headache, Alar ligaments, Transverse ligaments, Craniovertebral junction, Cervical junction, MRI

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Cases intractable headache: pathogenic research and new therapy

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Patients suffered from 20-49 years history of intractable headache with sleeping or depression disturbances. They have not any improvement after many years' pharmaceutical therapy. After 8-10 times' Modern Acupuncture (MAC) cure, their headache disappeared. The result of this study suggests that headache usually occurs in patients with Cervicobasilar Part (CBP) injury combining with social, mental and hormone disturbances. The essential problems of headache are possibly formed by CBP biological structure injury to block cervical nerves roots in C1-C3 level which innervate on the head cutis. Because there are no algesireceptors in the brain tissues like in other organs, so that the headache is only the pain on the derma and subcutaneous tissues of the head. The clinical therapy will be

focused on the CBP to achieve satisfied result. MAC is a new acupuncture set upon human anatomy and Neuroanatomy that taking on the column vertebrae near the radix nerve where respondent to all of organs, body or extremities. The new headache pathogen and therapy have been proposed in this paper.

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Recurrent neck pain and headaches in preadolescence associated with mechanical dysfunction of the cervical spine

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Background Recurrent neck pain and/or headaches in adults can be initiated and exacerbated by aberrant cervical spinal mechanics including forward head posture, reduced cervical range of motion, trigger points in cervical musculature and cervical joint dysfunction. The contribution of dysfunctional mechanics in the cervical spine to recurrent neck pain and/or headaches in children is unknown.

Objectives To establish if there were differences in the cervical biomechanics in preadolescents who had recurrent neck pain and/or headaches as compared to those who were symptom-free.

Methods In a cross-sectional observational study, Swedish preadolescents (n = 131) completed a questionnaire and 110 students were examined to establish head posture, active cervical range of motion, trigger points in cervical paraspinal musculature, and passive cervical joint functioning. Parents completed an informed consent form which had additional questions. Data were analyzed using descriptive statistics.

Results Recurrent neck pain/ headaches was reported by 40% (n = 52). There was an even gender distribution of preadolescents with neck pain/headaches and an increase in prevalence as students transitioned into adolescence as well as a gender shift with female preponderance. Joint dysfunction in the lower cervical spine was a significant finding associated with neck pain and/or headache in those pre-adolescents with symptoms. More than half of all the students examined had forward head posture, upper cervical joint dysfunction and trigger points the suboccipital muscles. There was significant discrepancy between parental report and self-report of both trauma and frequency of symptoms.

Conclusions Neck pain/headaches in preadolescents were significantly associated with cervical joint dysfunction. Children and parents may present different historical information. There were altered biomechanics in the upper cervical spine in the majority of the preadolescents examined. Future studies should follow a cohort of preadolescents through adolescence to investigate if this is a factor in the increasing prevalence of neck pain/headaches seen in the adolescent population.

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Precipitating and relieving factor of migraine in 200 Iraqi Kurdish patients

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Objectives To study precipitating and relieving factors of migraine headache in a group of Iraqi Kurdish patients including the effect of

fasting in Ramadan, and to estimate the percentage of family history of migraine.

Patients and methods A review of a series of 200 migraine case from different parts in Kurdistan region in the North of Iraq attending the out-patient Neurology clinic at Rizgary Teaching Hospital and a private Neurology clinic at Erbil City was carried out during the period between October 2007 to May 2008. The precipitating factors and relieving factors for migraine headache were registered and tabulated to be compared with others. Case definition of migraine was according to the International Headache Society (IHS) criteria.

Results 33% of patients were at the age range 30–39 years. 40.5% of patients had first attack at the age between 20–29 years. Stress or psychological upset is the commonest triggering factor (80%), followed by increasing physical activity (68%), change in whether (65.5%), relation to fasting (65%). Fasting in Ramadan was a triggering factor for headaches in 65% of patients. No significant association have been found with any of the triggering factors in regarding to sex difference. Relieving factors of migraine in our studied sample were NSAID in 50% of patients, and sleep (45.5%). 61% of the studied sample had positive family history of migraine, 32.5% of them mentioned maternal history of migraine.

Conclusions Psychological upset and stress was and excessive physical activity were the commonest triggering factors of migraine headache, while NSAID was the commonest relieving factor of migraine in this population, family history is present in 61% of migraine patients which is mostly of maternal root.

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Effects of microiontophoresed calcitonin gene-related peptide (CGRP) and CGRP-antagonists on trigeminothalamic transmission

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Objectives Calcitonin gene-related peptide (CGRP) receptor antagonists are effective in treating acute migraine. The main site of antinociceptive action of CGRP receptor antagonists is likely to be within the central nervous system. However, this was only demonstrated at the level of second order neurons within the trigeminocervical complex. To test the effect of CGRP receptor antagonists at further sites within the trigeminovascular nociceptive pathway we have performed electrophysiological recordings from neurons in the venteroposteromedial (VPM) nucleus of the thalamus of rats. We investigated the effect of microiontophoresed CGRP and CGRP receptor antagonists on cell firing evoked by electrical stimulation of the superior sagittal sinus (SSS) or by microiontophoresis of L-glutamate.

Methods Male Sprague Dawley rats ($N = 7$) were anesthetized with pentobarbitone (60 mg kg^{-1}) and cannulated for anesthesia, physiological monitoring and drug administration. Thalamic cells ($N = 13$) with facial receptive fields and trigeminocervical input, identified by electrical stimulation of the SSS, were recorded using electrophysiological techniques. We tested the effect of microiontophoresed CGRP and the CGRP receptor antagonists olcegepant and CGRP8-37 on neuronal firing in the VPM, evoked by electrical stimulation of the SSS or microiontophoresed L-glutamate.

Results Microiontophoresis of control, CGRP and olcegepant had no effect on neuronal firing, evoked by SSS-stimulation or L-glutamate evoked. In comparison to control, a 14% reduction of cell firing was

seen when CGRP8-37 ejection was tested on SSS-stimulation induced firing ($t_{21} = -2.397$, $P < 0.05$) or L-glutamate evoked cell firing in the VPM ($t_{16} = -2.173$, $P < 0.05$). Although microiontophoresis of CGRP had no effect on L-glutamate evoked firing, CGRP did increase the background-activity ($t_{13.1} = -2.904$, $P < 0.05$) by 25%.

Conclusion This is the first report showing local CGRP-mediated effects on thalamic nociceptive trigeminovascular neurons, which further extends the potential site of action of this novel class of anti-migraine treatments.

Conflict of interest Oliver Summ received a fellowship by the European Federation of Neurological Societies and fellowship by MSD.

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Immunological profile of herpes associated migraine: pathogenesis and treatment

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Cytokines may be a cause of the migraine pain: in fact a high levels of chemokines could stimulate the activation of trigeminal nerves, the release of vasoactive peptides or other biochemical mediators, such as nitric oxide, and then to cause inflammation. Herpes virus switch from latency to re-activation within trigeminal ganglia could be also trigger of trigeminal activation, inflammation and pain release. In fact, it appears that HSV replicates in sensory neurons after primary and/or secondary infection, inducing cell-cell spread in neuronal ganglia without causing lyses. If the replication process ensues, a particular gene expressed by the virus becomes active vs. or inactive (which balances with perpetuating LAT). At the earliest stage of recurrence, there is already an intense inflammatory response with inflammatory cytokines release. Herpes virus re-activation themselves or together with cytokines release may be a cause of the migraine pain: could stimulate the activation of trigeminal nerves, the release of vasoactive peptides or other biochemical mediators, such as nitric oxide, and then to cause inflammation. In parallel, pain syndrome cause to release of “pain hormone” - substance P, which influence on immune cells. 20 patients with migraine had been investigated by PCR-analysis. HSV-1 had been found in 100% cases. In our study, Substance P, is added in 3-dimensional collagen matrix, reduces migration activity of CD16 + cells. The stimulatory effect on natural killer cells cytotoxicity had been noted. It is necessary to underline, that all mechanisms of migraine pathogenesis, had been previously discovered and discussed, can be combined via HSV-associated theory.

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Protective effects of flunarizine on cerebral mitochondria injury induced by cortical spreading depression under hypoxic conditions

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Cortical spreading depression (CSD) may induce potentially harmful mitochondrial lesions under hypoxic conditions. Flunarizine may have a protective effect on cerebral mitochondria. We established a

rat CSD model and explored whether cerebral mitochondria injury is induced by CSD under normal and hypoxic conditions and whether flunarizine has a protective effect on cerebral mitochondria.

Seven randomly selected Groups of SD rats received as follows: no intervention (control Group I); 1 M NaCl injections to the left parietal cortex (Group II); 1 M KCl injections to the left parietal cortex (Group III); intraperitoneal flunarizine (3 mg/kg) 30 min before KCl injections (Group IV); 14% O₂ inhalation for 30 min before NaCl injections (Group V); 14% O₂ inhalation followed by KCl injections (Group VI); 14% O₂ inhalation and intraperitoneal flunarizine followed by KCl injections (Group VII). Following treatment, the rats were sacrificed by decapitation and brains removed for the analysis of number, amplitude, and duration of CSD, mitochondria transmembrane potential (MMP) and oxidative respiratory function.

The duration of CSD was significantly longer in the Group that received additional oxygen than KCl alone. However, the number and duration of CSD in the Group that received flunarizine in addition to oxygen was significantly lower than the Group that received oxygen and KCl. Similarly, MMP in Group VI was significantly lower than in Group III, and MMP in Group VII was significantly higher than in Group VI. State 4 respiration in Group VI was significantly higher than in Group III and State 3 respiration in Group VII was significantly higher than in Group VI. Respiration control of rate in Group VII was also significantly higher than in Group VI.

Aggravated cerebral mitochondria injury might be attributed to CSD under hypoxic conditions. Flunarizine can alleviate such cerebral mitochondria injury under both normal and hypoxic conditions.

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Modulation of cortical spreading depression and trigeminal nociception by nociceptin/orphanin FQ

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Migraine is a primary vascular headache which is characterized by recurrent moderate to severe throbbing headache. Activations of cerebral cortex and trigeminal nociceptive system are essential steps in pathogenesis of migraine. The control of these systems is extremely complex and involves several chemical messengers, both small molecule transmitters and peptides. Nociceptin/orphanin FQ (N/OFQ) is known as a neuropeptide with close similarity to the opioid peptides, while its effect in migraine is not fully understood. In this study, we will investigate whether there is a modulation of N/OFQ in the trigeminal nociception induced by cortical spreading depression (CSD). The CSD is an electrocorticographic phenomenon which is believed to underlie the transient neurological deficit observed during the aura phase of migraine. Intrathecal administration of N/OFQ significantly increased amplitude, number of peaks and area under the curve (AUC) of CSD. Additionally, expression of TRPV1 in the trigeminal ganglia (TG) and number of Fos-immunoreactive neurons in the trigeminal nucleus caudalis (TNC) evoked by the CSD were facilitated. N/OFQ modulation is likely to intensify the trigeminal nociception by increasing cortical excitability. Orphan opioid receptor-like 1 (ORL-1), the receptor of N/OFQ, may be a future target for pharmaceutical treatment of migraine.

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Are CGRP antagonists inherently slowly acting drugs in migraine?

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Migraine patients want to be pain free and a quick onset of action. Two new CGRP antagonists, olcegepant and telcagepant, have been studied in migraine. After i.v. olcegepant the maximum effect was observed after 60 min (2.5 mg) and 120 (5 mg). This is rather slow for an intravenously administered anti-migraine drug. For oral telcagepant 300 mg the maximum effect (as judged from the difference to placebo) was about 4 hours.

Compared to rizatriptan 10 mg the effect of telcagepant 300 mg up to 2 hours was slower in onset of action, with sumatriptan 100 mg in between. At 1 to 2 hours rizatriptan 10 mg (40%) was superior to telcagepant (26%). (p < 0.01).

There are thus some indications from both studies of the CGRP antagonists, olcegepant and telcagepant, that there is compared to other drug a somewhat slow onset of action of CGRP antagonists in migraine. If correct, this could indicate that for this treatment principle, CGRP antagonism, the action takes place in a so-called hypothetical "deep compartment".

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Headache, migraine and cardiovascular risk factors: the hunt population-based study

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Background Migraine with aura (MA) has been found to be a risk factor for cardiovascular disease including ischaemic stroke and myocardial infarction. Studies have also reported a higher prevalence of unfavourable cardiovascular risk factors among migraineurs, but results have been conflicting as to whether this is restricted to MA or also holds true for migraine without aura (MO). The aim of the current study is to examine the relation between headache and cardiovascular risk factors in a large scale cross-sectional population-based study.

Methods A total of 51,383 subjects (age ≥ 20 years) completed a headache questionnaire in the population-based Nord-Trøndelag Health Study in Norway 1995-1997 (HUNT 2). Framingham 10-year risk for myocardial infarction and coronary death could be calculated for 46,482 (90.5%) of these. Parameters measured were blood pressure, body mass index, serum total and high-density lipoprotein cholesterol.

Results Compared to controls Framingham risk score was elevated in non-migraine headache sufferers (OR 1.17, 95% CI 1.09-1.25), migraineurs without aura (OR 1.16, 95% CI 1.06-1.27) and most

pronounced among migraineurs with aura (OR 1.53, 95% CI 1.21–1.94). Framingham risk score increased with headache frequency for all headache types. For non-migrainous headache and MO the increased risk was accounted for by unhealthy lifestyle factors, while such factors did not explain the elevated risk associated with MA.

Conclusions Both MA, MO and non-migrainous headache are associated with an unfavourable cardiovascular risk profile, but different mechanisms seem to underlie the elevated risk in MA than in the other headache types.

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Onabotulinumtoxin-A treatment reduces adverse impact of chronic migraine (CM): PREEMPT clinical program HIT-6 results

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Objective Assess effect of treatment with onabotulinumtoxinA (BOTOX[®]) on headache impact in patients with chronic migraine (CM) (ICHD-II migraine and ≥ 15 headache days/month).

Background CM is a burdensome neurological disorder characterized by pain, disability, and activity limitations. Reducing CM impact is an important treatment goal.

Methods PREEMPT program included 2 phase III multicenter, double-blind, placebo-controlled studies evaluating efficacy and safety of onabotulinumtoxinA in CM. HIT-6, a validated headache-impact measure, was administered at baseline and every 4 weeks. Each of the 6 individual questions score from 6–13, resulting in a total HIT-6 score ranging from 36–78, with higher scores reflecting greater adverse impact. We computed change in HIT-6 relative to baseline at each timepoint and present pooled data through end of the 24-week, double-blind phase of these studies. Negative change scores reflect reductions in headache impact.

Results 1384 subjects included in pooled analyses (n = 688 onabotulinumtoxinA; n = 696 placebo). Mean baseline scores were comparable between treatment groups (all $P = \text{NS}$). Statistically significant (all $P < 0.001$ by Wilcoxon rank-sum test) between-group differences favoring onabotulinumtoxinA over placebo were observed for change from baseline in total HIT-6 score and all 6 individual question scores at all visits throughout the double-blind phase, except question 3 at Week4. Baseline and mean change from baseline scores (SD) at Week24 for onabotulinumtoxinA and placebo, respectively: Q1-Pain severity when having headaches: BL = 10.7(0.80)/10.7(0.89), Week24 = -0.6(1.30)/-0.2(1.12); Q2-Limit in ability to do usual daily activities: BL = 10.6(0.90)/10.6(0.94), Week24 = -0.6(1.33)/-0.2(1.11); Q3-Wish to lie down when having headaches: BL = 11.5(1.18)/11.5(1.16), Week24 = -0.7(1.54)/-0.4(1.35); Q4-Too tired for work/daily activities due to headache past 4 weeks: BL = 10.6(0.95)/10.6(1.02), Week24 = -0.9(1.53)/-0.4(1.39); Q5-Irritation because of headache past 4 weeks: BL = 11.3(1.29)/11.2(1.24), Week24 = -1.2(1.92)/-0.6(1.64); Q6-Limit in ability to concentrate past 4 weeks: BL = 10.8(0.85)/10.8(0.94), Week24 = -1.0(1.54)/-0.4(1.33); Total HIT-6 score: BL = 65.5(4.05)/65.4(4.32); Week24 = -4.8(7.04)/-2.4(6.09).

Conclusions Treatment of CM with onabotulinumtoxinA is associated with reductions in headache impact as measured by HIT-6.

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Conflict of interest Dr. Lipton receives research support from the NIH [PO1 AG03949 (Program Director), PO1AG027734 (Project

Leader), RO1AG025119 (Investigator), K23AG030857 (Mentor), K23NS05140901A1 (Mentor), and K23NS47256 (Mentor)], the National Headache Foundation, and the Migraine Research Fund; serves on the editorial boards of Neurology and Cephalalgia and as senior advisor to Headache, has reviewed for the NIA and NINDS, holds stock options in Neuralieve Inc. and Minster Inc; serves as consultant or has received honoraria from: Allergan, Autonomic Technologies, Boston Scientific, Bristol Myers Squibb, Eli Lilly, Endo, GlaxoSmithKline, Minster, Merck, Nautilus Neuroscience, Neuralieve, Novartis, and Pfizer.

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Onabotulinumtoxin-A treatment improves quality of life in patients with chronic migraine (CM): MSQ results from PREEMPT

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Objective Determine effect of onabotulinumtoxinA (BOTOX[®]) treatment on health-related quality of life (HRQoL) in adults with CM (ICHD-II migraine and ≥ 15 headache days/month).

Background CM is a primary neurological disorder with significant physical/emotional disability, reduced HRQoL, and interrupted workplace productivity/social activities. The Migraine-Specific Quality of Life Questionnaire (MSQ) measures how migraines adversely affect patients' HRQoL and daily performance over the preceding 4 weeks.

Methods The PREEMPT clinical program included 2 phase 3, 24-week double-blind, placebo-controlled, multicenter studies evaluating efficacy and safety of onabotulinumtoxinA in CM with injections of onabotulinumtoxinA or placebo at baseline and week 12, followed by 32-week, open-label phase of 3 injection cycles. HRQoL, measured by 14-item MSQ v2.1, across 3 domains (Role-Restrictive, Role-Preventive, Emotional-Functioning) was obtained at baseline and every 12 weeks. Item scores range from 1 to 6, with lower scores reflecting worse impact of CM on HRQoL. A positive change from baseline reflects HRQoL improvement. Pooled results of all 14 questions from the double-blind phase are presented.

Results 1384 subjects were included in the predefined pooled analyses (n = 688 onabotulinumtoxinA; n = 696 placebo). Baseline mean of each MSQ question score was comparable between treatment groups. Significantly more improvements in HRQoL were observed in the onabotulinumtoxinA group than placebo group for all individual question scores from baseline to week 12 ($P \leq 0.002$), week 24 ($P < 0.001$), and for each domain (week 24, $P < 0.001$). Mean change from baseline scores (SD) at week 24 for onabotulinumtoxinA and placebo, respectively: Q1-Family: 0.9(1.24)/0.4(1.18); Q2-Leisure: 0.9(1.29)/0.5(1.17); Q3-Activity: 0.8(1.21)/0.4(1.16); Q4-Work: 0.9(1.29)/0.4(1.21); Q5-Concentrate: 0.8(1.26)/0.4(1.22); Q6-Tired: 0.7(1.36)/0.3(1.27); Q7-Energy: 0.9(1.37)/0.5(1.25); Q8-Cancel: 0.6(1.24)/0.4(1.15); Q9-Help: 0.6(1.31)/0.2(1.20); Q10-Stop: 0.7(1.32)/0.3(1.17); Q11-Social: 0.7(1.35)/0.4(1.27); Q12-Frustrated: 1.1(1.63)/0.6(1.45); Q13-Burden: 0.8(1.50)/0.4(1.41); Q14-Afraid: 0.8(1.56)/0.4(1.49).

Conclusions Treatment of CM with onabotulinumtoxinA produced statistically significant and clinically meaningful improvements in

HRQoL. HRQoL improvement was maintained with repeated injections of onabotulinumtoxinA.

Study support Allergan, Inc., Irvine, CA.

Conflict of interest Dr. Silberstein has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

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Onabotulinumtoxin-A treatment reduces pain intensity in adults with chronic migraine: pooled results from the double-blind, placebo-controlled phase of PREEMPT

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Objective Assess the efficacy of onabotulinumtoxinA (BOTOX®) for the prophylaxis of headache (HA) in adults with chronic migraine (CM).

Background CM is a prevalent, disabling, and undertreated neurological disorder. Few preventive treatments have been investigated, and none is specifically indicated for CM.

Methods Two phase 3, 24-week, double-blind, parallel-group, placebo-controlled studies (PREEMPT 1 and 2), followed by 32-week, open-label phases evaluated the efficacy, safety, and tolerability of onabotulinumtoxinA in CM (ICHD-II migraine and ≥ 15 HA days/month). Qualified subjects were randomized (1:1) to injections of onabotulinumtoxinA (155U–195U) or placebo every 12 weeks for 2 cycles, and then received 3 open-label cycles. The primary efficacy variable was mean change from baseline in frequency of HA days per 28 days (primary endpoint, Week 24). Additional variables included mean change from baseline in frequency of severe HA days and in the daily HA severity score, an assessment of patient's extent of daily suffering from HA, per 28-day period. Data from the double-blind phase are presented.

Results 1384 adults were randomized to onabotulinumtoxinA ($n = 688$) or placebo ($n = 696$). Pooled analyses demonstrated a large mean decrease from baseline in frequency of HA days, with statistically significant between-group differences favoring onabotulinumtoxinA over placebo at week 24 (-8.4 vs -6.6 ; $P < 0.001$). Additional statistically significant between-group differences favoring onabotulinumtoxinA over placebo at Week 24 were found in reductions from baseline in the mean frequency of severe HA days (-4.5 vs -3.0 ; $P < 0.001$). Fewer onabotulinumtoxinA-treated patients had a daily average HA score of severe compared to placebo at Week 24 (3.5% vs 7.6% ; $P = 0.004$).

Conclusions OnabotulinumtoxinA treatment reduced HA severity compared to placebo. The comprehensive results from the PREEMPT clinical program demonstrate that onabotulinumtoxinA is effective in the preventive treatment for CM.

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Conflict of interest Dr. Silberstein has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

Catherine Turkel, PharmD, PhD is full time employee of Allergan Inc., Irvine, California, USA.

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Onabotulinumtoxin-A for chronic migraine: PREEMPT trials establish a safe and effective dose and injection paradigm

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Objective To establish a safe and effective onabotulinumtoxinA dose and injection paradigm for patients with chronic migraine (CM).

Background CM is a prevalent, disabling, undertreated neurologic disorder for which few preventive treatments have been investigated and none is specifically indicated. Various onabotulinumtoxinA dose and injection paradigms have been evaluated in studies for prevention of headache including migraine, but until recently, none is uniformly safe and effective for the treatment of CM.

Design/methods The PREEMPT clinical program (two phase 3, 24-week, double-blind, parallel-group, placebo-controlled studies, followed by a 32-week, open-label phase) evaluated the efficacy and safety of onabotulinumtoxinA in CM (ICHD II migraine and ≥ 15 headache days/month). Randomized patients received a minimum dose of 155 U onabotulinumtoxinA or placebo administered as 31 fixed-site, fixed-dose injections across 7 specific head/neck muscle areas (corrugator, procerus, frontalis, temporalis, occipitalis, cervical paraspinal, and trapezius). Patients with predominant pain location(s) could receive up to 40 U additional onabotulinumtoxinA (maximum dose 195 U) or placebo injections to 1 or both sides in up to 3 muscle groups (occipitalis, temporalis, and trapezius). Using a sterile 30-gauge, 0.5 inch needle (with a Luer Lock) intramuscular injections of 0.1 mL/site (5 U) of onabotulinumtoxinA or placebo were administered every 12 weeks (double-blind: 2 cycles), followed by onabotulinumtoxinA (open-label: 3 cycles).

Results The PREEMPT dose (onabotulinumtoxinA 155 U to 195 U) and injection paradigm demonstrated that onabotulinumtoxinA yielded significant improvements over placebo across multiple headache symptom measures including reduction in headache days: -8.4 onabotulinumtoxinA/ -6.6 placebo; $p < 0.001$ (pooled data). OnabotulinumtoxinA using this injection paradigm was safe and well tolerated. No new safety findings emerged throughout the 56-week studies.

Conclusions/relevance OnabotulinumtoxinA injections using the “modified” follow-the-pain model were safe and effective in the PREEMPT clinical program and provides an evidence-based injection strategy to optimize clinical outcomes for patients with CM.

Study supported by Allergan, Inc.

Conflict of interest Dr. Blumenfeld has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

Dr. Dodick has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

Dr. Silberstein has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

Catherine Turkel, PharmD, PhD is full time employee of Allergan Inc., Irvine, California, USA.

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Onabotulinumtoxin-A treatment improves HRQOL and reduces the impact of chronic migraine: 56 week results from the PREEMPT clinical program

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Objective Determine the impact of onabotulinumtoxinA treatment on health-related quality of life (HRQoL) in adults with chronic migraine (CM).

Background CM is disabling and associated with low HRQoL, diminished workplace productivity, and high healthcare resource utilization.

Design/methods PREEMPT included two phase 3 studies. Each had a 24-week, double-blind phase (2 injection cycles of onabotulinumtoxinA or placebo) followed by a 32-week, open-label phase (3 onabotulinumtoxinA injection cycles). The Headache Impact Test (HIT)-6, used to measure the disabling impact of headaches on patients' lives, was administered at baseline and every 4 weeks during the double-blind phase, and at Weeks 28, 36, 48, and 56. The Migraine Specific Quality of Life Questionnaire v.2.1 (MSQ), which captures information about long-term migraine impact on HRQoL in 3 domains: Role Restrictive, Role Preventive, and Emotional Functioning, was administered at baseline and Weeks 12, 24, and 56. Pooled 56-week data are presented.

Results Baseline mean total HIT-6 scores were comparable between groups ($p = 0.638$); 93.1% were severely impacted (≥ 60). At all time points in the double-blind phase, onabotulinumtoxinA treatment was associated with significant reductions in HIT-6 scores compared to placebo treatment ($p < 0.001$). At all open-label visits there were significant within-group improvements from baseline in mean HIT-6 scores: 48.8% of patients achieved a mean HIT-6 score of less-than-severe impact (< 60). In the open-label phase, significant differences favoring onabotulinumtoxinA treatment in the double-blind phase were observed at all visits, except Week 56. OnabotulinumtoxinA significantly improved overall HRQoL at all visits in the double-blind phase for all MSQ domains ($p < 0.001$). Significant HRQoL improvements were also observed at the Week 56 exit visit.

Conclusions/relevance Treatment of CM with onabotulinumtoxinA is associated with improved functioning and HRQoL. Effects are maintained with repeated injections. The magnitude of HRQoL improvement is statistically significant and clinically meaningful.

Study supported by Allergan, Inc.

Conflict of interest Dr. Lipton receives research support from the NIH [PO1 AG03949 (Program Director), PO1AG027734 (Project Leader), RO1AG025119 (Investigator), K23AG030857 (Mentor), K23NS05140901A1 (Mentor), and K23NS47256 (Mentor)], the National Headache Foundation, and the Migraine Research Fund; serves on the editorial boards of *Neurology* and *Cephalalgia* and as senior advisor to Headache, has reviewed for the NIA and NINDS, holds stock options in Neuralie Inc. and Minster Inc; serves as consultant or has received honoraria from: Allergan, Autonomic Technologies, Boston Scientific, Bristol Myers Squibb, Eli Lilly, Endo, GlaxoSmithKline, Minster, Merck, Nautilus Neuroscience, Neuralie, Novartis, and Pfizer.

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Onabotulinumtoxin-A for treatment of chronic migraine: 56-week analysis of the PREEMPT chronic migraine subgroup with baseline acute headache medication overuse

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Objective Evaluate efficacy and safety of onabotulinumtoxinA (BOTOX[®]) as headache prophylaxis for PREEMPT chronic migraine (CM) subgroup overusing acute headache pain medications (AHPM).

Background CM is a prevalent, disabling, and undertreated neurologic disorder. Up to 73% of CM patients overuse AHPM.

Design/methods PREEMPT included two phase 3 multicenter studies. Each had a 24-week double-blind phase with 2 injection cycles of onabotulinumtoxinA (O) or placebo (P) and a 32-week, open-label phase with 3 injection cycles of onabotulinumtoxinA. Criteria for medication overuse (MO-yes) subgroup included subjects who during the 28-day baseline had taken AHPM ≥ 2 days/week, and had taken simple analgesics ≥ 15 days/month and/or other AHPM types ≥ 10 days/month (eg, triptans). Investigators were trained not to enroll patients who used frequent opioids. 56-week pooled results for patients in the PREEMPT MO-yes subgroup strata are reported.

Results Of 1384 PREEMPT subjects, 65.3% ($n = 904$) met MO-yes criteria (O/O: $n = 445$, P/O: $n = 459$). Most (69.9%) had multiple analgesic MO; few ($n = 2.7\%$) had opioid MO. For the MO-yes subgroup at Week24, statistically significant between-group decreases from baseline favoring O vs P were observed for primary (headache days, $p < 0.001$) and all secondary efficacy endpoints: migraine days ($p < 0.001$), moderate/severe headache days ($p < 0.001$), cumulative headache hours ($p < 0.001$), headache episodes ($p = 0.028$), and percentage with severe Headache Impact Test (HIT)-6 category ($p < 0.001$). During the open-label phase, further large mean decreases were observed through Week56 compared to Week24. Overall, few MO-yes patients (4.1%) discontinued due to adverse events (AEs). The overall AE incidence was 72.6%. Treatment-related AEs were 32.5%.

Conclusions/relevance Most PREEMPT patients had baseline MO; very few had opioid overuse. PREEMPT subpopulation analyses demonstrated that repeated treatment with onabotulinumtoxinA is an effective, safe, and well-tolerated headache prophylactic treatment for CM patients with non-opioid 28-day baseline MO, resulting in clinically meaningful improvements for multiple headache symptom measures.

Study supported by Allergan, Inc.

Conflict of interest Dr. Silberstein has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals. Catherine Turkel, PharmD, PhD is full time employee of Allergan Inc., Irvine, California, USA.

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Onabotulinumtoxin-A for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phase of the PREEMPT clinical program

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Objective The PREEMPT clinical program assessed the efficacy and safety of onabotulinumtoxinA (BOTOX[®]) for the prophylaxis of headaches in adults with chronic migraine (CM).

Background CM is a prevalent, disabling, and undertreated neurologic disorder. Few preventive treatments have been investigated; none is specifically indicated for CM.

Design/methods Two phase 3, 24-week, double-blind, parallel-group, placebo-controlled studies (PREEMPT 1 and 2) followed by a 32-week, open-label phase, evaluated the efficacy and safety of onabotulinumtoxinA in CM (ICHD II migraine and ≥ 15 headache days/month). Qualified subjects were randomized (1:1) to injections of onabotulinumtoxinA (155 U-195 U) or placebo every 12 weeks for 5 (2 double-blind, 3 open-label) cycles. Key endpoints were mean change from baseline in frequency of headache days (primary PREEMPT 2) and headache episodes (primary PREEMPT 1) at Week 24.

Results Pooled analyses of 1384 randomized adults (onabotulinumtoxinA n = 688, placebo n = 696) demonstrated a large mean decrease from baseline for key endpoints (headache days and headache episodes), and for almost all secondary variables favoring onabotulinumtoxinA at Week 24 (headache days: -8.4 onabotulinumtoxinA, -6.6 placebo; $p < 0.001$; headache episodes -5.2 onabotulinumtoxinA, -4.9 placebo; $p = 0.009$) and all other time points. The percent of patients that had $\geq 50\%$ reduction from baseline in headache days at Week 24 was significantly greater for onabotulinumtoxinA (47.1% onabotulinumtoxinA, 35.1% placebo; $p < 0.001$). The only efficacy variable that did not show a significant difference at Week 24 was overall acute headache medication use (all categories; $p = 0.247$). However, a significant between-group difference in triptan use reduction was observed ($p < 0.001$). Most AEs (62.4% onabotulinumtoxinA, 51.7% placebo) were mild to moderate in severity, with few discontinuations (2.8% onabotulinumtoxinA, 0.7% placebo) due to AEs.

Conclusions/relevance This pooled analysis of the PREEMPT trials supports the efficacy, safety, and tolerability of onabotulinumtoxinA for the prophylaxis of headache in adults with CM.

Study supported by Allergan, Inc.

Conflict of interest Dr. Dodick has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

Dr. Lipton receives research support from the NIH [PO1 AG03949 (Program Director), PO1AG027734 (Project Leader), RO1AG025119 (Investigator), K23AG030857 (Mentor), K23NS05140901A1 (Mentor), and K23NS47256 (Mentor)], the National Headache Foundation, and the Migraine Research Fund; serves on the editorial boards of Neurology and Cephalalgia and as senior advisor to Headache, has reviewed for the NIA and NINDS, holds stock options in Neuralie Inc. and Minster Inc; serves as consultant or has received honoraria from: Allergan, Autonomic Technologies, Boston Scientific, Bristol Myers Squibb, Eli Lilly, Endo, GlaxoSmithKline, Minster, Merck, Nautilus Neuroscience, Neuralie, Novartis, and Pfizer.

Dr. Silberstein has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

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Effectiveness of flunarizine treatment in patients with medication overuse headache: a case-series study

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Introduction Medication overuse headache (MOH) implies secondary headache on a daily or near daily basis, for 15 days or more a month for 3 months and chronic migraine CM is the most common subtypes of MOH in speciality care.

There are no patients' studies with MOH's criteria according to the appendix of ICHD-2 treated with flunarizine.

Aim of the study We report our experience of flunarizine in patients with MOH y CM.

Patients and methods Of a database of 800 outpatients with migraine we selected those with MOH. They had several moderate-severe migraine attacks per month and frequent headache (≥ 15 days per month) and overused medication. They had never received prophylactic treatment before. All patients received the same treatment from the first day: Suppression of the medicine of abuse and establishment of treatment with flunarizine 5 mg/day.

The patients were evaluated initially and to the fourth month of treatment. Effectiveness was assessed by:

- Change in mean number of days with headache and severe migraine attacks in the previous month and at the fourth month of treatment.
- Responder rate.

Results Of 164 ITT outpatients with MOH and treatment with flunarizine, 148 (90.2 %) patients continued the treatment and 123 (75%) responded to the treatment and left the abuse. Responder rate 68%.

There was significant decrease ($p = 0.0001$) in mean number of days with headaches: 14.9 to 6.7 days and severe attacks at the fourth month: 9.1 to 3.9 ($p = 0.0001$). The mean percentual reduction in number of days with headaches was: 65.4% and severe migraines at the fourth month: 56.0%. Side effects: 40% patients, none of them was serious.

Conclusions Flunarizine showed effectiveness when used as the initial drug in the prophylactic treatment of MOH and CM, together with the suppression of the medication of abuse.

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Headache in the emergency department: a growing phenomenon - first italian longitudinal study

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Objective The aim of this research was to assess the prevalence of primary headache (PH) in the emergency department (ED) in Lazio region in a four year longitudinal study.

Methods We assessed the trend in the number of patients discharged with an ICD 9CM diagnosis of PH between 2005 and 2008 and the direct costs (DC) related to this phenomenon.

Results Our results show that although the overall number of patients going to the ED in Lazio decreased in this period (mean of 2.171 million patients/year), the number of patients who visited the ED for PH gradually increased. Indeed, the prevalence of 0.67% in 2005 (14825 patients) rose to 0.77 in 2008 (16556 patients), which represents an increase of 15% in the number of patients and of over 20% in the DC, from 2,445,525 euros to 2,937,187 euros.

Conclusion This study, longitudinal, first in the Italian and in the international literature, show, for the first time in our population, an important rise in the number of visits to the ED for PH, which results in a significant increase in the DC. Probably a closer collaboration between headache centres and the ED may help reduce the burden of PH.

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Sustained efficacy of occipital nerve stimulation in drug-resistant chronic cluster headache after up to 5 years treatment

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Background Drug-resistant chronic cluster headache (drCCH) is a devastating condition for which various invasive procedures have been tempted without any satisfactory effect. Our prospective pilot study of great occipital nerve stimulation (ONS) in 8 drCCH patients showed encouraging results at 15 months (Magis 2007).

Methods We recruited 15 patients with drCCH according to the previously published criteria of intractability (Goadsby 2006). They were implanted with suboccipital stimulators on the side of their headache. Long-term follow-up was achieved by questionnaires administered during a headache consultation and/or by telephone interviews.

Results One patient had an immediate post operative infection of the material. Mean time with ONS was 28.8 months (range 3-60 months). Nine of the 14 remaining patients were totally pain-free (64%), 2 patients had an improvement in frequency exceeding 90% and one patient a 89% amelioration. Two patients did not respond or described mild improvement. Intensity of residual attacks was not improved by ONS. Four patients (29%) were able to reduce their prophylaxis. Common technical problems were battery depletion (N = 8/14, 57%) and material infection (N = 3/15, 20%). Recurrent battery replacement (until 2/ year in one patient) is now avoided by the availability of rechargeable batteries. Clinical peculiarities associated with ONS were occurrence of infrequent contralateral attacks (N = 5/14, 36%), and/or isolated ipsilateral autonomic attacks (N = 5/14, 36%). Rapid attack recurrence after stimulator switch off was reported by 7/12 improved patients (58%). Two patients found ONS-related paresthesias unbearable; one had his stimulator removed, the other switched it off though he was objectively ameliorated. Subjectively, nine patients are very satisfied by ONS and one patient moderately satisfied.

Conclusions Our long-term follow-up confirms the efficacy of ONS in drCCH, which remains a safe and well-tolerated technique. The occurrence of contralateral attacks and isolated autonomic attacks in nearly 50% of ONS responders may have therapeutic and pathophysiological implications.

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Spontaneous CSF leak presenting as headaches and movement disorder

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Headache, often but not always orthostatic, is the most common clinical manifestation of spontaneous CSF leak. Many patients may report additional symptoms. We present three patients, a 59-year-old man and two women 49 and 60 years old, with spontaneous CSF leak, headache, and movement disorder. The headache was orthostatic in one patient, exertional in another patient who also had orthostatic nausea, while the third patient had lingering bifrontal headache and pronounced head pressure sensation plus gait unsteadiness. All had substantial movement disorder that had appeared along with the development of the other symptoms and consisted of choreiform movements in two patients and cervical dystonia in one. Diffuse pachymeningeal gadolinium enhancement and imaging evidence of sinking of the brain was noted in head MRI of all three patients. CSF opening pressure was low in two patients (5 mm and 60 mm H₂O) and 120 mm H₂O in the third patient. Active CSF leak was confirmed by CT-myelography in all three. CSF leak ceased spontaneously in one patient with time, one patient was treated successfully with epidural blood patches. One patient required surgery to stop the CSF leak. On follow-up, two patients were entirely asymptomatic with complete resolution of headaches and the abnormal movements (chorea in one, cervical dystonia in the other). The third patient, who was only 8 weeks postoperative, had noted marked and steady improvement beginning approximately 4 weeks following the surgery. Chorea and cervical dystonia may sometimes occur as manifestations of CSF leak and can be expected to resolve with cessation of the leak.

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Neck pain is highly prevalent in migraine and tension-type headache: a cross-sectional population study

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Background Neck pain is a common complaint from patients with primary headaches. It may contribute to head pain, disability and should be considered when treating headaches. However, the prevalence of neck pain in primary headaches is largely unknown.

Objective To assess the prevalence of neck pain in subjects with migraine and tension-type headaches (TTH).

Methods We recontacted a sample of 1000 subjects, who were invited to participate in a population study 12 years earlier. In addition, 300 new subjects were invited. A total of 834 subjects completed a diagnostic headache interview and provided self-reported data on neck pain, and 518 completed a Quantitative Sensory Testing study. Subjects were assigned to the following groups: migraine, TTH or coexistent headache if both disorders were present. Pericranial tenderness was recorded from 8 right- and left-sided locations using

pressure-controlled palpation method. A local tenderness score for each of the 8 locations was calculated by summations of both sides with maximum possible score = 6.

Results The 1-year prevalence of neck pain was 68.9%. Multiple regression analysis adjusted for gender, primary headache and age demonstrated that subjects with neck pain had higher local tenderness score in neck muscle insertions (3.4 ± 0.1 vs. 1.9 ± 0.2 , $p = 0.003$) and trapezius muscle (4.3 ± 0.1 vs. 2.9 ± 0.2 , $p < 0.001$) compared to subjects with no neck pain. A higher proportion of subjects with than without primary headaches had neck pain (86.4% vs. 57.1%; OR = 3.45, 95% CI = 2.37–5.02, $p < 0.001$). Using a model adjusting for age and gender, the prevalence of neck-shoulder pain was highest in coexistent headache (90.1%), followed by pure TTH (88.7%) and migraine (77.6%), in comparison to subjects with no headache (57.1%) ($p < 0.05$ for all 3 group comparisons).

Conclusion Neck-shoulder pain is highly prevalent in primary headaches from the general population. Prevalence is highest in coexistent headache, followed by pure TTH and migraine.

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Effect of kynurenic acid on sensitivity to cortical spreading depression in rats

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Background Migraine is sexually dimorphic and associated in 20% of patients with an aura. Cortical spreading depression (CSD) is most likely the neurophysiological correlate of the migraine aura (Lauritzen, 1994) and there is some evidence in rat that it can activate the trigeminovascular system thought to be responsible for the headache (Bolay et al., 2002). CSD is associated with glutamate release and can be blocked by NMDA receptor antagonists (Nellgard & Wieloch, 1992). Kynurenic acid (KYNA) is the only endogenous NMDA receptor antagonist in the brain.

Objective To determine if exogenous administration of KYNA is able to modify KCl-induced CSD in rat and if the effect differs between males and females.

Methods Male and female adult Sprague-Dawley rats were divided into 4 groups ($n = 8$ /group) receiving intraperitoneal injections of L-kynurenine sulphate (L-KYN, a KYNA precursor; 300 mg/kg) combined with probenecid (PROB, an organic acid transporter inhibitor; 200 mg/kg), L-KYN alone (300 mg/kg), probenecid alone (200 mg/kg) or saline (NaCl 0.9%). Half an hour after the injections, CSD were elicited under chloral hydrate anesthesia by applying over the occipital cortex a cotton ball soaked with 1 M KCl. The electrocorticogram was recorded (DC–100 Hz) with ipsilateral parietal and frontal electrodes for

1 hr. We studied treatment-induced changes of cortical KYNA concentrations with HPLC in 7 additional animals per group.

Results CSD occurrence L-KYN + PROB, L-KYN and PROB significantly decreased the CSD number per hour in female rats, while in males only L-KYN + PROB significantly decreased CSD frequency. HPLC dosages in both sexes L-KYN + PROB and L-KYN significantly increased the cortical KYNA level.

Conclusion These results show that interventions increasing the levels of cortical kynurenic acid are able to decrease the sensitivity of the cerebral cortex to cortical spreading depression. KYNA could thus be a possible candidate for the treatment of migraine with aura.

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Lost productive time and cost due to headache in chronic (CM) and episodic migraine (EM): results from the AMPP study

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Background CM is associated with work-related consequences.

Objective To estimate and compare lost productive time (LPT) over the lifespan between CM and EM sufferers and quantify the per person cost of reduced productivity.

Methods In 2005, questionnaires were mailed to 24,000 severe headache sufferers identified from a 2004 US population survey. Valid returns were obtained from 18,500 severe headache sufferers aged 18 + . The analysis sample included respondents who had ICHD-2 defined migraine, were employed either full or part-time and completed the Work and Health Questionnaire. Respondents were divided into EM (<14 headache days/month and CM (≥ 15 headache days/month). LPT was based on self-report and calculated as the sum of missed hours plus reduced productivity hour equivalents. Rate ratios (RR) for LPT scores were calculated adjusting for age and gender. The interaction between EM/CM and age was analyzed to characterize the effects of EM and CM on LPT across the lifespan. Per-person cost analyses are underway and will be presented estimating the annual cost of LPT.

Results The analysis sample included 6,319 respondents with EM and 298 with CM. Rates of LPT were higher in females than males (RR = 1.06; 95%CI = [1.02, 1.09]) and in those with CM than EM (RR = 1.36; 95%CI = [1.16, 1.60]). Additionally, the interaction effect indicated that rates of LPT differed between CM and EM and the difference increased between the two populations over the lifespan (RR = 1.01; 95%CI = [1.01, 1.02]). The main effect of age approached but did not significantly impact LPT (RR = 1.01; 95%CI = [0.99, 1.00]).

Conclusions Rates of LPT were significantly higher in CM than in EM and in females than males. Though the RR for the interaction of LPT with age in CM and EM is modest on a yearly basis, the effect becomes substantial over many years. LPT associated with CM reflects a substantial individual and societal burden.

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(Investigator), K23AG030857 (Mentor), K23NS05140901A1 (Mentor), and K23NS47256 (Mentor)], the National Headache Foundation, and the Migraine Research Fund; serves on the editorial boards of Neurology and Cephalalgia and as senior advisor to Headache, has reviewed for the NIA and NINDS, holds stock options in Neuralie Inc. and Minster Inc; serves as consultant or has received honoraria from: Allergan, Autonomic Technologies, Boston Scientific, Bristol Myers Squibb, Eli Lilly, Endo, GlaxoSmithKline, Minster, Merck, Nautilus Neuroscience, Neuralie, Novartis, and Pfizer.

Aubrey Manack, PhD is full time employee of Allergan Inc., Irvine, California, USA.

Daniel Serrano, PhD has worked on research grants as a consultant with the following companies: Allergan, Merck & Co., Endo Pharmaceuticals, Map Pharmaceuticals, GlaxoSmithKline, Ortho-McNeil-Janssen Pharmaceuticals, Ortho-McNeil Neurologics.

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Rates and predictors of remission from chronic migraine (CM) to episodic migraine (EM): results from the AMPP study

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Objective To estimate remission rates for CM and assess potential predictors of remission from CM to EM.

Background Each year, approximately 2.5% of episodic migraineurs develop CM (i.e., progression). Though rates and predictors of progression have been studied, data are limited on CM remission and persistence.

Methods In 2005, questionnaires were sent to 24,000 severe headache sufferers identified in a previous US population survey who were followed annually between 2005–2009. Participants studied had CM (ICHD-2 migraine criteria and ≥ 15 headache days/month) in 2005 and 3 consecutive years of follow-up data. To assess predictors of remission, two groups were compared: *persistent* CM (i.e., CM in 2005 and CM or high-frequency EM [HFEM:10-14 headache days/month] in 2006 and 2007) and *remitted* CM (i.e., CM in 2005 but low-frequency EM [LFEM:0-9 headache days/month], probable migraine, tension-type headache, other episodic headache, or no headache in 2006 and 2007). Demographic variables, body mass index (BMI), depression, age-of-migraine onset, allodynia, acute and preventive medication utilization, and headache-related-disability (MIDAS) were examined as predictors by assessing between and within group effects.

Results Subjects included 383 individuals with CM in 2005 who contributed 3 years of data; 64% (n = 292) were classified as *persistent* CM while 26% (n = 100) were classified as *remitted* CM. With regard to predictors of remission, all models were adjusted for age, sex, race, population density, geographic region and income. Exploratory analyses suggested that depression, MIDAS, BMI, age of migraine onset, allodynia, acute medication utilization by class and overuse did not significantly predict remission. Current use of preventive medication predicted remission in that participants utilizing preventives were half as likely to remit [OR(95%CI) = 0.48(0.28,0.84)].

Conclusions Over 2 years, the majority of CM sufferers were *persistent*. Preventive treatment was associated with a lower rate of

remission, perhaps because CM sufferers on prevention are a more severe subgroup with a worse prognosis.

Conflict of interest Dr. Buse has acted as a consultant or received research support from Allergan Pharmaceuticals, MAP Pharmaceuticals, Merck Inc., and Iroko Pharmaceuticals.

Dr. Lipton receives research support from the NIH [PO1 AG03949 (Program Director), PO1AG027734 (Project Leader), RO1AG025119 (Investigator), K23AG030857 (Mentor), K23NS05140901A1 (Mentor), and K23NS47256 (Mentor)], the National Headache Foundation, and the Migraine Research Fund; serves on the editorial boards of Neurology and Cephalalgia and as senior advisor to Headache, has reviewed for the NIA and NINDS, holds stock options in Neuralie Inc. and Minster Inc; serves as consultant or has received honoraria from: Allergan, Autonomic Technologies, Boston Scientific, Bristol Myers Squibb, Eli Lilly, Endo, GlaxoSmithKline, Minster, Merck, Nautilus Neuroscience, Neuralie, Novartis, and Pfizer.

Aubrey Manack, PhD is full time employee of Allergan Inc., Irvine, California, USA.

Michael Reed, PhD has worked on research grants as a consultant with the following companies: Allergan, Merck & Co., Endo Pharmaceuticals, Map Pharmaceuticals, GlaxoSmithKline, Ortho-McNeil-Janssen Pharmaceuticals, Ortho-McNeil Neurologics.

Daniel Serrano, PhD has worked on research grants as a consultant with the following companies: Allergan, Merck & Co., Endo Pharmaceuticals, Map Pharmaceuticals, GlaxoSmithKline, Ortho-McNeil-Janssen Pharmaceuticals, Ortho-McNeil Neurologics.

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Association of a notch 3 gene polymorphism with migraine susceptibility

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Cerebral Autosomal Dominant Arteriopathy with Subcortical infarcts and leucoencephalopathy, an autosomal dominant disease, shares common symptoms with migraine. More than 65% of all CADASIL mutations occur in exons 3 and 4 of the Notch 3 gene. A number of synonymous polymorphisms have also been identified in these exons. This study investigated the role of C381T (rs 3815188) and G684A (rs 1043994) single nucleotide polymorphisms (SNP) in exons 3 and 4 respectively of the Notch 3 gene in migraine. The first study found a significant association between the C381T variant and migraine (P = 0.005), specifically in migraine without aura (MO) (P = 0.002) sufferers, in a population of 275 migraineurs and 275 control individuals matched for age, gender and ethnicity. The G684A variant was also found to be significantly associated with migraine (P = 0.015), specifically in migraine with aura (MA) sufferers (P = 0.001). The follow-up study in 300 migraineurs and 300 control individuals did not show replicated association of the C381T variant with migraineurs (P = 0.245). However the G684A variant was again shown to be significantly associated with migraine (P = 0.004), specifically with MA (P = 0.003). Our findings support the hypothesis that synonymous polymorphisms in the Notch 3 gene, particularly the G684A, may play a role in migraine.

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Assessing educational needs of American Headache Society (AHS) members in the field of chronic migraine (CM)

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Objectives To assess the attitudes and educational needs of AHS members in the area of chronic migraine.

Background Little is known about the educational needs and preferences of AHS members who treat CM.

Design Invitations to complete a 14-item web-based questionnaire were sent to 3,206 recipients via e-mail. A total of 194 responses (6%) form the basis of this report.

Results AHS members identified the following disorders as their “most challenging” clinical problems: chronic migraine with or without medication overuse (80.9%); tension-type headache (12.2%); cluster headache (5.9%); hemicrania continua (3.7%); and migraine with or without aura (1.1%). Chronic daily headache (CDH) including CM accounted for more than one quarter of all headache patients for 62% of survey participants, and for more than half of all headache patients in one third of participants. More than half of respondents (56.5%) stated that more than a quarter of their CM patients had unmet treatment needs. Though the vast majority of respondents were “familiar” with the ICHD-2 definition of CM (92.6%) and its revision (ICHD-2R, 85.4%), only half correctly identified the features required for diagnosis (51.9%). Similarly, only half of the responders expressed a moderate understanding of the mechanism underlying chronic migraine (53.2%). Most respondents were interested in learning more about chronic migraine with or without medication overuse. Preferred educational platforms included continuing medical education (CME) accredited educational meetings (52.4%), peer-reviewed journal articles (40.1%), web-based educational materials (32.1%), and mail-based educational materials (17.6%).

Conclusions Through a survey, AHS members identified CM as their greatest headache challenge. The majority reported that they manage CM patients with unmet treatment needs. Respondents over-estimated their knowledge of diagnostic criteria for CM, and wanted to learn more about mechanisms and treatment. CME meetings remain the educational venue of choice for most AHS members.

Conflict of interest Dr. Buse has acted as a consultant or received research support from Allergan Pharmaceuticals, MAP Pharmaceuticals, Merck Inc., and Iroko Pharmaceuticals.

Dr. Dodick has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

Dr. Grosberg serves on a scientific advisory board for Kowa Pharmaceuticals American Inc. and Merz Pharmaceuticals; has received honoraria for speaking engagements or educational activities from Merck and Nautilus Pharmaceuticals; and received institutional research support from Allergan Inc., Merck, GlaxoSmithKline, Endo Pharmaceuticals, Boston Scientific, Neuralie Inc., Advanced Bionics, ProEthics, Minster Pharmaceuticals, and Capnia.

Dr. Lipton receives research support from the NIH [PO1 AG03949 (Program Director), PO1AG027734 (Project Leader), RO1AG025119 (Investigator), K23AG030857 (Mentor), K23NS05140901A1 (Mentor), and K23NS47256 (Mentor)], the National Headache Foundation, and the Migraine Research

Fund; serves on the editorial boards of Neurology and Cephalalgia and as senior advisor to Headache, has reviewed for the NIA and NINDS, holds stock options in Neuralie Inc. and Minster Inc; serves as consultant or has received honoraria from: Allergan, Autonomic Technologies, Boston Scientific, Bristol Myers Squibb, Eli Lilly, Endo, GlaxoSmithKline, Minster, Merck, Nautilus Neuroscience, Neuralie, Novartis, and Pfizer.

Nicholson R.A. Funded by NIH grant NS048288. Provided consultative services for Endo Pharmaceutical, Merck & Co during the past 12 months. Sheftell F. Over the last several years: Ad Boards, Speakers Bureaus, and Clinical Trials, Consultancy: GSK, Merck, Pfizer, AstraZeneca, OMP, Endo, BMS, Novartis, MAP, Allergan, Zogenix, NuPathe, Valeant, Takeda, Minster, Advanced Bionics, Lilly, Abbott, Forrest, Neuralie, Neurochem, Medco, Optinose, Nautilus.

Use patent: Montelukast in the prophylaxis of migraine.

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Posttraumatic and postsurgical nummular headache

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Objective To describe 6 new cases of posttraumatic NH and 2 new cases of postsurgical NH.

Background NH is a rare primary headache disorder characterized by focal and well-circumscribed head pain. Though most cases arise without precipitants, herein we describe eight patients with NH onset temporally linked to head trauma or surgery.

Methods Case series.

Results Of 35 consecutive patients with NH seen since 2004, 6 had posttraumatic (5 women, 1 man) and 2 had postsurgical (2 women) NH. All patients had a history of either mild (n = 5) or major (n = 1) head trauma, sinus surgery (n = 1), or craniotomy surgery (n = 1) immediately preceding the onset of the NH. Age at onset ranged from 13 to 63 years (mean, 47 years). The temporal pattern was chronic and continuous in 7 and episodic in 1. Head pain occurred in a round (n = 3), oval (n = 4), or bean-shaped (n = 1) area, ranging in size from 1.5 cm–6.5 cm. The pain was parietal (n = 4), frontal (n = 3), or parieto-occipital (n = 1) in location. Three patients reported mild or moderate pain, but 5 reported severe pain. Five patients reported superimposed exacerbations lasting minutes to days. Five patients reported sensory disturbances (i.e., allodynia, hyperalgesia) within the region of spontaneous pain. Prophylactic treatments were generally ineffective in 5 of 7 treated patients. Nonsteroidal anti-inflammatory drugs and opiates provided incomplete relief. Prior or coexistent headache history included chronic migraine (n = 4), posttraumatic hemicrania continua (n = 1), or episodic tension-type headache (n = 1). Comorbid depression or anxiety was documented in 50%.

Conclusions NH may arise as an immediate sequela of head trauma or surgery. In the cases with allodynia or hyperalgesia, posttraumatic NH may represent a focal form of complex regional pain syndrome. In our series of patients, prophylactic and abortive medications typically employed in the treatment of other headache disorders produced varying, generally unsatisfactory, results.

Conflict of interest Dr. Grosberg serves on a scientific advisory board for Kowa Pharmaceuticals American Inc. and Merz Pharmaceuticals; has received honoraria for speaking engagements or educational activities from Merck and Nautilus Pharmaceuticals; and received institutional research support from Allergan Inc., Merck, GlaxoSmithKline, Endo Pharmaceuticals, Boston Scientific, Neuralie Inc., Advanced Bionics, ProEthics, Minster Pharmaceuticals, and Capnia.

Dr. Lipton receives research support from the NIH [PO1 AG03949 (Program Director), PO1AG027734 (Project Leader), RO1AG025119 (Investigator),

K23AG030857 (Mentor), K23NS05140901A1 (Mentor), and K23NS47256 (Mentor)], the National Headache Foundation, and the Migraine Research Fund; serves on the editorial boards of Neurology and Cephalalgia and as senior advisor to Headache, has reviewed for the NIA and NINDS, holds stock options in Neuralieve Inc. and Minster Inc; serves as consultant or has received honoraria from: Allergan, Autonomic Technologies, Boston Scientific, Bristol Myers Squibb, Eli Lilly, Endo, GlaxoSmithKline, Minster, Merck, Nautilus Neuroscience, Neuralieve, Novartis, and Pfizer. Dr. Napchan serves in the Advisory Board Iroko Pharmaceuticals, Speakers Bureau: Zogenix.

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The prevalence of red ear syndrome in the juvenile primary headaches

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Introduction Red ear syndrome (RES), is a rare disorder characterized by burning pain and cutaneous erythema in the ear. For first we described a link between RES and pediatric migraine.

The aim of this study has been to establish frequency, sensibility and specificity of RES in a pediatric migrainous population and possible association with other clinical migrainous features.

Methods Medical records of the children admitted for headache between 1st December 2004 and 30st November 2005, were consecutively studied. A semi-structured interview about their headache and the presence of the RES was administered.

Results We visited 226 children (4–17 years) with headache in the study period. According to IHS criteria we classified the migraine in 172 children (76.5%), the other primary headaches in 54 children (23.5 %). The prevalence of RES was in 42 cases (18.5%). It occurred in 40 (23.25%) migrainous children and only two case (3.6%) respectively in the other headache group. RES resulted statistically more prevalent in migraine ($p < 0.0001$), and got a high specificity (96.3%) and PPV values (95.3%) versus low sensibility (25.3%) and PNV values (28.3%). The univariate statistical analysis showed a statistically significant association of RES with male gender, throbbing pain, vomiting and phonophobia. It was confirmed by multivariate stepwise logistic regression model for throbbing pain [OR 2.7 (CI 1.1–7); $p = 0.04$], male gender [OR 2.1 (CI 1–4.7); $p = 0.05$] and vomiting [OR 2.5 (CI 1–4.5); $p = 0.05$].

Discussion Our study shows that red ear syndrome is not infrequent in migraine. It may be an useful clinical marker in the diagnosis of pediatric migraine. The evidence of an association of the RES with some migraine features partially provoked by the parasympathetic systems supports the hypothesis of a shared pathophysiological background (for example, via the activation of the trigeminal -autonomic reflex).

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Distribution of occlusal forces in the maximum intercuspal position (MIP) among adolescents with tension-type headache (TTH)

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Introduction The psychosocial stress and related emotional problems almost always induce motoric reactions of facial mimic and masticatory muscles and are among the most probable causes of TTH.

The aim of the study was to investigate the prevalence of occlusal dysfunctions due to an increased activity of masticatory muscles in adolescents with TTH.

Material and methods The study comprised 56 students of a secondary school: 36 of them had TTH, 6 showed chronic TTH for 252.5 days per year and 30 had frequent episodic TTH for 98.1 days per year on average. The remaining 20 students constituted the control group. TTH was analysed in accordance with the IHS criteria. The influence of the perceived stress was evaluated using the PSS-10 Cohen's scale. Four value ranges were distinguished: 0–25 scores - probable; 26–50 - slight; 51–75 - moderate; and above 75 - strong reaction to stress. The occlusal conditions were assessed using the T-Scan II computer system. A contact of the opposing teeth in the maximum intercuspal position (MIP) and the centre of occlusal forces (COF) were recorded. The results were statistically analysed.

Results An asymmetric distribution of occlusal forces in the front area of the dental arch was identified in 75% of the diagnosed students with TTH, while a symmetric distribution of occlusal forces was observed on the whole dental arch in 80% of the controls and on incisors and molars in 20% of them. The prevalence of moderate or strong reaction to stress was recognised in 50% of the students with TTH, while a slight reaction was identified in 70% of cases in the controls.

Conclusions TTH correlated with the degree of the perceived stress, resulting in changes in occlusion conditions and leading to a significant dislocation of MIP and COF in the direction of the front arch.

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The efficacy of wet-cupping in the treatment of tension and migraine headache

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Wet-cupping is an ancient medical technique still used in several contemporary societies, but little empirical study has been devoted to test its efficacy to treat tension and migraine headache. Using a pre-post research design, 70 patients with chronic tension or migraine headache were treated with wet-cupping. Three primary outcome measures were considered at the baseline and 3 months following treatment: headache severity, days of headache per month, and use of medication. Results suggest that, compared to the baseline, mean headache severity decreased by 66% following wet-cupping treatment. Treated patients also experienced the equivalent of 12.6 fewer days of headache per month. We conclude that wet-cupping leads to clinical relevant benefits for primary care patients with headache. Possible mechanisms of wet-cupping's efficacy, as well as directions for future research are discussed.

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Response of short-lasting primary headaches to occipital nerve stimulation (ONS)

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Objective To explore novel therapies for medically intractable SUNCT, SUNA and primary stabbing headache.

Background SUNCT/SUNA and primary stabbing headaches are clinically different entities. However, they share the feature of very brief attacks, which constitutes a major limitation for acute therapy approaches. SUNCT/SUNA and primary stabbing headaches respond selectively to a limited number of preventive medications; in certain cases these do not offer satisfactory relief, are not tolerated or both. ONS is a relatively novel therapy showing promising efficacy results, good tolerability, with a low risk profile in a number of medically intractable primary headaches.

Methods The response was recorded in four patients with SUNCT following bilateral ONS therapy in three cases and unilateral ONS stimulation in one patient respectively and two patients with SUNA following unilateral and bilateral ONS treatment respectively. Of the four ONS treated patients with primary stabbing headache, two received unilateral stimulation.

Results All primary stabbing headache patients responded well to ONS therapy. Both SUNA patients had almost complete cessation of the attacks. Two SUNCT patients had excellent response to bilateral ONS, one SUNCT patient showed a 50% response to bilaterally administered ONS and one patient had no benefit from ONS applied on the pain side only.

Conclusions Our observations indicate that ONS is a promising therapeutic approach for patients with primary stabbing headache and SUNCT/SUNA. This therapeutic approach appears particularly attractive for headache conditions not suitable for acute treatment and for which the preventive alternatives are limited.

Keywords ONS, medically intractable primary headache conditions, SUNCT, SUNA, primary stabbing headache.

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Altered response of trigeminocervical complex neurons after lesioning the dopaminergic A11 nucleus, and the effect of dopamine and serotonin receptors

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Introduction Both 5HT_{1B/1D} and dopamine receptors are known to play a role in treatment of migraine headache, as activation of those receptor groups in the trigeminocervical complex inhibits transmission of nociceptive signalling from this nucleus. The A11 nucleus of the posterior hypothalamus, provides the only known source of descending dopaminergic innervation to the dorsal horn and was identified as the possible source of inhibitory dopamine to the trigeminocervical complex. Lesioning of the A11 nucleus was shown to facilitate transmission of nociceptive signaling from the trigeminocervical complex.

Methods Extracellular recordings were made in the rat trigeminocervical complex in response to electrical stimulation of the dura mater and mechanical noxious and innocuous stimulation of the periorbital skin. The A11 nucleus was lesioned and, following a period of observation of the facilitated response, one of the following drugs was administered intravenously:

5HT_{1B/1D} receptor agonist,

D₂-like receptor agonist,

D₂-like receptor agonist with a 5-HT_{1B/1D} receptor agonist,

D₂-like receptor agonist with a 5-HT_{1B/1D} receptor antagonist

Results Both the 5HT_{1B/1D} receptor agonist and the D₂-like receptor agonist with 5-HT_{1B/1D} receptor antagonist inhibited firing in the trigeminocervical complex evoked by noxious stimuli, returning it to pre-lesion baseline. However the response to innocuous stimuli remained in a

facilitated state. The D₂-like receptor agonist and the D₂-like receptor agonist with 5HT_{1B/1D} receptor agonist both had a greater inhibitory response to noxious stimuli so that cell firing dropped to below the pre-lesion baseline, while the response to innocuous stimuli was inhibited enough so that cell firing returned to baseline.

Conclusions It seems likely that trigeminovascular traffic is affected by at least two antinociceptive pathways, one serotonergic and one dopaminergic, that act simultaneously on neurons in the trigeminocervical complex, and that both systems need to be functioning for effective inhibition of nociceptive transmission to take place.

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Recurrent migraine and transient stroke-like episode in child with Sturge-Weber syndrome: a case report

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The clinical features of the Sturge-Weber syndrome(SWS) Type I include headaches (30 ~ 45%), epilepsy (75-90%), hemiplegia (30%), glaucoma (30%), and mental retardation (50% of patients and 75% of those with seizures). The relationship between headaches, seizure clusters, and stroke-like episodes is related to the pathogenesis of SWS. The risk of stroke in patients with SWS increased because preexisting perfusion and metabolic defects subject them to prolonged phases of oligemia, a characteristic of migraine-induced stroke. We present case of a 9 year-old female with SWS type I, glaucoma, hemiparesis, and normal psychomotor development, who presented recurrent severe migraine and transient stroke-like episodes, separated by complete recovery. She was managed with oxcarbazepine for seizure, amitriptyline for migraine, and aspirin for stroke like episodes without surgical treatment. After one year, she didn't have seizure and stroke like event but does have mild headache (1/month). Her quality of life and hemiparesis was improved. We recommend that it is need aggressively prompt treatment for recurrent seizure, migraine, and stroke-like episode.

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The effects of tianshu capsule on blood flow dynamics, and vaso-active substances in migraine models

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Purpose To investigate the effects of TianShu Capsule (TSC) on blood flow dynamics, and vaso-active substances in blood plasma or brain in migraine models.

Methods After subcutaneously administration of nitroglycerin (NTG) and tube-feeding TSC, we used radioimmunoassay and spectrophotometry to measure the contents of calcitonin gene-related peptide (CGRP), nitric oxide (NO) and nitric oxide synthase (NOS) in rat plasma; we evaluated the distribution of NOS₁, CGRP in rat trigeminal nucleus caudalis using immunohistochemistry, and monitored the systolic maximal blood flow velocity with Transcranial Doppler in rabbit internal carotid artery.

Results TSC could inhibit the NTG-induced increasing of NO, NOS and CGRP in plasma, attenuates NOS1 and CGRP expression in the brainstem, and reversed the vasodilation effect of NTG.

Conclusion TSC could modulate the unbalance of vaso-active substances and neurotransmitters during the migraine attacks and resulted in relief of the headache.

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Treatment of cluster headache using peripheral nerve stimulation; a case report

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Introduction Cluster headaches are one of the most severe and disabling types of headache. Control of cluster headaches can be difficult to achieve despite multiple pharmacological modalities available in the field of pain management. Peripheral nerve stimulation (PNS) has been used to treat patients with injuries to a specific nerve; including application to occipital, ilioinguinal, supraorbital, and trigeminal neuralgia. Recently this type of treatment is utilized to control different headaches including chronic cluster headaches.

Materials and methods The patient is a 39 year old female with intractable cluster headaches for the past 12 years who failed conservative therapy and had short lasting pain relief after supraorbital and auriculotemporal nerve blocks. She underwent a successful trial of percutaneous placement of an 8-electrode lead in the left supra-orbital region. During the 2 day PNS trial, the patient reported complete resolution of headaches. Two weeks later the patient underwent subdermal implantation of a permanent lead and RestoreULTRA (Medtronic Inc.) rechargeable generator.

Results After final implantation, the patient reported excellent control of headaches. The frequency of her cluster headaches significantly decreased from 5-7 per day to 1 episode every one to two months. The patient was able to terminate the cluster headache in 2-3 minutes after turning the PNS on. She discontinued use of all medications including opioids. The patient also reported other positive outcomes including the ability to return to social and occupational activities. At 12 months post-implant, the patient continued to report good control of the cluster headaches and improved functional status.

Conclusion PNS appears to be a therapeutic alternative for patients with chronic intractable cluster headaches who in the past exhausted all available treatments. This technique is a relatively easy to perform, effective, and safe procedure. The therapy is reversible should patients lose its pain-alleviating effect or headaches resolve.

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Aspirin vs propranolol: comparative study of their interactions with other drugs in the prevention of migraine

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Aim The aim of the present study is to be shown the interactions of aspirin or propranolol in the prevention of migraine.

Material and methods There were studied the interactions of aspirin or propranolol with other drugs.

Results As regards its interactions with anticoagulants, such as coumadin, aspirin may cause severe lifethreatening bleeding. Concomitant use of aspirin with antihypertensives, such as beta-blockers, has been shown to decrease their antihypertensive effect, while aspirin combined with antineoplastic, such as methotrexate, tends to increase its toxicity through bone marrow suppression and liver toxicity. Aspirin combined with probenidid may lead to reduced

urinary excretory action. Co- administration of aspirin with antihistamines, such as phenylpropanolamine, may cause severe hypertensive crises. Combination of aspirin with corticosteroids increases the risk of ulceration of the gastrointestinal tract. Regarding the interactions of propranolol with hypoglycaemics, they may lead diabetic patients to hypoglycaemic coma with increased blood pressure. The administration of propranolol is contraindicated in asthmatic patients who receive broncodilators due to high risk of severe bronchospasm. Antihypertensives, such as nifedipine with propranolol may cause heart failure and severe hypotension. Co-administration of propranolol with glycosides may cause severe bradycardia and lead to death. Antiarrhythmics, such as verapamil, with propranolol may cause severe sinoventricular obstruction with severe myocardial depression due to negative cumulative inotropic action.

Conclusions Aspirin or propranolol may function as a preventive shield against migraine only when used properly.

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An analysis of patients with primary headache at a tertiary care hospitalA. Malik¹, A. Zafar², S. Ali¹¹Jinnah Postgraduate Medical Centre, Karachi, Pakistan;²Liaquat National Hospital, Karachi, Pakistan

Background Headache is one of the most common reasons for neurological consultation. The estimated life time prevalence of any headache approaches 90% in men and 95% in women. Headache has been classified into primary and secondary headache disorders. The four categories of primary headache include migraine, tension type headache, cluster headache and trigeminal autonomic cephalgias, and other primary headaches. As primary headache is a common health care problem and there is not enough data on types of primary headache in our population, therefore, we have designed this study with the aim to identify different types of primary headache and their characteristics.

Objective To identify different types of primary headache and to describe demographic characteristics as age and sex.

Methods This is a prospective, observational study, carried out at a tertiary care hospital over the period of 1 year. Data was analyzed by spss version 15.0.

Result Total of 1071 patients with diagnosis of primary headache were included in the study. 720(67.2%) were female and 351(32.8%) were male. Migraine was the commonest type of headache, seen in 744(69.5%) patients followed by tension type headache, seen in 318(29.7%). other types of headache as cluster headache and paroxysmal hemicrania continua were very uncommon. Among patients with migraine, migraine without aura was the commonest subtype.

Conclusion Primary headaches are more frequent in females as compared to males. Migraine is the commonest type of primary headache followed by tension type headache. Further epidemiological studies are needed to identify the characteristics of headaches in our population.

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Evaluation of knowledge of specific migraine attacks treatments according current French recommendations by first-time consulters in a tertiary headache centre

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The prevalence of migraine in France is between 12 to 21%. Around a quarter of patients have a significant impact in their daily life. However, there is an inadequate therapeutic management of migraine attacks by migraine sufferers in French general population, characterised by exceedingly high level of analgesic use and few use of specific treatments such as triptans.

The aim of our study was to evaluate the knowledge and the satisfaction of specific migraine attacks treatments according current French recommendations by first-time consulters in a tertiary headache centre.

We evaluated these items by a self-administered survey in each new consultant for migraine (IHS codes 1.1, 1.2 and 1.7). All patients were referred by their GP. Patients who had already consulted a neurologist, those who had consulted for chronic migraine, and those who had consulted again in our centre were not included. We have prospectively interviewed during 2 months 57 episodic migraine sufferers (44 females, 13 males; mean-age: 39.2 years). The duration of migraine disease was 10 years or more in 52.6% patients. Almost ¾ of patients were informed that NSAIDs and triptans are effective treatments and ¾ had already used at least one NSAIDs and/or one triptan for migraine attacks. Around 2/3 of patients were not satisfied with triptans despite an early intake. Only half of patients did change the triptan in case of failure for the next migraine attacks.

The knowledge and the use of recommended acute treatments for migraine attacks is much more higher in patients who consult for the first time in a tertiary headache centre in comparison with the French general migraine population. However, we have to improve the education of such patients because the majority are not aware about the absence of class effect with the triptans.

Conflict of interest C. Lucas has perceived personal fees for activities (consulting, clinical research) with Allergan, Almirall SAS, Astra Zeneca Pharmaceuticals, Boehringer Ingelheim, Bouchara Recordati, Glaxo-Smith Kline Inc, Menarini, Merck, Pfizer Inc, Sanofi-Aventis, Servier.

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Greater occipital nerve blockade with lidocaine in pregnant migraine patients

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Objective To present a case series of pregnant patients treated with greater occipital nerve blockade (GONB) for acute migraine attacks.

Background Acute treatment options for migraine are limited in pregnancy because of safety and teratogenicity concerns. Based on reports of safe use of lidocaine in pregnancy, GONB may provide a safe and effective treatment option.

Methods GONB was offered to pregnant patients presenting to a hospital's labor and delivery service for acute migraine. All nerve

blocks were performed in the greater occipital nerve regions bilaterally with 4 mL of 1% (10 mg/mL) lidocaine HCl at each site. Pain scores were captured immediately before the procedure and 1 and 24 hours after the blockade.

Results Three patients were treated with GONB, including one who was treated for two separate acute attacks. Two patients were in the third trimester and one was in the second trimester. All patients had a history of episodic migraine without aura, and one patient had evolved to chronic migraine (CM) 2 years previously. Acute headache duration ranged from 2 to 10 days, and the CM patient reported severe daily headache that predated her gestation. All patients had normal examinations (except for GON tenderness), MRI and MRV. All patients were tried on intravenous metoclopramide, diphenhydramine, and a narcotic (codeine, oxycodone, morphine). Pre-treatment pain ranged from 5 to 8/10. After GONB all patients experienced complete relief within an hour. At 24 hours, only the CM patient had recurrent pain. GONB were well tolerated, and all patients experienced cephalic numbness. Two patients delivered healthy babies and the third patient was having an uneventful pregnancy when last seen at 33 weeks gestational age.

Conclusions In a small series, GONB with lidocaine appears to be a safe and often effective acute migraine treatment for pregnant women. Larger and randomized studies are warranted.

Conflict of interest Dr. Buse has acted as a consultant or received research support from Allergan Pharmaceuticals, MAP Pharmaceuticals, Merck Inc., and Iroko Pharmaceuticals.

Dr. Grosberg serves on a scientific advisory board for Kowa Pharmaceuticals American Inc. and Merz Pharmaceuticals; has received honoraria for speaking engagements or educational activities from Merck and Nautilus Pharmaceuticals; and received institutional research support from Allergan Inc., Merck, GlaxoSmithKline, Endo Pharmaceuticals, Boston Scientific, Neuralieve Inc., Advanced Bionics, ProEthics, Minster Pharmaceuticals, and Capnia.

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Dr. Napchan serves in the Advisory Board Iroko Pharmaceuticals, Speakers Bureau: Zogenix.

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Study of the prevalence of patent foramen ovale in patients with migraine headaches

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Subjectives Migraine is a common primary headache disorder whose etiology remains unknown. Coexistence of migraine and patent foramen ovale (PFO) has been reported in many studies. The aim of this study was to evaluate the prevalence of PFO in patients with migraine with aura (MA) and those without aura (M) and in a healthy age-matched control group.

Material and methods We evaluated 50 patients (38 females) suffering from migraine with aura, 75 without aura (58 females) and 50 normal

controls (25 females). PFO was detected by the contrast transcranial Doppler study using standard agitated saline test and Valsalva manure and confirmed by transesophageal echocardiography.

Results The presence of PFO was found in 19/50 (38 %) patients with MA compared to 15/75 (20%) without aura, and in 9/50 (18%) control subjects. The observed differences of PFO prevalence between MA and M groups and also the difference between MA patients and the control group was statistically significant ($p < 0.05$).

Conclusions According to our study results it suggests that at least some attacks of migraine with aura may be associated with patent foramen ovale and probably due to paradoxical embolism.

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Laughing headache: a new case report and literature review

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Laughing is an uncommon provoking factor for headache and only few cases have been reported to date. Simonds in his 1956's study points out laughing as a trigger of sudden and transient headache as well as coughing, snoring, straining, sneezing or stooping. Laughing headache is considered as a particular form of exertional headache (EH). In the absence of intracranial abnormalities, the pain mechanism remains uncertain but the main hypothesis is that laughing headache is secondary to transient and reversible intracranial hypertension such as during a sudden valsalva maneuver. Recently Donnet and coll explored an alternative hypothesis: in a preliminary study they had demonstrated that in some cases EH can be due to increase in venous pressure, secondary to an undiagnosed venous stenosis revealed by specific MRI sequences. We report a new case of EH where headache was provoked almost exclusively by outbursts of laughing. General and neurological examination was normal despite of an abdominal obesity with a BMI at 35. Blood and CSF tests were normal. Brain MRI excluded parenchymal lesion, venous stenosis or thrombosis. There was no Chiari malformation but intravenous hypertrophic Paccioni granulations were detected. This original case leads us to discuss other possible mechanisms for pain associated with laughing. In this case several factors such as obesity and intravenous hypertrophic Paccioni granulations may have played a role, in the absence of others classical factors. A review of published laughing headache case reports is suggested and different etiologies discussed.

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Cerebellar distribution of CGRP and its receptor components, CLR and RAMP1, in rat

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Clinical and experimental results have revealed a fundamental role of CGRP in primary headaches. Moreover, in acute attacks of migraine there is evidence of cerebellar activation.

Immunofluorescence method with specific antibodies against CGRP, CLR and RAMP1 (Eftekhari 2010) were used to study the distribution

of CGRP and its receptor components (CLR and RAMP1) in rat cerebellum.

CGRP immunoreactivity was only found intracellularly in the cerebellar Purkinje cell bodies, whereas CLR and RAMP1 were detected on the surface of the Purkinje cell bodies and in their processes. The elaborate dendritic tree of Purkinje cell fibers was distinctly visualized with the RAMP1 antibody. In addition, profoundly stained fibers spanning from the molecular layer into the medulla was observed with the RAMP1 antibody. Judged from the high density of immunoreactive cells expressing CGRP, RAMP1 or CLR, and from the double staining of CGRP and RAMP1 it is likely that most, if not all, Purkinje cells express both the peptide and the receptor components, but with different localizations. Double staining with RAMP1 and the glial cell markers GFAP and S-100 revealed an almost identical staining pattern of the antibodies in the area of the cell body surfaces. However, as judged by confocal microscopy, no double staining was present. Instead, it was discovered that the glial cells tightly surrounded the Purkinje cells which easily could be interpreted as colocalization in the epifluorescence microscope.

Our observations demonstrate that there is a rich expression of CGRP and CGRP receptor elements in the cerebellum which points towards a functional role of CGRP in cerebellar Purkinje cells. Recent advances in the biology of the cerebellum indicate that there may be a role in nociception. The recently discovered CGRP receptor antagonists, that have demonstrated improvement in migraine pain and associated symptoms, could have an effect on cerebellar CGRP receptors.

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Clinical and encephalographical effects of amitriptyline for patients with a chronic migraine without aura

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Purpose of study To reveal the electroencephalographical features of application of amitriptyline in prophylactic treatment of chronic migraine without aura.

Groups and methods 31 patients with a chronic migraine without aura accepted amitriptyline in doses 0,05 - 0, 075 g/per day;

29 patients accepted amitriptyline in the same doses in combination with cinnarizin (0,075 g/per day);

30 patients accepted cinnarizin in doses (0,075 g/per day).

All patients were clinical examined and EEG studied by the device Neurofax (Germany) on traditional methodology before and after two-month treatment. A clinical criterion was frequency of migraine attacks.

Inclusion criteria Age 19-45 years of both sex; accordance to the diagnostic criteria of ICDH II for a chronic migraine without aura.

Exclusion criteria Reception of neurotropic drugs for the last 3 months prior to the study.

Results 3 groups of patients with the different dynamics of disease flow on a background treatment were defined: with the reliable diminishing of amount of attacks; without the reliable change of amount of attacks; with the reliable increase of amount of attacks.

In the group of patients accepted cinnarizin, neither clinical nor EEG dynamics were registered.

Discussion Known pharmacological effect of amitriptyline is strengthening of catecholamines influences on the postsynaptic membrane of neurons due to the increase of their amount or decreasing the rate of turnover. Study results allow to define EEG markers of patients with successful and not successful treatment by amitriptyline. Drawn a conclusion about different pathogenesis of increase of brain excitability for patients with a migraine and role of different concentration of

catecholamines in the mechanism of migraine development. Possibility of the differentiated prescribing of amitriptyline from EEG data was shown.

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Risk factors for the chronification of migraine

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According to the concept suggested by Bigal & Lipton, the transition from episodic migraine to frequent episodic migraine and chronic migraine manifests itself in clinical, physiological, and possibly anatomical changes in pain-processing structures of the brain and central nervous system. Various risk factors have been mentioned for these relatively frequent, and notably bidirectional, processes. Based on a systematic literature search (search terms: migraine or migraine illness, chronification) in MEDLINE for 1950 - February 2010, the parameters discussed as risk factors for progression or chronification were analysed regarding frequency of mention from 15 overview works proving this information.

Twenty-six risk factors emerge (in order of number of mentions): overweight (12), medication overuse (11), headache frequency (10), age (9), depression (7), low education (7), female gender (7), caffeine consumption (food and drink, medications) (7), anxiety disorders (6), head injuries (6), other pain syndromes (5), genetic factors (4), sleep disorders (4), sleep apnoea (4), allodynia (3), Caucasian (3), arthrosis / musculoskeletal pain (2), diabetes (2), psychiatric illnesses (2), physical or sexual abuse (2), proinflammatory states (2), prothrombotic states (2), opioid / barbiturate overuse (1).

In the overview works, differences are apparent in type and number of mentioned risk factors, possibly due to the subjective selection and evaluation of studies underlying these reviews. The largest limitation of explanatory power is that almost none of the studies considered all possible factors as confounders, and this limitation was neither sufficiently accounted for in the results, nor appropriately discussed. Moreover, the examined case numbers are often problematically small in relation to the number of parameters considered in the multifactorial analyses. The mentioned risk factors thus continue to be fraught with uncertainty regarding their clinical relevance. It is first necessary to reach a consensus regarding which parameters should be vitally examined in studies on the chronification of migraine.

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Epileptic seizures in children with SLE: case series

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Objective Systemic lupus erythematosus is a multisystem autoimmune disease characterized by circulating autoantibodies and immune complexes. The disorder most commonly affects young female. Involvement of the nervous system is one of the most profound manifestations of disease.

To evaluate the frequency and risk factors of epileptic seizures in children with SLE.

Methods 65 patients with JSLE were studied, with follow-up ranging from 4 to 10 years. Risk factors associated with acute and recurrent epileptic seizures in JSLE were determined.

Results Eight (12.4%) patients with epileptic seizures were identified. Seizures occurred at the onset of JSLE in 3 (37.5%), and

after the onset of JSLE in 5(62.5%) patients. Six (75%) patients had acute symptomatic seizures, and 1 (12.5%) had recurrent epileptic seizures. One patient who presented epileptic seizures had anti-phospholipid syndrome and interictal epileptic abnormalities on EEG.

Conclusion Despite the relatively common involvement of CNS in SLE, presentation of this disorder with neurologic symptoms appears to be uncommon. True incidence of seizures in SLE is difficult to determine, owing to multiple potential etiologies. Epileptic seizures were observed in 12.4% (JSLE) patients. The case who had recurrent seizure was associated with antiphospholipid antibody syndrome.

Keywords SLE, Seizure, Antiphospholipid syndrome.

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Necrosis lingual caused by ergotamine in a patient affected by arteritis of gigantic cells

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Ergotaminic derivatives are substances widely used for the relief of pain during migraine attacks.

Since the 1918 isolation by Stoll the ergotamine were the reason of numerous tests that demonstrated its efficiency and helped to formulate the neurovascular theory through its vasoconstrictor and modulator effect of the trigeminal process of pain (1).

Such vasoconstrictor effect could work as ischemic trigger over a vascular territory previously compromised because of an arterial vasculitic process (2).

Up to 40% of the patients with arteritis of gigantic cells presents infrequent symptoms such as, dry cough, sore throat, and tongue symptoms such as pain, and glossitis (3).

The lingual necrosis is an unusual manifestation of the arthritis of gigantic cells, however, at the same time it constitutes the first cause of ischaemic of tongue.

We present a patient who suffered from necrosis of the tongue caused by ergotamine. For this reason we diagnosed the arteritis of gigantic cells.

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Neurovascular dishabituation in patients with migraine without aura

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Background Absence of habituation during VEP measurements has extensively been studied in patients with migraine [1,2]. It is unclear whether this electrical phenomenon is accompanied by hemodynamic anomalies. In healthy controls, VEP-habituation is well-known and hemodynamic refractory effects are observed in the net BOLD-responses to repetitive visual stimuli [3], i.e. a decreased amplitude and

increased latency in time-to-peak for interstimulus intervals less than 6 seconds. Interictal hemodynamic differences between patients with migraine without aura and healthy controls have not been investigated.

Methods In this study, we measure interictal hemodynamic responses with functional magnetic resonance imaging in patients with migraine without aura and compare them with responses from healthy controls. Net responses to paired visual stimuli with varying interstimulus intervals are calculated. Several characterizing parameters of the responses are quantified. ANOVA and post-hoc Bonferroni tests are used for statistical analysis (significance level = 0.05).

Results and discussion Refractory effects are not observed in patients. There is no amplitude decrease, nor increased latency in time-to-peak in patients, not even for the shortest interstimulus interval, whereas in controls, refractory effects are found for all parameters of the net responses for an interstimulus interval of 1 second (amplitude and time-to-peak: $p < 0.001$; width: $p < 0.01$). The nonlinearities (i.e. differences in measured vs. expected responses) fade away with longer interstimulus intervals and have disappeared at the interstimulus interval of 6 seconds.

The absence of refractory effects in patients with migraine without aura reflects the neurovascular correlate of the absence of habituation in this patient group. Multi-modal data acquisition (VEP/fMRI) or follow-up of patients taking prophylactic drugs may be subject to further research.

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A case of cardiac cephalalgia without angina

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Background Cardiac cephalalgia is a rare condition, first proposed in 1997, and since 1966 there have been 34 cases described in literature. Cardiac cephalalgia was classified in International Classification of Headache Disorders (ICHD-I) under the group ‘headache attributed to disorder of homeostasis’ and was renamed to ‘cardiac cephalalgia’ in the second edition of ICHD-II in 2004. During an episode of myocardial infarction or angina, 6% of patients will demonstrate cephalalgia from the onset of the episode, concomitantly with the major symptom of chest or arm pain.

Case report The unique feature of the female patient with cardiac cephalalgia we present was that, she didn’t have retrosternal pain, although she fulfilled all the criteria of ICHD-II. Instead, she came to medical attention in Emergency Department of our hospital due to symptoms of first-time in life, intense, vasomotor type cephalalgia, combined with vomiting. The duration of the headache was 50 minutes the time that it was necessary for effective medical therapy of myocardial ischemia. Electrocardiography (ECG) in the Emergency Department revealed changes consistent with acute myocardial infarction which was also confirmed by laboratory tests. Neurological examination and CNS imaging including CT, MRI and MRA were negative.

Discussion Cardiac Cephalalgia is a rare syndrome that many cardiologists are skeptical regarding its existence. The mortality rate of patients due to cardiac disorders causing cephalalgia is close to 12%.

Therefore every neurologist should consider evaluation for cardiac causes in patients with acute cephalalgia which does not seem to have a neurological etiology.

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The epidemiology of migraine in armenia: preliminary results of simultaneous multicenter study

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Objectives Headaches are highly common complaints addressed to physicians, and take 3rd place among pain syndromes. High abundance and economical burden of headaches are prioritizing medical assessment and treatment. Currently there are many studies of headaches epidemiology in the world, meanwhile there is a lack of attention toward this problem in Armenia.

Aim Aim of our study was investigation of prevalence of migraine in Armenia.

Study design Special questionnaires were created (correspondingly to diagnostic criteria and recommendations of International Headache Society) and distributed among matching population in the capital city, other cities and villages. From 2000 questionnaires we had completed about 500. In study were included 489.

Results From included 489 (356 women/ 133 men) patients we had following distribution Yerevan, Vanadzor and Ararat valley (207, 94, 188 correspondingly). Age of participants was 18-60 yrs. Data analysis revealed that: 92 (19%) (79 f/ 13 m) of respondents suffer from migraine without aura, 33 (6%) (31 f/2 m) from migraine with aura, - 356 (72%) (257 f/ 99 m)

Conclusion All together our data is matching with similar international studies, but we had some prevalence of Tension type headaches in women in villages. Another issue is that despite of wide distribution, many doctors are mistaking cluster type headaches with trigeminal neuralgic types or migraine. More educational work toward understanding and correct assessment of headaches must be done.

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Age at onset and gender ratio in cluster headache: clinical observations over 15 years

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Objectives Cluster headache (CH) is considered as a disorder of young men which predominantly begins at age 20 to 40 years. In recent studies M:F ratio ranges 4.4:1 to 2.5:1.

Materials and methods We reviewed the clinical charts of 10560 consecutive outpatients referred to our Headache Centre from 1995 to 2009. All data were collected prospectively and assembled in a database since 1995.

Results A total of 221 patients (165 males and 56 females), constituting 2.1% of the whole population of headache sufferers, fulfilled the ICHD-II diagnostic criteria for CH. The overall M:F ratio was 2.9:1 and interestingly it was 5.1:1 within the age of 55, and over this

cut-off age it completely reversed, resulting 0.8:1. The mean age at onset was 36.9 ± 15.6 (range 13 to 84). We diagnosed 30 cases with CH (3.1 according to ICHD-II), 155 episodic CH, 30 chronic CH and 6 probable CH. In females the mean age at onset, being 46.7 ± 18.9 , was significantly higher than in males, resulting 33.6 ± 12.7 . Out of the 43 patients aged over 65 years, 24 were females and in this elderly subpopulation the prevalence of chronic CH was remarkably higher than in previous ages, accounting for 25.6.6%. In patients below 65, chronic CH was found in 9.5% of cases.

Discussion The onset of CH seems to be independent of the life period of the patients, even if the average age of onset peaks towards the third decade. Apparently peculiar to the female distribution, an increased frequency appears to occur in middle-age and elderly patients.

Conclusions In the elderly group females represented the majority of cases, in contrast with the evident male preponderance in the previous decades. To our knowledge we report the largest case series of CH elderly patients published in the literature to date.

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Kinematics of headaches related to occipital-cervicothoracolumbar mal-posture: significance of axial muscles in headaches

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Axial posture is not static but rather a dynamic process represented by alignment of the body's anatomical units in relationship to one another at any given time. Posture affects body locomotion, energy expenditure, and risk of falls. Posture can be influenced by multiple factors; i.e. aging, gender, bone loss, muscle strength, and occupation. The most disfiguring effect of axial loss of muscle strength and bone is the anterior wedging of the thoracic spine due to the effects of gravity on the natural thoracic kyphosis, forward position of the cervical spine and head. We regularly treat patients with neck pain and/or headache in our outpatient clinic. Here, we report cases with headache and neck pain of hyperkyphosis (thoracic kyphosis $> 50^\circ$), who had tried other measures for pain relief without success. All had neurological and musculoskeletal evaluations and full assessment of gait and physical activity.

Intervention All subjects, after their preliminary evaluations, were provided with instructions to improve their occipital -cervicothoracolumbar kinesiology through specific muscle strengthening exercises. Our mechanical intervention included use of orthotics when necessary and posture training through reeducation of axial muscles with or without use of orthotics. The kinesiology and efficacy of these techniques will be discussed.

Conclusion Headaches are complicated and their etiology needs elaborate work ups. In this presentation we discuss the headaches related to overuse of posterior cervical muscles in the setting of mal-posture of the spine.

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Quadriplegic migraine in identical twins

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A 38 year old Hispanic woman presented to Montefiore Medical Center with a history of recurrent headaches since age 30. Headaches began as bifrontal pressure-like pain and vertigo. The episodes progressed to quadriplegia lasting 5-10 minutes during which time she was unable to speak but remained fully aware of her environment and was able to open and close her eyelids. As the quadriplegia abated she experienced severe, diffuse headache with photophobia and sonophobia lasting hours to days. The only trigger identified was lack of sleep. Episodes came on 4-5 times per month. One year previous an MRI of the brain revealed a Chiari malformation. Surgical correction of the Chiari malformation did not improve her headaches. She obtained some reduction in intensity of headache while on topiramate but the frequency was unchanged. The patient had an identical twin with similar headaches beginning at age 20, except that her prodrome consisted of photopsia, restriction of visual field and unilateral sensory symptoms prior to the onset of quadriplegia. A third sister suffered from migraine without motor manifestations. The patient was observed for 6 days with EEG monitoring but failed to have any episodes during the hospitalization. Genetic screening for hemiplegic migraine revealed a mutation in the CACNA1A gene with a G to A transition at nucleotide position 2826, codon 942, which was reported to be "of unknown significance". In summary, we describe monozygotic twin sisters whose migraine headaches are preceded by quadriplegia/locked-in-syndrome and have an identified mutation in a gene associated with familial hemiplegic migraine.

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Headaches in patients with systemic lupus erythematosus: a prospective case-control study

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Background-objective Whether headache, and in particular migraine, belongs to the spectrum of neurological manifestations of systemic lupus erythematosus (SLE) remains uncertain. We conducted a retrospective, followed by a longitudinal, one-year assessment of patients with SLE versus healthy controls, and patients with multiple sclerosis (MS), an organ-specific autoimmune disease affecting the nervous system.

Methods At baseline, patients with SLE, MS and 1:1 matched healthy controls for age, gender and level of education were examined for the presence of headache during the prior year (classification criteria of the International Headache Society); anxiety, depression and quality of life were also assessed. Prospective follow-up using specific headache diaries was then performed at 3, 6, 9, and 12 months.

Results Seventy two patients with SLE, 72 paired controls and 48 patients with MS participated in the study. Migraine was prospectively diagnosed in 21%, 23 % and 22 % of lupus, multiple sclerosis patients and controls, respectively, which was almost identical with data derived from the retrospective evaluation. Aura, migraine frequency and consumption of analgesics were comparable between lupus patients and controls. Frequent Tension Type Headache was equally observed in SLE and controls (both 17%) and MS (19%). In contrast, Chronic Tension Type Headache was significantly increased in patients with SLE (12.5%) and MS

(8.3%), compared to controls (1.4%). SLE patients had significantly more anxiety and depression, and worse quality of life than controls, but headache was not associated with these differences. Any type of headache could not be related to a particular clinical manifestation, type of auto-antibody or overall disease activity in SLE.

Conclusions Migraine should be no longer regarded as a neurologic manifestation of systemic or organ-specific clinical autoimmunity. A higher risk of chronic tension type headache in SLE and MS is probably due to the increased psychological burden associated with these diseases.

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Computer-animated relaxation therapy in children between 7 to 13 years of age with tension-type headache: a pilot study

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Objectives To examine the effects of modified progressive relaxation therapy assisted by computer-animated SEMG at the trapezius muscles. To collect the children's experiences with therapy.

Background Tension-type headache are the most common type of headache illnesses in childhood (Anttila, 2006; Zwart et al. 2004). Interventions with children younger than the age of twelve are challenged by the child's limited ability to participate in cognitive approaches. This study aimed at evaluating the effect of a computer-animated progressive relaxation therapy with children seven to thirteen years of age with frequent or chronic tension-type headache.

Methods Nine children, mean age 10.9 (+/-1.7) years attended a 9 session-modified relaxation therapy and biofeedback. The therapy (Bernstein and Borkovec, 1973) was modified for younger children with pictograms of relaxation exercises for every day use. In sessions the child exercised the technique followed by SEMG-biofeedback at the trapezius muscles (Nexus-10). The feedback provided was music and animations visualizing tension-level. Root mean squares and mean median frequencies were extracted. Pain was measured with Visual-Analogue-Score. Outcome measures were

- headache frequency and intensity
- pericranial tenderness
- tension patterns
- logbook notes, at baseline, postintervention and at 3-month follow-up

Results The results showed a mean improvement of 45% (+/-51) of headache frequency at 3 month follow-up versus baseline (reduction $P \leq 0.03$). Total tenderness score was reduced from mean value 24.6 (6.6) to 18.8 (8.5) from baseline to three month follow up ($P \leq 0.08$). The children expressed a growing understanding of body reactions, and an acquired ability to regulate these. This study suggests that children below the age of 13 need both the dialog and guidance from a participant observer in order to achieve body-awareness.

Conclusion This study, though an uncontrolled pre-post design, suggests that computer-animated relaxation therapy is an applicable learning strategy with younger children with tension-type headache.

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A proactive approach towards migraine patients in general practice: a pragmatic randomized controlled trial

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Objective Optimizing treatment of patients with frequent migraine attacks in general practice by implementing a proactive intervention by general practitioners (GPs). Main goal: a pro-active approach of headache complaints by ensuring adequate management of attacks, stimulating use of prophylaxis and treatment of medication overuse headache.

Design Cluster randomized trial with randomization by GP.

Setting 64 general practices in the Netherlands.

Participants Patients using ≥ 2 triptans per month.

Outcome measures Primary outcome measure: Headache Impact Test (HIT-6) at 6 months. We defined 2.3 points as clinically relevant. Secondary outcome measures: health-related quality of life (EQ-5D), migraine characteristics, medication use and a cost-effectiveness evaluation.

Intervention GPs in the intervention group received training and supporting materials on treatment of migraine according to the guideline for headache treatment from the Dutch College for General Practice. Subsequently, they invited participants for a consultation to evaluate their current migraine therapy. GPs in the control group were asked to continue usual care.

Results We included 490 patients (233 intervention group, 257 control group). The evaluation consultation was attended by 193 (83%) of the intervention patients. After the consultation, 41 patients (18%) started prophylaxis, 27 (12%) continued current prophylaxis, and in 22 (9%) patients the prophylactic treatment was changed. At 6 months the HIT-6 scores in the intervention group were improved 3.1 points, however the difference was only 0.5 points compared to the control group ($p = 0.083$). In patients who did not use prophylaxis at baseline the HIT-6 score improved 0.7 points more in the intervention group compared to the control group ($p = 0.010$).

Conclusions An educational intervention for GPs and a proactive approach of migraine patients resulted in the initiation or change of prophylaxis in 27% of participants. However, the difference in reduction of headache complaints between the intervention group and the control group was not clinically relevant.

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Predictors of headache impact (HIT-6) by migraine status: results from the american migraine prevalence and prevention (AMPP) study

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Background Migraine is a common, disabling neurologic disorder which can impact all aspects of sufferers' lives. Chronic migraine (CM) has been

demonstrated to have even greater impact than episodic migraine (EM) on headache-related-disability, health-related quality of life, direct and indirect costs, and comorbid medical and psychiatric conditions.

Objective To identify predictors of headache impact in EM and CM sufferers in the population.

Methods The AMPP study is a longitudinal, US population-based, mailed survey. Participants eligible for this analysis were respondents to the 2009 survey who met criteria for either CM (ICHD-2 criteria for migraine and ≥ 15 headache days/month) or EM (ICHD-2 criteria for migraine and < 15 headache days/month). The Headache Impact Test (HIT-6) is a validated six-item questionnaire that measures the impact of headache over a 4 week recall period. A series of four hierarchical regression models were fit. Analyses were stratified by CM and EM. Order of predictor-block entry constituting the model hierarchy included demographics (gender, age, population density, household income, US geographic region), headache characteristics [(migraine symptoms, pain intensity, headache-related disability (MIDAS Grade)], depressive and anxious symptomatology, and current preventive headache medication use, respectively.

Results 27,253 questionnaires were fielded and 20,107 were returned yielding a sample of 373 participants with CM and 6,796 with EM. For CM, predictors of HIT-6 score included pain intensity (b(SE) = 0.86(0.16), $p < 0.001$), headache-related disability (b(SE) = 1.35(.26), $p < 0.001$), depression (b(SE) = 2.52(1.0), $p = 0.01$), and anxiety (b(SE) = 0.2(0.07), $p = 0.003$). Demographic variables and preventive medication use were not predictive. For EM, predictors of HIT-6 score were similar to those for CM but also included age (b(SE) = -0.03(0.01), $p = 0.04$) and preventive medication use (b(SE) = 1.26(0.32), $p < 0.001$).

Discussion The impact of CM and EM, as measured by HIT-6, is associated with pain intensity, disability, depression, and anxiety. Age and use of preventive medications are unique predictors of HIT-6 scores for EM.

Conflict of interest Dr. Buse has acted as a consultant or received research support from Allergan Pharmaceuticals, MAP Pharmaceuticals, Merck Inc., and Iroko Pharmaceuticals.

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Bifocal nummular headache: a series of three new cases

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Objective Nummular headache (NH) is a new entity described in 2002 and defined as a chronic head pain felt in a small, well-circumscribed, coin-shaped area, according to the appendix of the International Classification of Headache Disorders II (ICHD-II). The temporal pattern is variable and in situ exacerbations have been described. More than 150 cases of NH have been reported from different countries, and, among them, four patients localized their pain in two separate areas. We present a new series of bifocal NH.

Methods We reviewed all patients diagnosed with NH at the headache units of two tertiary hospitals searching for cases with head pain in two different areas.

Results Three patients (2 female and 1 male; age at onset: 30, 61 and 69 years) had bifocal NH. Neuroimaging studies were performed in all cases with no abnormalities. The shape and size of both painful areas were identical in each patient. The painful areas were located at symmetrical points of either side in two patients (two parietal and two occipital areas, respectively), while the third patient had both symptomatic areas on the same side of the head (temporal and parietal). The chronological pattern was synchronous in one patient, whilst the other two showed an additive pattern with unifocal pain evolving to bifocal pain after 6 months and 30 years, correspondingly. Pain intensity was slightly lower at the latter point in these two cases. In two patients a preventive was prescribed (carbamazepine and gabapentin). In the only synchronous case, the painful areas showed an unequal response to therapy.

Conclusion This series reinforces the proposal of bifocal NH as a variant of NH, thus enlarging its clinical spectrum. Pathogenic mechanisms of NH might be active in different areas in certain patients.

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Epicrania fugax with backward radiation. clinical characteristics of 5 new cases

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Objectives Epicrania fugax (EF) is a novel syndrome described as a paroxysmal and brief head pain, starting in posterior cranial regions and rapidly spreading forward through a linear or zigzag trajectory to ipsilateral eye. Two patients with comparable clinical features stemming from frontal scalp to posterior regions have been recently described and proposed as backward radiation epicrania fugax (BREF). We report a new series of 5 BREF and compare their clinical characteristics with 12 forward radiation EF (FREF).

Methods Since first description of BREF in February 2010, 5 patients (3 males, 2 females) with this clinical picture have been attended at our neurology outpatient office. Comparison is established with 12 EF patients (4 males, 8 females).

Results Magnetic Resonance Imaging and blood tests were performed in all cases with no abnormalities. Pain was strictly unilateral in all patients and was described mainly as electric or stabbing. We found no significant differences between BREF and FREF respectively in age at onset (50 ± 10.6 vs 38.2 ± 15.6 years), attacks intensity (6.4 ± 2.3 vs 7.1 ± 1.8 in a 0-10 visual analogical scale) and duration (16.6 ± 24.4 vs 10.2 ± 16.1 seconds). Number of episodes per day was lower in BREF, not reaching statistical significance (2 ± 3.4 vs 13.2 ± 18 , $p = 0.05$). 7 (58.3%) in FREF but none in BREF group

presented an interictal pain in stemming area. 5 (41.6%) cases in FREF and 1 (20%) in BREF group associated autonomic symptoms. **Conclusion** This series reinforces the proposal of EF as a new headache variant or a new headache syndrome. Clinical picture of brief pain paroxysms starting in anterior scalp and radiating backwards does not fit known headaches or neuralgias and might correspond to a reverse variant of EF, which clinical characteristics are comparable to FREF.

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Prevalence of migraine and headache in Moroccan schoolchildren

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Objective To determine the prevalence rate of migraine in school children aged 6 to 13 years in the city of Agadir.

Background This study is the first survey of migraine in children in Morocco.

Methods 1999 subjects were randomly selected using a multistage clustered sampling procedure. A combination of a questionnaire and clinical interview with examination was used between January and June 2004. 586 children who had reported having moderate or severe headache were invited with their parents to the School's medical room for an interview and clinical examination by a neurologist. 97% attended. Diagnosis of migraine headache was made according to the International Classification of Headache 2004.

Results Participation rate was 93.7% (1874 of 1999). According to the interview and clinical examination, 9.7% fulfilled the criteria for migraine headache. The prevalence of migraine increased with age. Among girls, the prevalence was 10.2% but for boys it was 9.2%. The highest prevalence for girls (25%) occurred at age 12, but for boys the highest prevalence (20%) occurred at age 13. The mean age of onset of migraine was 7.9 years. 52.6% had a frequency of occurrence of one to two attacks per month. In 58%, the headache lasted one to four hours. 64.3% had bilateral location. 78.8% had pulsating quality. Symptoms that were constantly experienced with the headaches were phonophobia 86.2%, photophobia 72% and nausea 61%.

84% had a family history of headache. 30% of subjects had missed school because of migraine attack in the previous 3 months. Doctor attendance rate was very low. 86.7% of migraine sufferers had never consulted a doctor for headache. Of the remaining 13.3% who had seen a doctor, a diagnosis of migraine was not made.

Conclusions Migraine is a common health problem among school children in Agadir. It is still mostly under-estimated and under-diagnosed.

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Chronic and episodic migraine - functional and organic distinctions

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Chronic migraine is complication of episodic migraine. It is considered to be headache during 15 days or more each month within at

least three months period. Chronic migraine should response to treatment with triptans or ergot after eight days at most.

Methods We studied 78 patients with migraine, all female 22 to 52 years old (35,7 years old in average). 46 patients had episodic migraine and 32 patients had chronic migraine. The protocol included neurological examination, questionnaire form filling, doppler ultrasound study, EEG, 3T contrast brain MRI. The MRI protocol included T1WI, T2WI, Diffusion-tensor imaging (DTI), Diffusion-weighted imaging, T2* GRE pulse sequence and MR-angiography.

Results Patients with chronic daily headache had additional complaints concerning disability, memory impairment, reduced attention. MIDAS scale showed 8,3 total in patients with episodic migraine and 25,8 total in patients with chronic migraine. In patients with chronic migraine EEG study showed diffuse functional cortex disorganization. Doppler US results showed increased perfusion in MCA of relevant brain hemisphere with headache location. MRI study detected lesions in brain white matter in 78% of total patients and in 100% of chronic migraine patients. White matter lesions varying in size between 2 and 8 mm were visualized mostly in frontal and temporal lobes in subcortical area. Multiple lesions were found in patients with chronic migraine. Single lesions were found typically in patients with episodic migraine. FLAIR imaging proved to be the optimal MRI pulse sequence for detection of migraine lesions. The number of lesions does not depend on presence of migraine aura but depends only on migraine attacks frequency and duration of disorder.

Conclusion There is an organic difference between chronic and episodic migraine which requires special attention from medical society. White matter lesions in brain MRI reflect the intensity of the disease.

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Living knowledge of the healing plants: results from a cross-sectional study in Kishoreganj district of Bangladesh

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Various types of body pains are common afflictions affecting people throughout the world. A more debilitating type of pain arises from migraines and headaches, which is believed to affect at least 13% of the world's population, mostly the elderly. Since regular use or over-use of various pain-killer drugs may have side-effects, an alternative route to treat pain is through use of plants provided by the traditional medicinal practitioners and which are generally believed to be without any side-effects. The present study was carried out in Kishoreganj district of Bangladesh; to gather information on plants used to treat various types of pain. Extensive interviews were conducted of the traditional medicinal practitioners and information collected as to plants or plant parts used and the ailments treated. All plants were identified and vouchers were stored at the Bangladesh National Herbarium; under the author's collector series. Plants used to treat migraines and headaches included *Santalum album* (L.), *Periploma indica* (L.), *Coccinia cordifolia* (L.) Cogn., *Datura metel* (L.), *Achyranthes aspera* (L.), *Bacopa monnieri* (L.) Pennell, *Aloe vera* (L.) Burm.f., *cocos nucifera* (L.), *Ipomoea aquatica* Forssk., *Ocimum gratissimum* (L.), *Iawsonia inermis* (L.), *Cinnamomum*

camphora (L.) Sieb., and *Nigella sativa* (L.). Plants used to treat general body pains included *Olea europaea* (L.), *Curcuma longa* (L.), *Chenopodium ambrosioides* (L.), *Musa sapientum* (L.), *Nicotiana tabacum* (L.), *Brassica napus* (L.), *Alternanthera glabra* Moq., *Allium cepa* (L.), and *Linum usitatissimum* (L.). *Paederia foetida* (L.), *Amaranthus viridis* (L.), and *Wedelia chinensis* (osbeck) Merr. was used to treat stomach pains, while *Cissus quadrangularis* (L.), *Randia dumetorum* (retz.) Poir., and *Allium sativum* (L.) was used to treat rheumatic pains. Information on indigenous use of plants has led to discovery of many medicines in use today. Scientific studies conducted on the above-plants may lead to discovery of more effective drugs than in use at present.

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Local administration of herbal medicine in treating insomnia disorder: an ethnographic case study from Habiganj district of Bangladesh

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Insomnia disorder is the most common sleep disorder which affected more than 18300000 people in Bangladesh. 7600000 people develop chronic insomnia disorder with symptoms of difficulty falling asleep for more than 30 minutes and last for more than 01 month. Patients with insomnia disorder in Bangladesh took 2900000 sleeping pills each year for insomnia disorder. However, there were still some side effects about sleeping pills such as allergy, amnesia, hallucination etc. Because of the side-effects of modern medicines and because of the inability of modern medicines to cure insomnia disorder, international scientific interest has re-focused on the traditional uses of medicinal plants to find effective cure for insomnia disorder as well as hundred of other disorders. A study of traditional health practitioners in Habiganj district of Bangladesh suggested that some of the herbal medicines prepared from medicinal plants might be quite effective for insomnia disorder. Interviews were conducted with the help of a semi-structured questionnaire and medicinal plant samples as pointed out by the traditional health practitioners were collected and identified at the Bangladesh National Herbarium. In the current study 24 medicinal plants belonging to 23 genera and 21 families were found to be used to treat insomnia disorder. These medicinal plant family names included *Fabaceae* Lindl., *Rutaceae* Juss., *Convolvulaceae* Juss., *Piperaceae* Bercht. & J.Presl, *Papaveraceae* Juss., *Apocynaceae* Juss., *Cucurbitaceae* Juss., *Solanaceae* Juss., *Amaranthaceae* Juss., *Plumbaginaceae* Juss., *Lamiaceae* Lindl., *Meliaceae* Juss., *Linaceae* S.F. Gray, *Ranunculaceae* Juss., *Santalaceae* R.Br., *Scrophulariaceae* Juss., *Asparagaceae* Juss., *Asphodelaceae* Juss., *Arecaceae* Schultz-Schultzenstein, *Lythraceae* J.St-Hil., and *Lauraceae* Juss.. It was noted in this study that the patients were quite satisfied with treatment by the traditional health practitioners. It is important that modern scientific studies be conducted on these medicinal plants towards isolation and identification of compounds through which insomnia disorder can be effectively treated.

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Headache frequency in Germany remains constant from 1995–2009: results from yearly population-representative cross-sectional studies

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Population-based cross-sectional studies on the prevalence of headache disorders are available for several countries, but there are only few studies on the development of this prevalence over longer time periods. Now, for the first time, data are presented for the German Federal Republic for the period 1995-2009. Due to relevant methodological differences, the data for 2006-2008 are not considered.

The cross-sectional studies were implemented as surveys once yearly by Ipsos GmbH, from 1995 as PAPI, and from 2005 in the form of CAPI. Randomly selected German-speakers aged 14 and over living in private households throughout Germany were surveyed (N = 10898 - 12538). The following sociodemographic data were measured: gender, age, school education, occupation, current job, net household income, and in random order, up to 31 illnesses, including self-diagnoses of headache and migraine, which as self-diagnoses by the sufferers are not in accordance with ICHD-2.

Headache prevalence has remained stable over the years, at 58.8 - 62.5% (women: 67.3 - 70.7%; men: 48.4 - 54.3%). There is no difference between West Germany and East Germany (former GDR). Urban populations (city size > 50,000 inhabitants) show, in the sliding 4-year average prevalences, a trend towards a 3-4% peak higher headache prevalence than the population in small towns or cities or in rural areas. No differing headache prevalences can be discerned either for different occupations or for different net household incomes. Only the highest net income group (> €3,500) shows a trend towards higher 4-year average prevalences. On the one hand, the results correlate well with the results from a large American study, which also found a trend towards higher headache frequency in large cities. However, in contrast to the American findings, in Germany, no trend towards a higher prevalence in the shares of the population with a low income is apparent.

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Characteristics and self-medication of headache in germany 2007/2008 - results of a representative population survey

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So far, very few population-based cross-sectional studies are available on characteristics of headaches, and particularly over-the-counter treatments. New data for the German Federal Republic are presented here.

This representative cross-sectional study was conducted as an omnibus survey in 2007/2008 through “Computer-Aided Personal Interviews”. 15,802 persons were surveyed, selected through random-route procedures. Participants were aged 14 years and over, German-speakers, and living in private households throughout Germany.

Besides sociodemographic data, in random order, 31 illnesses were assessed, including self-diagnosis of headache and migraine (non-ICHD-2-compliant), headache characteristics and data on the use of headache preparations.

48% of participants suffered from headache within the last year and 41.3% within the last 4 weeks (proportion of women 61.4% and 63.1%, respectively). Headaches had occurred for 2 - 10 years in 43.6% (women 42.9%, men 44.5%) and for > 10 years in 39.8% (women 42.5 %, men 35.5%). For 63.3% of sufferers, headache severity had remained the same compared to previous years; for 18.6% it was stronger, and for 14.1% weaker. Headache frequency was constant for 58.1% of sufferers, increasing for 18.5% and decreasing for 19.7%. The stronger the headache, the more frequent complaints of further illnesses and the more frequent the doctors' consultations. Nevertheless, the proportion of sufferers with strong headache who consulted doctors lay at only 24%.

Independently of the time window (4 weeks vs. 12 months), approximately 81% of sufferers (approx. 64% women) took headache preparations. Highly predominantly, 1 - 2 different preparations were used (85%); only 0.3% mentioned ≥ 5 . Over 97% of participants took headache medication on a maximum 10 days per month. < 1% of sufferers took over six tablets daily. Medication doses correlated with pain severity.

In summary, headaches occur frequently; improvements and deteriorations over time are approximately equally frequent. Acute medication is used frequently and predominantly responsibly.

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Differences in the use of analgesics for self-medication of headache - results from a German representative population survey 2007/2008

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The majority of headache sufferers successfully treat their headaches with over-the-counter migraine and headache remedies. So far, differences in the use of these treatments have barely been examined. First data are available from a German population-based cross-sectional study conducted in 2007/2008.

This representative study was conducted as an omnibus survey in 2007/2008 through “Computer-Aided Personal Interviews”. 15,802 German-speakers aged 14 and over from private households in Germany were selected through the random-route procedure and surveyed.

Besides sociodemographic data, 31 illnesses were assessed in random order, including self-diagnoses of headache and migraine (non-ICHD-2-compliant), headache characteristics and detailed data on preparations used (including brand name) and manner of use.

4,665 headache sufferers provided information regarding utilisation duration and dosage of the examined 7 proprietary medicinal product brands, and 3 medications predominantly containing the generic active ingredients (acetylsalicylic acid [ASA], ibuprofen, paracetamol). Five of these 10 user groups indicated taking these preparations for longer than 3 consecutive days within the last year: a proprietary drug with 1000 mg ASA (4.24 days), ibuprofen-containing preparations (3.69 days), proprietary drugs with 400 mg or 200-400 mg ibuprofen-lysinate (3.29 or 3.14 days, respectively) and ASA-containing products (3.04 days). By contrast, combination analgesic with 250 mg ASA, 200-250 mg paracetamol, and 50 mg caffeine were taken for max 2.88 days, and effervescent tablets with 300 mg ASA and 200 mg paracetamol for max 2.12 days. Permitted daily doses were exceeded for the ibuprofen-lysinate- or ASA-containing proprietary drugs marked with the brand name addition “migraine”, and for the ibuprofen-containing medicines. Of these, up to one fifth of headache sufferers took more than the highest daily dosage recommended in the patient instruction leaflet. For paracetamol or the fixed combination analgesics, by contrast, this was only observable in approx. 1%. Besides other factors, the medication description appears to influence utilisation behaviour.

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Prevalence and clinical characteristics of primary headache in Korea: a nationwide population-based survey

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Background and purpose Since International Classification of Headache Disorders was announced in 1988, many epidemiological studies on migraine have been performed. However, the epidemiology of headache disorders in Asian countries is only partly documented. We investigated the prevalence and clinical characteristics of primary headache in Korea in 2009.

Methods Among Koreans of 19 years old or above, we randomly selected 1,507 target population by stratified random sampling with clustering, regarding area, age and gender. Face to face survey was conducted by structured interview using 29-item questionnaire in 2009. The questionnaire includes basic demography, headache characteristics, associated symptoms, occupation, income, headache related disability, and use of medical care. Headache characteristics and associated symptoms were constructed to sort out migraine and tension-type headache based on ICHD-II and to investigate clinical characteristics of both headache disorders.

Results One year prevalence of all types of headache was 61.4%. The overall prevalence rates were 6.0% (9.2% in females and 2.9% in males) for migraine and 30.7% (29.3% in females and 32.2% in males) for tension type headache. The prevalence of migraine peaked at the ages of 40-49 years in overall and female cases, respectively, but of 19-29 years in males. Almost one-third of migraineurs reported as being substantially or severely impacted by migraine (HIT-6 scores ≥ 56). Only 28.9% of migraineur visited doctors for their

headache and 4.4% of migraineurs knew their correct diagnosis. Migraine patients most commonly treated their headache (51.6%) with OTC drugs and only 18.7% of migraineur treat their headaches with prescription drugs in last one year.

Conclusions While the prevalences of migraine and tension type headache in Korea are lower than those in Western countries, they are similar to those of other Asian countries. Although headache related disability is substantial, headache patients still remain inadequately diagnosed and treated.

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Effects of cortical spreading depression (CSD) on C-FOS expression in rat periaqueductal grey matter

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Background The migraine aura is likely due to Cortical Spreading Depression (CSD), a neuro-glial event associated with propagating depolarisation followed by prolonged neuronal inhibition. It is not clear if CSD is also responsible for the activation of the neuronal systems causing the migraine headache and the associated autonomic symptoms. The periaqueductal grey matter (PAG) is involved in pain and autonomic control and possibly in migraine pathophysiology.

Objective Our objective was to search for neuronal activation induced by experimental KCl-induced CSD in the PAG.

Method We induced CSD during 2 hours by cortical application of KCl in anesthetized rats (n = 6 per group) treated daily for 1 month with NaCl or lamotrigine (LTG) (15 mg/kg) and used non-stimulated animals as controls. Fos immunocytochemistry was performed on serial transverse sections of the brain stem and immunoreactive nuclei were counted in rostral (*Bregma* -6.5 mm) and caudal (*Bregma* -8 mm) PAG using an image analyzing system. We used the Mann-Whitney U test to compare controls to CSD + NaCl and the latter to CSD + LTG.

Results The number of Fos-immunoreactive nuclei was significantly reduced in both rostral and caudal PAG after CSD, more so in LTG-treated rats. The median number of Fos-positive neurons in rostral PAG was 126 [75% CI: 64-294] in controls, 42 [29-50] in the CSD + NaCl group (p = 0.03) and 16 [14-27] in the CSD + LTG group (p = 0.02). The respective numbers in caudal PAG were 75 [54-134], 38 [37-41] (p = 0.03) and 31.5 [21-35] (p = 0.2).

Conclusion CSD significantly decreases neuronal activity in the periaqueductal grey matter which might promote the occurrence of central sensitization and headache during attacks of migraine with aura, as well as associated autonomic disturbances.

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Involvement of latent Herpes Zoster Virus in the development of forehead allodynia and aggravation of cluster headache (2nd report)

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Background and aim Joseph R and Rose FC reported the possibility of an association between cluster headache and herpes simplex in 1985 (Joseph R et al. BMJ 1985; 209: 1625-6.). We, however, lately experienced several cases developed forehead allodynia and aggravated cluster headache after onset of herpes zoster. Accordingly, we deemed latent herpes zoster virus (varicella-zoster virus, VZV) infection in the trigeminal and occipital innervations areas may be involved in the development of forehead allodynia and aggravation of cluster headache. The aim of the present study is to confirm an association between cluster headache and herpes zoster. We still reported an interim result of the present study at the 14th International Headache Congress 2009 in Philadelphia.

Methods We conducted a retrospective review of 27 patients (female vs male = 1:2, mean age 38.0 ± 8.6 yrs) diagnosed with migraine (based on the ICHD-II) who had measured values of antibody titer to VZV. Ethic aspect was considered based on the ethic guideline of clinical research published in Japan.

Results VZV antibody titer in 70% of 27 patients was increased with reactivation. In 4 patients, VZV antibody titer in episodic duration was trended to be high. Thus, VZV antibody titer was expected to detect initiation of episodes of cluster headache. It was deemed that central sensitization in the trigeminal and occipital innervations areas is developed due to reactivation of VZV. We further investigated DNA test in serum, but not detected antigen of VZV in pre- and post-episodic points so far.

Discussion We're further investigating DNA test in tears to detect antigen of VZV in pre- and post-episodic points on the basis of a method by Furuta et al (J Clin Microbiol 2001).

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PDE8A expression in the rat brain. implications for migaine?

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Phosphodiesterase 8A (PDE8A) is an enzyme responsible for the hydrolysis and inactivation of cAMP. It modulates the levels of intracellular cAMP available for signal transduction. The only available inhibitor, although unspecific, is dipyrindamole which is known to cause headache. Only few reports had addressed the presence of PDE8A in the brain and none in the pain pathway. We investigated the distribution of PDE8A in male Sprague-Dawley rats with emphasis on migraine related structures such as dura, cerebral arteries, trigeminal ganglion, trigeminal nucleus and thalamus by immunohistochemistry. This was supplemented by protein extraction from selected regions followed by Western blotting. We show that in both the brain and the trigeminal ganglion, PDE8A was confined to neuronal perikaryal cytoplasm as well as to processes extending from these perikarya. The neurons exhibiting PDE8A-immunoreactivity were widely distributed in the forebrain, brain stem, and cerebellum as well as in the trigeminal ganglion. Immunoreactive neurons were located in the olfactory bulb, the septal area, zona incerta, and reticular nucleus of the thalamus. In the brain stem, strong immunoreactive neurons were present in substantia nigra and the sensory trigeminal nucleus. Outside the brain parenchyma, PDE8A immunoreactivity was present in the dura mater, and in the neurons of the

trigeminal ganglion. The localization of PDE8A involves brain areas of pain transmission, motor function, cognition, vegetative functions, and olfaction. Development of selective PDE8A inhibitors or activators is needed for a further understanding of the functional role of PDE8A in the brain and in migraine in particular.

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Experience with onabotulinumtoxinA (BOTOX) in chronic refractory migraine: focus on severe attacks

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Objectives To analyse our experience in the treatment of chronic migraine (CM) with onabotulinumtoxinA (BTA) and specifically in its effects over disabling attacks.

Patients and methods Patients with CM and inadequate response or intolerance to oral preventatives were treated with pericranial injections of 100-150 Units of TBA every three months. Patients filled in a headache diary. In addition, we specifically asked on the effect of BTA on the frequency of disabling attacks, consumption of triptans and visits to emergency for the treatment of severe attacks.

Results This series comprises a total of 34 patients (3 males), aged 24-68 years old. All except 3 met IHS criteria for analgesic overuse. The number of sessions with BTA ranged from 1 to 15 (median 3). Nine (26%) responded (reduction of > 50% in headache days). However, the frequency of severe attacks was reduced an average of 53.1% (range 30-90%) in 82% of the patients. Twenty-two (76%), out of the 29 patients who were taking oral triptans, reduced triptan consumption an average of 50% (from 22 to 11 tablets per month). Those 6 patients who used subcutaneous sumatriptan reduced its consumption a mean of 69.1% (from 4.5 to 1.5 injections per month). For the whole series, visits to emergency decreased from an average of 24 to 4 per month (-83%). Six patients complained of mild adverse events, transient local cervical pain being the most common.

Conclusions In clinical practice, treatment with BTA reduces the frequency of disabling attacks, the consumption of triptans and the need of visits to emergency at least by at least half. This makes this treatment option profitable both clinical and pharmaco-economically.

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Prevalence of right-left shunts on CTCD in chronic migraine and medication overuse headache: a cross-sectional study

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Background Various epidemiological studies show that a patent foramen ovale (PFO) is more prevalent in episodic migraine with aura. There is also circumstantial evidence from observational studies

that endovascular closure of a PFO ameliorates migraine with and without aura. Recently, it was suggested that PFO may be related to attack frequency and highly prevalent in chronic migraine.

Objective Assess the prevalence of a right-left (R-L) shunt on contrast enhanced transcranial Doppler (cTCD) in patients suffering from chronic migraine (CM: ICHD-II A1.5.1) or medication overuse headache (MOH: ICHD-II A8.2).

Methods This was a multicentre study involving 3 European Headache Centers. For logistical reasons, recruitment was asymmetrical: 102 patients in Liège, 48 in Copenhagen, 9 in Essen. cTCD was performed according to international recommendations (Angeli et al 2001, Droste et al 2002) at rest and during Valsalva manoeuvres. R-L shunts were graded according to the 3 grade International Classification System.

Results Fifty-seven CM and 102 MOH patients were included. In the CM group a R-L shunt was detected at rest in 12.3%, during Valsalva in 36.8 %; 10.5% had grade 3 shunts. In the MOH group, 30.4% of patients had a R-L shunt among whom 14.7% at rest and 12.8% grade 3. Migraine with aura attacks occurred in 53 % of CM and 28% of MOH; a R-L shunt was found in 44% of the former (28% grade 3), in 37% of the latter (31.6% grade 3). There was no significant difference between the two patients groups.

Conclusion Prevalence of R-L shunts in CM (36.8%) and MOH (30.4%) is at the higher range of that reported in normal controls (35%). This is at odds with Nahas et al (2009) who found a 66% prevalence. The difference could be due to a lower proportion of migraine with aura patients in our study.

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Illness perception: a discourse analysis of migraineurs from the general population

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This study aimed at describing the cognitive representations of migraine through the migraineurs' discourse on a representative sample of subjects taken by random from the GRIM 3 study which was an epidemiological cross-sectional study led on a representative sample of the French general population. We perform a quantitative analysis of discourse using the ALCESTE software. It enables us to automatically quantify a text in order to extract the most significant structures from it. A statistical analysis is performed so as to check that the over-representation of structures isn't due to chance. The automatic analysis of discourse is a way used in this work to enable filtration of the researchers' projections that can often be noticed in procedures of content analysis. An interview grid was worked out in order to gather the representations of migraine through nine open-ended questions. The population was composed of 51 subjects (11 men and 40 women) aged 19 to 74 (m = 41,25 years). The analysis shows that throughout the corpus, the word "migraine" doesn't appear spontaneously and to the subjects, headaches only are successive crises,

not a global disease that may require long-run treatment. In fact, it seems that migraine as a chronic disease is not well understood; the people rather have this successive crises type of representation. In the reactions to the crises, it may be intriguing not to find any clue evoking the field of catastrophizing. However, the cognitive coping strategy of resignation is to be found. The favourite interlocutor to start a therapeutic education of the patient is the general practitioner since subjects say they do not expect anything of the kind from the media. The results allow us to propose interventions that include patient education and cognitive and behavioral therapy centred on the feeling of loss of control and resignation.

Conflict of interest C. Lucas has perceived personal fees for activities (consulting, clinical research) with Allergan, Almirall SAS, Astra Zeneca Pharmaceuticals, Boehringer Ingelheim, Bouchara Recordati, Glaxo-Smith Kline Inc, Menarini, Merck, Pfizer Inc, Sanofi-Aventis, Servier.

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Exercise as migraine prophylaxis - a randomized controlled study using relaxation and topiramate as controls

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Objectives The aim of the study was to evaluate exercise in migraine prophylaxis and to compare it with well documented pharmacological and non pharmacological alternatives.

Patients and methods This was a three armed randomized, controlled trial. After a baseline period, 103 patients with 2 - 8 migraine attacks/month were randomized to one of three treatments (exercise, topiramate or relaxation) during a period of 12 weeks. Exercise consisted of indoor cycling for 40 minutes, three times/week. Relaxation was done with a physiotherapist once a week at a clinic and daily with a CD at home. The topiramate group was followed by a neurologist. Migraine attack frequency, migraine days/month, pain intensity, acute medication use, quality of life and oxygen uptake were evaluated throughout the study. Long-term follow up was done 3 and 6 months post treatment.

Results Out of the randomized patients, 91 patients were included in the intention to treat analysis. There was no significant difference between the groups regarding migraine attack frequency during the last month of treatment compared to baseline ($p = 0.95$). There was a significantly higher decrease in pain intensity in the topiramate group compared to exercise and relaxation ($p = 0.04$). In the exercise group, oxygen uptake increased significantly compared to the other groups ($p < 0.01$). No differences between the groups were found concerning any of the other secondary variables. No adverse events were reported by patients in the relaxation or the exercise groups, but by eight patients (33%) in the topiramate group.

Conclusion Exercise may be an option for the prophylactic treatment of migraine in patients who do not benefit from, or want, daily medication.

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Reproducibility of salivary CGRP level measurements after capsaicin stimulation in human volunteers

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Objective To assess capsaicin-induced i) secretion of salivary calcitonin gene-related peptide (CGRP); and ii) day-to-day reproducibility and reliability of salivary CGRP measurements in humans.

Background CGRP is assumed to play a key role in migraine pathophysiology and can also be found in mandibular trigeminal nerve endings. Irritants such as capsaicin activate these nociceptive fibres, resulting in CGRP secretion. This model can be used to study trigeminal sensitization, but few data are available on optimum capsaicin concentration and day-to-day reproducibility.

Methods Thirteen healthy volunteers were exposed on two consecutive days to 8 increasing concentrations of Madame Jeannet pepper extracts containing capsaicin. Extracts were intermittently applied on the tongue during 5 minutes and secreted saliva was collected. Saliva volume (ml), protein content (mg/ml) and CGRP (pg/ml;pg/5 min) were measured. Optimum capsaicin concentration was defined as the concentration with highest CGRP secretion (linear-regression model) whilst heat-sensation was still tolerable. Day-to-day reproducibility was assessed using repeated-measures ANOVA with day number and capsaicin concentrations as factors.

Results On both days, maximum salivary CGRP content (pg/ml; mean[SD]) using highest extract concentration was significantly higher than at baseline (Day 1:13.2[6.7] vs. 10.3[2.0], $p = 0.011$; Day 2:13.3[3.3] vs. 9.1[3.6], $p = 0.004$). CGRP secretion correlates positively with extract concentration on day 1 ($p = 0.028$) and day 2 ($p < 0.001$). This was reproduced in a second study (not-diluted extract: 161.6[80.9] vs. baseline: 99.4[7.2] (pg/5 min.), $p = 0.037$), showing CGRP increase even after adjusting for possible capsaicin/CGRP cross-reactivity. Not-diluted extract was tolerated by all participants. Assessing day-to-day reproducibility showed a significant ($p = 0.001$) effect for extract concentration (pg/ml); not for day number ($p = 0.136$) or day/concentration interaction ($p = 0.600$).

Conclusion Salivary CGRP concentrations are positively correlated to orally applied capsaicin concentrations. Highest concentrations are measured after stimulation with non-diluted pepper extracts. Measurements of salivary CGRP are reproducible on a day-to-day basis without evidence for day-to-day depletion or sensitisation effects.

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Chronic headache in paediatric age

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Introduction In 2004 we underlined that chronic headache was an emerging phenomenon not present during the preceding decades.

Aim To update the casuistry of chronic headache in children and indicate possible impact of psychological factors. We can establish now that in the period 2004–2010 we can see the following proportions when comparing the number of cases of affected adults with the number of affected children. Psychometric measures were compared to the ones given in 2004 to observe their relevance.

Results The proportion of cases of children affected by a given chronic headache is expressed as the ratio x children : 1000 adults, both affected by a specific headache. Chronic migraine 120:1000 (male: female = 4 : 6) total number 84, chronic cluster headache 100:1000 (male : female = 4 : 6, age 15–18) total number 80, chronic tension-type headache 300:1000 (male : female = 12 : 3) total number 16, chronic paroxysmal hemicrania 1000: 1000 (male: female 2 : 6) total number 32, new daily persistent headache 1000:1, (male female1:10) total number 22. Results of psychometric tests regarded chronic headache sufferers compared with those ones of a sex-age matched control group of exempts (n = 170) and indicate no significant difference as stated by Parental Bonding Instrument, CBLC, Conners' Scale, Wang, Zung tests. Our casuistry stresses that:

- (a) new daily persistent headache occurs particularly in children,
- (b) chronic cluster headache is more frequent in young females than in males,
- (c) new daily persistent headache seems peculiar to males.

Conclusions Total number of children with chronic headache was 42 versus 1000 adults in 2004, after 6 years children are 234 :1000 with an increase over 5 times versus 2004 and augmentation over 450 times versus 1998 when only 5 child suffered from chronic headache versus 1000 adult chronic sufferers.

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Leuprorelin as therapy of chronic cluster headache refractory to conventional prophylactic therapies and deep brain stimulation: open label observation

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Aim To treat intractable chronic cluster.

Subjects and procedure Cluster headache (CH), an extremely painful syndrome may be refractory to therapies as carbolithium, verapamil, corticosteroids, topiramate and gabapentin. In completely refractory sufferers Deep Brain Stimulation (DBS) was used. The present observation included Group A: 67 (66 males, 1 females, mean age 42.4 ± 3.2 SD) chronic CH sufferers (attacks n = 3–6/day, duration 35–67 min) previously unsuccessfully treated with mentioned prophylactic medication and Group B: 4 (2 females, age 29–58) chronic cluster headache sufferers (attacks n = 7–11/ day, duration 47–110 min) previously unsuccessfully treated with prophylactic medications and DBS. All the enrolled subjects showed an acute abortive drug abuse: Sumatriptan in Group A (60–80 mg/s.c/day) or Tramadol (1500 ± 5.50 SD) sometimes (38% of the days) associated with Sumatriptan (24–42 mg/s.c/day/) in Group B. Leuprorelin 11,75 mg was given once a month in Group A, five times/month in Group B. The treatment duration in Group A was 2–3 months (mean 2.1 ± 1.0 SD). Fifty% relief was achieved during the first 14 days.

Results and conclusion The benefit consisted in a complete relief for a period of 10–15 months (mean 12.1 months ± 3.2 SD), following, 18 suffers had a relapse with 2–4 attacks/ day which disappeared in a week following 1 injection of leuprorelin. The other patients had no relapse during the following 4 years. Differently Group B need more frequent administration: 5 vials/month. Nevertheless, following 6 months they have no more than 0–4 attacks/month (mean 2.8 ± 1.9 SD) versus 7–11/ month . They also use no more tramadol nor abuse sumatriptan. Patients did not reported serious adverse effects; there is no drop-out. In males, deficit of sexual desire was abolished by concomitant use of testosterone 50 mg/day/orally.

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Migraine susceptibility and post-dural puncture headache; report from lumina

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Objectives To assess

- (i) whether migraine susceptibility increases the risk of developing post-dural puncture headache (PDPH);
- (ii) which factors increase this risk, and
- (iii) which factors predict longer PDPH duration.

Background Hypotheses on PDPH aetiology include loss of cerebrospinal fluid (CSF), and cerebral venous vasodilatation. Headache/migraine susceptibility may increase the risk of developing PDPH but no systematic studies have been performed. To our knowledge, this is the first study systematically comparing this risk in migraineurs to controls.

Methods Migraineurs and controls underwent lumbar puncture (LP) for CSF collection between 8.00–12.00a.m, using traumatic needles. Participants were contacted three days afterwards and when relevant, PDPH was diagnosed. PDPH prevalence was compared between groups using χ^2 -test. Factors significantly increasing PDPH risk or contributing to PDPH duration were identified using logistic/linear models, corrected for age, gender and BMI.

Results In total, 156 participants (107 migraineurs; 49 controls) underwent a successful LP. Forty-five (28.8%) developed PDPH, all within 3 days. This is comparable with data from earlier studies. Migraineurs suffered significantly less often from PDPH than non-migraineurs (21.7% vs. 42.8%; $\chi^2(1, n = 155) = 7.38$, $p = 0.007$). Using logistic models, the following factors were found to significantly increase the risk of developing PDPH: lower BMI ($p = 0.048$); being non-migraineur ($p = 0.046$), increased duration of fastening ($p = 0.030$), and higher reported headache-score directly after LP ($p = 0.001$). PDPH prevalence also depended on age (maximum at age 20–30yrs), albeit not significant. PDPH duration (spontaneous recovery; $n = 36$) was significantly longer when subjects had suffered from affective disorders ($p = 0.005$); when LP was performed in one effort ($p = 0.003$); and in subjects reporting higher stress during LP ($p = 0.009$).

Conclusion Our study shows that migraine susceptibility does not increase the PDPH risk. Factors that increase this risk are lower BMI; longer fastening prior to LP; and higher reported headache severity directly after LP. Possible explanations for this difference will be discussed.

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Propofol narcosis in refractory chronic cluster headacheM. Nicolodi^{1,2}¹Interuniversity Centre of Neurochemistry and Clinical Pharmacology, Florence, Siena, Italy;²Foundation Prevention and Therapy Primary Pain and Headache, Florence, Italy**Aim** To define usefulness of propofol in refractory cluster.

Procedure In five chronic cluster headache who reported none or very transitory (less than 30 days) benefit following deep brain stimulation, eptadone was overused (40 mg e.v./ 3 times/day) during 3-months treatment-period/yearly; patients were interviewed following 3-4 eptadone treatment-periods carried out in different medical structures. They stated they received no benefit and suffered drowsiness, disorientation and dizziness. Largely better result was achieved by using tramadol the use of which was continued in the years in extremely large doses (1500 mg/day \pm 5.5 SD). In spite of opiates abuse, the continuous onset of attacks led to 4/5-days lasting propofol narcosis. The communicated protocol was: injection in rapid succession of propofol, succinylcholine, fentanyl. First bolus of propofol was 200 mg, after propofol was given 7 mg/Kg/h. Narcotic treatment lasted 4-6 days varying with appearance of abnormalities regarding aminotrasferase levels, hepatic cytolysis, infections, thrombosis. Patients who underwent the treatment stated the approach was useful in giving a period of vacancy from pain.

Results Unfortunately the vacancy-period was shorter and shorter in the time starting with 2 months and reaching 2-4 days following the 4th narcotic treatment. When the benefit decreased patients started with tramadol till the next narcosis. As the vacancy period stopped the restarting of cluster headache attacks was excruciating with high daily number of attacks (7-11/day). Patients suppose there is no way to live otherwise.

Conclusion Propofol

- acting on GABA-A for immobilizing action is not proved to have activity on NMDA negative modulation,
- researches show propofol degenerative action on neural structures,
- GABA-A can transitorily modulate pain perception in spinal-cord, therefore, as regards 4-6 days propofol narcotic treatment, basic science data and clinical evidences suggest only transitory effects and not prophylactic properties in refractory chronic cluster headache associate to opioids abuse.

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Features of cluster headache refractory to conventional therapies and deep brain stimulationM. Nicolodi^{1,2}¹Interuniversity Centre of Neurochemistry and Clinical Pharmacology of Idiopathic Headache, Siena University, Florence, Italy;²Foundation Prevention and Therapy Primary Pain and Headache, Florence, Italy

Subjects' history Five subjects (3 males age range 29-58 years) suffering from chronic cluster headache (CH) had been evidenced to be absolutely refractory to conventional therapies: carbolithium,

verapamil, corticosteroids and open label therapies as topiramate and gabapentin as add on medications. CH was chronic since at least 2 years (mean 5.6 \pm 1.38 SD). Pain was fixed unilateral for at least 12 months and associated with the autonomic symptoms peculiar to CH. Frequency of the attacks/ day was from 7 till to 11, duration of attacks ranged from 47 to 110 min. Deep Brain Stimulation was performed following the same scheme in all the 5 subjects. Briefly, electrode implantation in the posterior hypothalamus -position as indicated by May et al-. Position checked by postoperative MRI. Only one out of the patients reported a benefit lasting 28 days after electrode implantation, after, a sharp relapse followed. The other patients never reported benefit. In 2 (1 male, 1 female) of them there was a switch of pain to the other side of the cranium. A second implantation produced no result.

Features and conclusion The chief characteristics of the refractory patients were: They have first and second degree consanguineous suffering from migraine. One of them also listed a first degree consanguineous suffering from episodic CH. Another one a third degree with CH. All these patients were prescribed opiates and started a large overuse/abuse of the opiate spurious compound tramadol (1500 mg/e.v./day \pm 5.50 SD) as well eptadone (40 mg e.v. three times a day). Tramadol and eptadone were not associated; the index of preference was favourable to tramadol periodically associated with sporadic over-use of sumatriptan (32 \pm 18 mg/s.c./day). The overuse/abuse of opiates is seemingly responsible for an "medication overuse/abuse cluster headache" crucial for "chronification" with "a pavement of hereditary pain proneness".

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Posttraumatic stress syndrome in relation to chronic posttraumatic headacheD. Kjeldgaard¹, H. Forchhammer², R. Jensen¹¹Danish Headache Centre, Department of Neurology, Glostrup, Denmark;²Department of Neurology, Glostrup Hospital, University of Copenhagen, Glostrup, Denmark

Introduction Minor traffic accidents, falls from a stair or other situations that can cause mild head traumas are not potentially life threatening events. Patients with chronic posttraumatic headache (CPTH) after such mild traumatic brain injuries (mTBI) may develop cognitive, somatic and affective symptoms that could imply, that the physical trauma have had a greater psychological impact than first expected. The objective of this study is to examine the occurrence of posttraumatic stress disorders (PTSD) in patients with CPTH after mTBI.

Methods The Harvard Trauma Questionnaire (HTQ) is a self-report scale including 17 items focusing on the trauma, and measures the intensity of the three core symptom groups; re-experiencing, avoidance, and hyper-arousal. The total score estimates whether or not a person suffers from PTSD. In a large research project regarding psychological profile and treatment of CPTH, 30 patients were consecutively included. Before entering psychological treatment in The Danish Headache Centre the patients completed the HTQ.

Results 20 women and 10 men were included (mean age 35 years, range 19-63). On average the trauma had occurred 38 months (range 10-119) prior to enrolment. The causes of injury were: 12 traffic accidents (40%), 2 sports injuries (7%), 11 falls (37%), 1 assault (3%) and 4 other causes (13%). Nine patients (30%) met all three core symptoms of PTSD, and additional 10 patients (33%) reached the sub-clinical level of PTSD. Only 11 patients (37%) had no PTSD symptoms. Of the three core symptom groups, hyper-arousal had the highest relatively score over-all.

Discussion These results suggest that 2/3 of the patients with CPTH have PTSD or the sub-clinical level of PTSD. This information could be important in relation to the planning of treatments; psychological as well as pharmacological treatments. Likewise, this overlap may also indicate shared pathophysiological mechanisms although the cause-effect relations are unknown.

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Assessment of the safety and tolerability of NXN-188 dihydrochloride in healthy volunteers and migraineurs

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NXN-188 Dihydrochloride (NXN-188) is being developed a first-in-class, immediate release, fast acting, oral acute migraine therapy with high oral bioavailability and dual action via inhibition of both the neuronal nitric oxide synthase (nNOS) enzyme and affinity for 5-HT_{1B/1D} receptors. Oral NXN-188 has been evaluated for safety and tolerability in four, single-dose, safety and pharmacokinetic Phase 1 studies in healthy male and female volunteers, one multi-dose safety and pharmacokinetic Phase 1 study in healthy male and female volunteers, and three single-dose Phase 2 safety and efficacy studies in male and female subjects with migraine headaches. These studies evaluated NXN-188 over 400-fold dose increments from < 2 mg to 800 mg with a total exposure to NXN-188 of 359 individuals. 191 subjects had a history of migraine headache. Across all studies, the number of subjects reporting at least one adverse event (AE) in the NXN-188 groups ranged from 20% to 75% compared to 19% to 100% in the placebo groups. The most commonly reported AEs in NXN-188 treated subjects were headache (4.8%), catheter site pain (3.9%), dizziness (5.8%), somnolence (3.6%), orthostatic hypotension (3.1%), and nausea (5.0%). The incidence of these AEs was similar in the placebo group. There was no apparent dose-related increase in AEs with increasing NXN-188 doses.

No serious adverse events related to NXN-188 have been reported, and no subject has prematurely discontinued a study because of an AE. The majority of AEs were mild in intensity. No medically relevant changes were observed with respect to vital signs, ECGs (including QTc interval), and laboratory evaluations and no difference was observed between treatment groups.

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Comparison of headache impact (measured by the HIT-6) by migraine status: results from the AMPP study

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Background Though developed in episodic migraine (EM), HIT-6 is being used in studies of chronic migraine (CM).

Objectives

1. To establish that HIT-6 is a useful measure of headache impact in CM.
2. To demonstrate that those with CM have greater headache impact compared to those with EM in a population sample.

Methods The American Migraine Prevalence and Prevention (AMPP) study is a longitudinal, population-based study. Subjects in these analyses were respondents to the 2009 survey who met criteria for either CM (ICHD-2 criteria for migraine and ≥ 15 headache days/month) or EM (ICHD-2 criteria for migraine and <15 headache days/month). The HIT-6 is a self-administered, six-item questionnaire that measures headache impact in the domains of lost time in work, school or social activities, pain severity, fatigue, frustration, and difficulty with concentration. Total scores range from 36-78 with response categories of “no impact” (<50), “some impact” (50-55), “substantial impact” (56-59), and “very severe impact” (60+). Descriptive statistics and a cumulative logistic imputation model were utilized to compare groups. **Results** 27,253 questionnaires were fielded in 2009 and 20,107 were returned yielding a sample of 373 participants with CM and 6,796 with EM. Compared to EM respondents, a higher proportion of persons with CM had “very severe impact” (73% vs. 42%). Those with EM had less headache impact with total scores in the ranges of “no impact” and “some impact” occurring approximately 10% and 14% more often in EM respectively. An ordinal logistic regression multiple imputation model revealed that CM respondents had significantly higher odds of greater impact as measured by HIT-6 categories compared to EM (OR = 3.50, 95%CI = (2.77,4.41), $p < 0.0001$).

Discussion These results demonstrate that the HIT-6 is useful in measuring headache impact in those with CM, and that those with CM experience greater headache impact compared to EM.

Conflict of interest Dr. Buse has acted as a consultant or received research support from Allergan Pharmaceuticals, MAP Pharmaceuticals, Merck Inc., and Iroko Pharmaceuticals.

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Aubrey Manack, PhD is full time employee of Allergan Inc., Irvine, California, USA.

Daniel Serrano, PhD has worked on research grants as a consultant with the following companies: Allergan, Merck & Co., Endo Pharmaceuticals, Map Pharmaceuticals, GlaxoSmithKline, Ortho-McNeil-Janssen Pharmaceuticals, Ortho-McNeil Neurologics.

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Increased automatic attention orienting to auditory stimulation in migraine patients

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Purpose Neurophysiological studies converge in showing that migraineurs exhibit abnormal information processing of environmental

stimuli between attacks. In the auditory modality, deficient intensity dependence of auditory potentials (IDAP) was demonstrated. Within IDAP paradigms, which randomly present stimuli at various intensity levels, a deficiency in the habituation of auditory event-related potentials (ERPs) in migraineurs compared with healthy subjects was reported. The aim of this study was to investigate short-term habituation (STH) and long-term habituation (LTH) of auditory ERPs in migraineurs, using a classic auditory habituation paradigm. We particularly focused on two components of the N1 wave:

- (1) the obligatory component resulting from sensory processing in the auditory cortex,
- (2) the orienting component resulting from non-specific frontal activation which is recorded when the stimulus appears after a long silent gap.

This last component is thought to reflect a mechanism capable of triggering a transient arousal response.

Methods 22 patients suffering from menstrually-related migraine and 20 age-matched female control subjects were enrolled in this study. Auditory ERPs were recorded in 3 sessions: in the middle of the menstrual cycle, before menses, and during menses. In each session, 200 trains of stimuli were presented, with an average of 10 stimuli per train (inter-train interval: 5.5–8 s).

Results Migraineurs exhibited a larger orienting response to the first stimuli of the trains than controls. They also showed a residual orienting component in response to the subsequent stimuli inside the trains. In contrast, the sensory component of N1 showed no difference between the two groups, with similar STH and LTH. An augmented orienting component was observed in the session before menses in both populations.

Conclusion Our results provide arguments for an increased orienting reaction to auditory stimuli in migraine and emphasize the role of the frontal cortex in the abnormal auditory information processing observed in migraineurs.

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Pregabalin in trigeminal neuralgia

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Trigeminal neuralgia is a common disorder of older adults. Most cases are idiopathic, although it might be secondary to tumor in the cerebellopontine angle, aneurysm of basilar artery or multiple sclerosis. Usually, the paroxysms of intense stabbing pain last for several weeks or months and is followed by periods of remission. Recurrence is very common. The most effective drug is carbamazepine and in up to 80% of the patients leads to improvement. However, half become resistant over a period of several years. The other recommended drugs, such as baclofen, phenytoin and gabapentin are less effective. Here, we present 10 cases of refractory trigeminal neuralgia that had good response to pregabalin. All of them have developed secondary depression and 4 have psychiatric features. One has not spoken for one year and had 20 kilogram weight loss. Gasserian ganglion block and ablation by radiofrequency were performed for nine patients, and vascular decompression was done for three of them.

Pregabalin in increasing dose, up to 400 milligram daily was associated with significant pain relief that led to the improvement of depression and abnormal behavior. In a two year follow up period, the drug lost its good efficacy in 2 patients but is working for the others. We did not see any significant adverse complication in the patients.

Conclusion It seems that pregabalin could be proposed as an effective and safe drug for trigeminal neuralgia.

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A phase 2 multicenter, randomized, double-blind, parallel-group, placebo-controlled study of NXN-188 dihydrochloride in acute migraine without aura

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NXN-188 Dihydrochloride (NXN-188) is being developed as an oral migraine therapy with dual action via inhibition of both the neuronal nitric oxide synthase (nNOS) enzyme and affinity for 5-HT_{1B/1D} receptors.

In this study subjects were randomized to receive either a single 600 mg dose of NXN-188 or placebo. Eighty-eight placebo and 86 NXN-188 subjects completed the study. Subjects were predominantly Caucasian (79.3%) and female (80.5%) with a median age of 39 years (18 to 63 years). The median number of previous migraines per month was one (range of one to three) for both groups.

The proportion of patients responding (measured as pain relief and need for rescue medication) at 2 hours and 4 hours post-treatment was of primary and secondary interest, respectively. Treatment comparisons were stratified by baseline headache severity. For the whole study population across time points from 2 to 24 hours, there is remarkable consistency across the comparisons. The numerical difference in response rates favors NXN-188 in all of the 58 pre-specified comparisons with 36 of these comparisons yielding p-values that are “statistically significant” at the nominal alpha level of 0.05. The magnitude of the difference between NXN-188 and placebo ranges from 5.3 to 27.2 percentage points, with a median of 20.6 percentage points, a clinically meaningful treatment difference.

NXN-188 was well tolerated with 19.3% of the placebo vs. 29.1% of the NXN-188 group experiencing an adverse event (AE), and this difference was not statistically significant. The most common events in the NXN-188 treatment group were nausea, abdominal pain, dizziness, chills, sensation of heaviness, and proteinuria. Most events were mild-to-moderate in severity, none of the subjects discontinued because of an AE; there were no Series Adverse Events.

The results of this phase 2 study support larger studies to continue the development of NXN-188 as treatment for acute migraine.

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Multiple cortical spreading depressions impair hippocampal long-term potentiation

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It is widely recognized that cortical spreading depression (CSD) is implicated in migraine aura. Moreover, CSD may be related to symptoms occurring during migraine attack such as amnesia. However, the direct evidence indicating that a series of CSDs might affect hippocampal function is scarce. Thus, the present study is designed to investigate the role of CSDs on hippocampal plasticity, long-term

potentiation (LTP). In the experiment, male Wistar rats weighing 150–300 g were divided into two groups (6 rats each), namely CSD and control groups. Multiple waves of CSD were elicited *in vivo* by topical application of KCl crystal on exposed cortex. In control group, solid NaCl was used instead. Forty minutes after, the rat was sacrificed and ipsilateral hippocampus was quickly removed. Transverse slices (400 μ m) of hippocampus were prepared for electrophysiological recording. Field excitatory postsynaptic potentials were recorded in the hippocampal CA1 and LTP was induced by tetanic stimulation. The results showed that KCl application induced a series of negative depolarization shifts. The total number of CSD waves was 7.4 ± 1.5 waves. The amplitude and area under the curve of each wave were 33.1 ± 4.5 mV and 901.6 ± 148.2 mV·s, respectively. These multiple CSDs significantly diminished the magnitude of hippocampal LTP. The levels of LTP in CSD-induced and control groups were 119.8 ± 16.2 and 138.2 ± 9.8 percent, respectively ($p = 0.04$). This study showed that the multiple waves of CSD led to the impairment of hippocampus function as indicated by a reduction of LTP magnitude. However, the exact mechanism how CSDs reduce hippocampal LTP needs to be further clarified.

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A 4-year follow-up of patients with medication-overuse headache included in a randomized multicentre study

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Objective The aim of this study was to evaluate the outcome in 61 patients with medication-overuse headache (MOH) who 4 years previously had been included in a randomized open-label prospective multicentre study.

Methods Sixty patients still alive after four years were invited to a follow-up investigation. Fifty patients (83%) participated, and of these, sixteen visited a neurologist, 22 were interviewed by telephone, two gave response by a letter, and ten were evaluated through hospital records. The mean observation time was 4.0 years.

Results At follow-up, the group of 50 persons had a mean reduction of 6.5 headache days/month, and a mean reduction of 9.5 days with use of acute headache medication/month compared to baseline. Headache index (HI)/month was reduced from 449 to 321. Sixteen persons were considered as responders (32%) due to a $\geq 50\%$ reduction in headache frequency from baseline, whereas 17 (34%) persons had headache ≥ 15 days per month combined with medication overuse. A significant inverse correlation ($p < 0.007$) was found between total Hospital Anxiety and Depression Scale score at baseline and being a responder, and between physical health component score (PCS-12) and medication days/month after 4 years.

Conclusions 4 year after inclusion in the randomized MOH study one-third of the patients had $\geq 50\%$ reduction in headache frequency from baseline, whereas one-third still met the criteria for MOH.

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Reduction of high-energy phosphates in the occipital lobe of migraine without aura patients: a ³¹P- and ¹H-MRS study

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Introduction Magnetic resonance spectroscopy (MRS), a technique to obtain biochemical information non-invasively, has been used in several migraine studies. Both proton MRS (¹H-MRS) and phosphorus MRS (³¹P-MRS) studies were mainly performed in migraine with aura. **Aim** The aim of this study was to perform absolute quantification of metabolites with ³¹P-MRS and ¹H-MRS in a homogeneous group of migraine without aura (MO) patients, who were not on prophylaxis. We were especially interested in the resting state brain energy metabolism of these MO patients.

Methods and subjects We compared 22 MO patients with 25 age- but not gender-matched controls. Patients experienced 2–8 attacks per month, were not using any prophylactic medication and were headache-free for at least 48 hours. MRS Spectra were acquired in the medial occipital lobe on a 3 T Siemens TrioTim system. Spectra were analyzed using jMRUI and Siemens software. Absolute quantification was performed using an external reference.

Results A significantly decreased phosphocreatine (PCr) was found in MO versus controls (4.09 ± 0.58 mM versus 4.85 ± 0.60 mM resp.; $P = 0.001$) and has been previously reported. Whereas adenosine triphosphate (ATP) was considered to be constant in previously published work, we found a significant decrease in ATP in MO patients versus controls (2.33 ± 0.63 mM versus 2.76 ± 0.59 mM resp.; $P = 0.023$). No significant changes in inorganic phosphate, adenosine diphosphate, pH and magnesium were found between MO patients and controls. Also no significant differences in proton metabolites (N-acetyl aspartate, creatine, choline, myo-inositol) were observed between MO patients and controls. ¹H-MRS did not show any quantifiable lactate in all subjects.

Discussion ³¹P-MRS demonstrated a significant decrease in the high-energy phosphates ATP and PCr in (a subgroup of) MO patients, implying impaired resting state brain energy metabolism and further pointing at a mitochondrial component in the pathophysiology.

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Prevalence of medication overuse headache in Sweden

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Introduction The general view is that medication overuse headache (MOH) is the third most common headache disorder in Sweden. There are, however, no previous studies based on Swedish epidemiological data and the prevalence of MOH in Sweden is thus unknown. **Objective** The aim was to estimate the prevalence of MOH in the general Swedish population and to analyze the extent of the disorder in different population groups.

Methods A randomly selected sample of 45 000 individuals (55% women) aged 15 years and above (mean age 52,7 years) was interviewed by telephone using a standardized questionnaire including the IHS 2006 diagnostic appendix criteria for MOH. The survey was performed between March 2009 and March 2010 by SIFO, a Swedish public opinion poll agency. The interviews also covered sociodemographic parameters, headache history and medication use.

Results A total of 867 subjects met the diagnostic criteria for MOH and the prevalence in Sweden is thus 1.93% (95% confidence interval $\pm 0,13$). The prevalence was higher among women ($2,7 \pm 0,20\%$) than men ($1,0 \pm 0,14\%$, $p < 0,001$). The mean age among those with MOH was 50,5 years and the mean duration of chronic headache was 14,6 years. MOH was less common among those who had attended university ($1,3 \pm 0,18\%$, $n = 15\ 954$) than among those who had not ($2,3 \pm 0,18\%$, $p < 0,001$). The primary headache was migraine in 50% and tension-type headache in 23%. A majority (66%) primarily overused simple analgesics, 20% overused combination analgesics, 7,5% overused triptans, 3,7% overused opioids and 0,8% overused ergotamine. The most commonly overused substance was paracetamol (44%).

Conclusion The prevalence of MOH in Sweden is $1,93 \pm 0,13\%$, which corresponds with what has been seen in other western countries. MOH is thus a considerable public health problem which warrants greater consideration within Swedish health care.

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Has the prevalence of primary recurrent headaches changed over a four year period? The Nord-Trøndelag health study

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Objective The aim of this study was to compare the prevalence of primary headaches among adolescents aged 16 to 20 years in Norway in two periods. Very few replicate studies have re-evaluated the prevalence of primary headaches in this age range.

Methods Two cross-sectional, population-based studies were conducted in Norway from 1995 to 1997 (Young-HUNT 1) and from 1999 to 2001 (Young-HUNT 2). In Young-HUNT 1, 2594 adolescents in 2nd and 3rd grade in upper secondary school (aged 16 to 20 years) completed a comprehensive questionnaire including one question regarding headache during the last 12 months. In addition, 1730 of the students were interviewed about their headache complaints. In Young-HUNT 2, 2373 adolescents aged 16-20 years completed the same questionnaire and 1655 were interviewed in the same way as the earlier survey. In the interviews, respondents were asked if they had experienced recurrent headache during the last year and, if so, the headache was classified as migraine, tension-type headache or non-classifiable headache.

Results The participation rate was 88% in Young-HUNT 1 and 81% in Young-HUNT 2. The overall prevalence of having had headaches during the last 12 months did not change significantly, 79.4% versus 77.5%; OR 0.89, 95%CI: 0.79-1.02, $p = 0.09$, whereas the prevalence

of recurrent headaches increased from 30.3% in Young-HUNT 1 to 35.4% in Young-HUNT 2 (OR 1.26, 95%CI: 1.09-1.46, $p = 0.002$). The prevalence of tension-type headache changed significantly from 19.0% to 21.9% (OR 1.20, 95%CI: 1.02-1.42, $p = 0.03$). Also the prevalence of migraine tended to increase (7.5% versus 8.7%, OR 1.18, 95%CI: 0.92-1.52, $p = 0.18$). The overall frequency of recurrent headache changed towards more monthly and less weekly headache.

Conclusions The overall prevalence of recurrent headaches increased significantly from Young-HUNT 1 to Young-HUNT 2. An increase was seen in all types of recurrent headaches and was significant for tension-type headache.

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The role of 17 β -estradiol withdrawal in the neurovascular pathophysiology of migraine

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The prevalence of migraine is 2-3 fold higher in females than in males; this seems to be related to (changes in) levels of female sex hormones. These changing hormone levels may regulate the synthesis and receptor expression of CGRP, mediating neurogenic dural vasodilatation. Moreover, 17 β -estradiol increases dural vasodilatation to endogenous α CGRP (caused by electrical stimulation), but not to exogenous α CGRP, suggesting that 17 β -estradiol may increase CGRP release from sensory nerves. Apart from stable hormone levels, their fluctuations may also influence the synthesis and receptor expression of CGRP. This study investigated dural vasodilatation to exogenous α CGRP after 17 β -estradiol withdrawal.

Rats were ovariectomized and, 7 days later, subcutaneously implanted with 21-day release pellets of 17 β -estradiol or placebo. On day 21, pellets were withdrawn and, on day 22, rats were prepared for intravital microscopy on a closed cranial window. Then, the vasodilatation to exogenous α CGRP (10 ng/kg-3000 ng/kg, iv) was investigated. An extra group without pellet removal was used as control.

Exogenous α CGRP induced a dose-dependent dural vasodilatation. There were no differences in vasodilatation between incubation with 17 β -estradiol or placebo pellet without removing the pellet, which is in line with previous findings. Furthermore, the vasodilatation to exogenous α CGRP in the group where the 17 β -estradiol pellet was removed was similar to that in the placebo group or where the 17 β -estradiol pellet was not removed. Our results suggest that one day withdrawal of 17 β -estradiol does not affect the vasodilatation to exogenous α CGRP. The effects of 17 β -estradiol withdrawal on the vasodilatation to *endogenous* CGRP (released by dural electrical stimulation) are currently being investigated.

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Efficacy of telcagepant in subgroups: pooled analysis of data from phase 3 studies

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Objective To evaluate the acute antimigraine efficacy of telcagepant in subgroups of patients.

Background Telcagepant is an oral CGRP receptor antagonist being evaluated for the acute treatment of migraine. It has been suggested that the efficacy of acute migraine treatments may vary in some subgroups, such as those with aura, menstrually-associated migraine, or a prior response to triptans.

Methods Post-hoc subgroup analyses of data from three randomized, double-blind, placebo-controlled trials in which patients treated a moderate/severe migraine headache with telcagepant 140-mg tablet/150-mg capsule (T140/150) or 280-mg tablet/300-mg capsule (T280/300). Based on information provided in a patient diary or a self-reported migraine-history questionnaire, subgroups analyzed included the following: baseline aura (with/without); menstrually-associated migraine attack in women (with/without); prior response to triptans ($\geq 75\%$ or $< 75\%$ response to prior triptan-treated attacks, no-use); prior response to NSAIDs ($\geq 75\%$ or $< 75\%$ response to prior NSAID-treated attacks, no-use).

Results The percentages of patients with 2-hour pain freedom in the overall population were 266/1253 (21.2%) for T140/150 and 311/1241 (25.1%) for T280/300. Generally similar percentages of patients with 2-hour pain freedom were seen across subgroups for T280/300, allowing for relatively small sample sizes in some cases. Baseline aura: with = 61/222 (27.5%), without = 250/1019 (24.5%). Menstrual migraine: with = 53/209 (25.4%), without = 145/557 (26.0%). Prior triptan response: $\geq 75\%$ = 153/606 (25.2%), $< 75\%$ = 63/279 (22.6%), no-use = 91/339 (26.8%). Prior NSAID response: $\geq 75\%$ = 39/134 (29.1%), $< 75\%$ = 158/648 (24.4%), no-use = 102/418 (24.4%). The pattern of results was similar for T140/150 although there was some variability across the prior NSAID response subgroups.

Conclusions These post-hoc findings suggest that the acute antimigraine efficacy of telcagepant is generally consistent across subgroups including menstrually-associated migraine attacks and those with/without aura, prior response to triptans, or prior response to NSAIDs.

Conflict of interest Dr. Dodick has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

Dr. Silberstein has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

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The effect of DHT on vascular reactivity

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Migraine attacks are two to three times more common in women than in men. In women, these attacks often take place before and during the menstrual period when female hormone levels fluctuate. The female hormone 17β -estradiol potentiates vasodilator responses to, e.g. acetylcholine and calcitonin gene-related peptide (CGRP), which may be relevant in view of the neurovascular nature of migraine. However, little is known about the effects of male hormones in migraine.

In this study we investigated whether treatment of female mice with the nonaromatizable androgen dihydrotestosterone (DHT) changes vascular reactivity.

All of our studies were performed on thoracic aortic vessels of female mice treated for 60 days with DHT (25 μ g/day) or placebo using continuous-release pellets. Treatment was initiated at prepubertal age P19.

Vasorelaxations to acetylcholine, CGRP and sodium nitroprusside (SNP) (measured after precontraction with the thromboxane analogue U46619), as well as contractions to 5-hydroxytryptamine (5-HT) were induced in thoracic aortas (\varnothing 2-3 mm).

Acetylcholine-induced relaxations were significantly smaller in aortas from DHT-treated mice than in those from placebo-treated mice (E_{\max} DHT = $40 \pm 21\%$ and E_{\max} placebo = $85 \pm 15\%$ respectively). Relaxations to CGRP (E_{\max} DHT = $99 \pm 3\%$ and E_{\max} placebo = $89 \pm 13\%$) and SNP (E_{\max} DHT = $91 \pm 8\%$ and E_{\max} placebo = $96 \pm 7\%$), as well as contractions to 5-HT (E_{\max} DHT = $91 \pm 8\%$ and E_{\max} placebo = $96 \pm 7\%$), did not show any difference in vascular reactivity between the treated and placebo groups.

The above data show that DHT specifically decreases the effect of acetylcholine on mice thoracic aortas. Because the relaxation to acetylcholine is of endothelial origin, our results suggest a decreased endothelial function after treatment with DHT, without deterioration of vascular smooth muscle function.

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Cranioselectivity of sumatriptan revisited

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Almost two decades ago sumatriptan was introduced, providing a great step forward in the treatment of migraine. Since concerns existed about the coronary side-effect potential of the triptans, we have formerly performed detailed studies on the cranioselectivity of the triptans.

We concluded that, based on the modest contraction that these drugs cause in the human coronary artery (HCA), triptans are generally safe, but should be contraindicated in patients with coronary artery disease. All of our studies (and those of others) were performed on proximal segments of the HCA, although myocardial ischemia may originate from both large and small HCA. Thus, we have now investigated whether the contractions to sumatriptan are different in proximal or distal parts of the HCA.

Concentration response curves to 5-hydroxytryptamine (5-HT) and sumatriptan were constructed in proximal (\varnothing 2-3 mm), distal (\varnothing 1000-1500 μ m) and small (\varnothing 500-1000 μ m) HCAs (2 M, 2 F; 37-62 yrs). Whereas sumatriptan induced significantly smaller contractions than 5-HT in proximal HCA (E_{\max} = $12 \pm 8\%$ and E_{\max} = $83 \pm 9\%$ respectively), contractions to sumatriptan in distal (E_{\max} = $53 \pm 31\%$) and small (E_{\max} = $54 \pm 17\%$) HCA were significantly higher, and equaled those to 5-HT (E_{\max} = $67 \pm 29\%$ in distal and E_{\max} = $53 \pm 18\%$ in small HCA).

Surprisingly, contractions to sumatriptan in distal HCA are in the same order of magnitude as those in the human meningeal artery (E_{\max} = $103 \pm 13\%$, Neurology 2000;55:1524). Thus, the above data in distal HCA suggest that triptans have a limited cranioselectivity. However, in the last years triptans have been used extensively, and myocardial ischemia is an extremely rare event. Therefore, our findings reconfirm that the triptans should remain contraindicated in patients with coronary artery disease, although the risk profile definitely favors their use in the absence of contraindications.

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Estrogen-dependent effect of 5-hydroxytryptophan on sensitivity to cortical spreading depression in rat

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Background Migraine is sexually dimorphic (male/female ratio 1:3) and thought to be a “low 5-HT” condition. Reduced serotonin transmission might be responsible for deficient pain control and for changes in cortical excitability. Dietary depletion of tryptophan, the 5-HT precursor, worsens migraine symptoms (*Drummond et al., 2005*).

Objective To determine if exogenous administration of 5-hydroxytryptophan (5-HTP) is able to modify KCl-induced CSD in rat and if the effect differs between males and females.

Methods Adult male and female Sprague-Dawley rats ($n = 8/\text{group}$) received intraperitoneal injections of 5-HTP (100 mg/kg) or saline (NaCl 0.9%). One hour after the injections, CSDs were elicited under chloral hydrate anesthesia by applying over the occipital cortex a cotton ball soaked with 1 M KCl. The electrocorticogram was recorded for 1 hr (DC-100 Hz) with ipsilateral parietal and frontal electrodes. For each female, the phase of the estrous cycle was determined by vaginal smear analyses which were done just before the electrophysiological recording.

Results 5-HTP administration has no effect on CSD frequency in males. In females, we observed an estrous cycle-dependent effect of 5-HTP: CSD frequency was increased during proestrus (high estrogen) phase (+27% vs control) and decreased during estrus and diestrus (respectively -67% and -74% vs control). There was no significant influence of the estrous cycle on CSD frequency in NaCl-treated female rats.

Conclusion These preliminary results suggest that an increase of serotonin levels does not alter the sensitivity to CSD in males while in females the change in sensitivity seems to depend on gonadal hormone levels. Hormone-dependent changes in central serotonin effects might thus contribute to the sexual dimorphism of migraine.

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Progression and consequences of brain lesions in migraine: the population-based camera-2 nine year follow-up MRI studyI.H. Palm-Meinders¹, H. Koppen^{1,2}, G.M. Terwindt¹, L.J. Launer³, J. Konishi¹, J.T.N. Bakkers⁴, P.A.M. Hofman⁵, H.A.M. Middelkoop¹, M.A. van Buchem¹, M.D. Ferrari¹, M.C. Kruit¹¹Leiden University Medical Center, Leiden, The Netherlands;²Haga Hospital, The Hague, The Netherlands;³Laboratory of Epidemiology, Demography and Biometry, NIH, Bethesda, MD, USA;⁴Slingeland Ziekenhuis, Doetinchem, The Netherlands;⁵Academic Hospital Maastricht, Maastricht, The Netherlands

Background We previously reported that migraine is an independent risk factor for subclinical cerebellar infarcts and, among women, high deep white matter lesion (DWML) load (Kruit MC, et al. JAMA 2004). We re-investigated the same population-based cohort (295 migraineurs; 140 controls) nine years later, to test for migraine-related progression of brain lesions and to evaluate cognitive consequences.

Methods Baseline and 9 yr follow-up brain MR images were acquired in 203/295 (response 69%) migraineurs with and without

aura (mean age 57 y, SD 8) and 83/140 (60%) controls (mean age 55 y, SD 7) with the same protocols/scanners. Blinded for diagnosis, images were semi-automatically analyzed for progression of prevalence and volume of DWMLs and cerebellar infarcts. DWML analyses were adjusted for age, hypertension, diabetes and level of education. Migraine diagnosis and presence of brain lesions were correlated with cognitive test results from both time points.

Results Cardiovascular risk factors were comparable between groups, although migraineurs were slightly older. None of the infarct-like lesions found at baseline vanished. We found ≥ 1 new cerebellar infarct in $n = 10$ (5%) migraineurs vs. none in controls ($p = 0.039$). These new lesions occurred in 6% of migraineurs without aura and 4% of migraineurs with aura, with no differences with respect to gender. There was no difference in incidence of infarcts in other locations between migraineurs and controls. Female migraineurs had a greater progression of DWML load (OR 2.1 [1.1-4.2]), which was stronger in those with a higher attack frequency. After adjustment for age and level of education we found no association between cognitive functioning and migraine diagnosis and/or DWML lesion load.

Conclusion During nine year follow-up, only migraineurs developed new cerebellar infarcts. In women, migraine is an independent risk factor for progression of high-DWML-load. However, DWMLs were not associated with cognitive functioning or decline.

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Nummular headache with and without exacerbations. comparative characteristics in a new series

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Objective Apart from the characteristic chronic pain in a well-circumscribed area, superimposed exacerbations have been described from first reports of Nummular Headache (NH). We present a new series of NH, comparing characteristics between exacerbations (ENH) and non exacerbations (NENH) cases.

Methods In a monographic headache outpatient office in a tertiary hospital, 43 (26 female, 17 male) out of 903 patients (4.7%) were diagnosed of NH (January 2008-May 2010). In each patient we considered baseline pain intensity, temporal pattern, relief provided with symptomatic treatment, and requirement and efficacy of preventive therapies. When exacerbations were present, we reviewed their quality, intensity and duration.

Results Neuroimaging studies were performed in all patients with no abnormalities. 25 cases (58.1%) presented in situ exacerbations. Mean intensity of exacerbations was 7.5 ± 1.4 (range 7-10 in a 0-10 visual analogical scale (VAS)) and they lasted 4 ± 10 minutes. Regarding exacerbations quality, most of them were stabbing. There were no differences between ENH and NENH group respectively, in age at onset (49.3 ± 17.6 vs 45.7 ± 20 years), sex (61 vs 60 % of females), baseline pain intensity (5.5 ± 2.6 vs 5.4 ± 1.8 in a 0-10 VAS), size of painful area (4.8 ± 1.5 vs 4.6 ± 1.1 centimetres), allodynia or other sensory symptoms (68 vs 61 %), baseline pain quality (38.8 vs 31.2 % pressing), or temporal pattern (48 vs 50% with no spontaneous remissions). There were no differences between both groups regarding relief with symptomatic therapy (82.6 vs 83.3 %), requirement of preventive therapy (64 vs 66.6%) and response to preventatives (77 vs 60%)

Conclusion In situ exacerbations superimposed on baseline pain are frequent in NH. ENH and NENH cases do not differ in demographic

and nosological characteristics. Presence of exacerbations does not predict needing or response to therapy.

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Lasmiditan (COL-144), a selective 5HT_{1F} agonist, is a rapid and effective oral treatment for acute migraine

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The efficacy and safety of a range of oral doses of lasmiditan, a novel selective 5HT_{1F} agonist, was explored in a prospective, randomized, double-blind, placebo-controlled, parallel-group dose-ranging study. 534 patients were screened at 43 sites in Europe. Eligible patients with migraine (IHS criteria 1.1 and 1.2.1 and not on prophylaxis) were randomly assigned (1:1:1:1) to receive oral lasmiditan (50, 100, 200 or 400 mg) or matching placebo to use as the first treatment of a new migraine attack provided the headache severity was at least moderate and not improving. 391 patients treated a single migraine attack with study medication at home and recorded their response over the following 48 hours using a diary card. Follow up in the clinic took place within 14 days of treatment.

The study met its primary objective, showing a significant dose response for headache relief at 2 h ($p < 0.0001$, Cochran-Armitage test for trend). All individual doses were significantly superior to placebo with placebo-subtracted 2 h response rates of 17–39%. Separation from placebo started as early as 30 min. The dose response for headache-free at 2 h was also significant ($p < 0.0005$). The 100 and 400 mg dose groups showed significant benefits in sustained headache response compared to placebo. Nausea, photophobia and phonophobia were significantly lower in the lasmiditan treated groups by 2–3 h though the study was not powered for these secondary endpoints.

There were no clinically significant changes in laboratory parameters or ECGs. The most common treatment emergent adverse events were related to the central nervous system. Chest symptoms were rare, occurring with a similar frequency across all groups including placebo. Lasmiditan, a novel molecule with a central site of action and without vasoconstrictive properties, is a rapid and effective acute treatment for migraine when given orally and warrants further investigation.

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Rates and risk factors for persistence of chronic migraine (CM) and chronic tension-type headache (CTTH) in the German Headache Consortium (GHC) study

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Background A recent population-based study suggested that headache frequency within CM varies from year to year.

Objectives To estimate rates and assess risk factors for persistency of CM and CTTH.

Methods The GHC study is a longitudinal population-based study of headache sufferers in which 18,000 people (aged 18–65 years in three regions of Germany) completed questionnaires at baseline ($n = 9665$), one year ($n = 6694$) and two years ($n = 6975$). CM respondents had migraine/probable migraine and ≥ 15 headache days/month; CTTH respondents had TTH/probable TTH and ≥ 15 headache days/month. Persistence was defined as headache chronicity over two years (ie, ≥ 15 headache days/month at baseline and during 2 follow-up years). To assess risk factors, two groups for each headache type were compared: those who met persistence criteria and those who did not.

Results At baseline, 177 respondents had CM and 71 had CTTH. Demographically, CM and CTTH were different: CM were predominantly females (73% vs. 47%), more likely to smoke (47% vs. 32%), less likely to drink alcohol (5.5% vs. 19%), and more likely to use (83% vs. 63%) and overuse (73% vs. 54%) acute headache medications. After two years, 14% had persistency of CM and 20% had persistency of CTTH. Medication overuse (MO) (OR 10.3; 95%CI[3.9–26.8]) and obesity (OR 2.3; 95%CI[1.1–4.8]) were associated with persistency of CM; stressful events such as unemployment/divorce (OR 1.9; 95%CI[0.7–4.9]) approached significance. Male gender (OR 7.7; 95%CI[1.6–37.5]) and MO (OR 25.1; 95%CI[2.4–258.9]) were significant predictors for persistency of CTTH. Full results will be presented but risk factors of age, smoking, disease duration, and low back/facial pain were not associated with persistency of CM or CTTH.

Conclusions The minority of CM and CTTH were persistent suggesting the ICHD-2 criteria are insufficient because they don't incorporate disease duration. CM and CTTH have differing risk factors for persistence; however, MO is an important factor for both.

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Pituitary headache without a tumour

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Headache is often seen in patients with pituitary tumours. It is unrelated to the size of the tumour, and will respond to the somatostatin analogue Octreotide, which suggests that it may be mediated by a humoral factor. I present a patient who seems to have a lymphocytic hypophysitis, and yet whose headaches have responded to Octreotide. This Press Photographer (b 1958) has had a continuous bifrontal headache since 2004. He had had several syncopal episodes, always associated with severe pain, and after one of these he was found to be hypopituitary, with a radiologically enlarged gland. This was biopsied in November 2007, showing only fibrous tissue containing mature lymphocytes. He has needed full replacement therapy since then, but the headache has persisted, and has not responded to valproate, citalopram or amitriptyline. Regular scans have continued to show some structural changes in the gland. In January 2009 he responded 'amazingly' to a trial of Octreotide. The gland was reexplored in September 2009, but a biopsy yielded only pituitary tissue with extensive fibrosis, infiltrated by lymphocytes and plasma cells. The headache persists, and still responds to Octreotide. The neurosurgeon considers it too hazardous to reexplore the gland.

This case is unusual - there is no convincing radiological or endocrine evidence of an adenoma. It is possible, of course, that the headache is

due to a very small persistent tumour within the fibrous pituitary gland, or even to the (inflammatory) process of fibrosis itself. His response to Octreotide could be non-specific, as the drug has some opioid properties, and the Octreotide could be working at another level within the central nervous system. Nevertheless identification of the humoral factor suppressed by the Octreotide might give a clue to the mechanism of headache in these cases.

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Neck and occipital pain location of migraine differed from that of tension type headache with new meridian system

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Background Primary headache has been underdiagnosed and undertreated even there are advanced technologies and new developed medications. How do we improve efficacy of diagnosis and treatment? One of criteria of headache is location. The literature documenting the location of neck and occipital pain of primary headache is sparse. There is no definite method to decide side and sites. We propose to use New Meridian and Acupuncture Points of Korean Hand Therapy (KHT) to determine the location.

Subjects and methods This study was performed to document the location of neck and occipital pain in 400 persons of primary headache from March 2007 to Feb. 2009 at Dept of Neurology, Busan National University Hospital, Korea. We evaluated tender or pain points of at CM 3 - CM 10 along gallbladder meridian of 200 migrainerus, and CI 1-1 - CI-8 along urinary bladder meridian of 200 tension type headache patients on physical examination using New Meridian System and Acupuncture Point of KHT.

Result Migraine patients showed neck and occipital pain along Gallbladder New Meridian and Acupuncture points on the right side (92/200), on the left side (75/200) and both side (33/200). Tension type headache patients showed neck pain along urinary bladder New Meridian Points on the right side (67/200), on the left side (105/200) and both side (28/200).

Conclusion Neck and occipital pain of primary headache is closely related with meridian systems esp. New Meridian System. Neck and occipital pain of migraine is closely related with Gall bladder meridian and that of tension type of headache is Urinary bladder meridian. Cervical neck pain should be considered one clinical feature of migraine headache and tension type headache. New method is of use and is ease to practice without difficulty.

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Two cases of cluster headache relieved by pregabalin

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Purpose Cluster headache is the most unique and painful of the primary headache disorders. It is characterized unilateral recurrent severe headache with cranial autonomic symptoms. Oxygen and triptan agent

have been demonstrated to be effective in the acute treatment of cluster headaches. Verapamil and topiramate has been shown to be effective for prophylaxis usually. I have two cases that were not controlled by verapamil and topiramate but relieved by pregabalin.

Case 1 A 42-year-old man who had been suffering from severe recurrent headache (10 > times) visited our department. Headache was mainly localized at left parieto-temporal area, accompanied always by ipsilateral lacrimation and conjunctival injection and ipsilateral rhinorrhea. The headache repeated daily 2-3 times and its duration was 20-30 minutes. Headache severity was 9 in visual analogue scale (VAS). On brain MRI and EEG, there were no abnormal findings. I gave him verapamil but it did not work. So I gave pregabalin to him. The headache was improved and VAS was 4.

Case 2 A 31-year-old woman who had been suffering from severe recurrent headache (6 > times) for 2 years visited our department. Her headache was mainly localized at left parieto-temporal area, accompanied always by ipsilateral lacrimation and conjunctival injection and ipsilateral ptosis and sweating. The headache repeated daily 1-2 times and its duration was 30-60 minutes. VAS was 9. On brain MRI and EEG, there were no abnormal findings. I gave her topiramate but her headache was not improved. So I gave her pregabalin. Her headache was improve and VAS was 2.

Conclusion I present two cases of cluster headache relieved by pregabalin. In case of headache refractory to verapamil and topiramate, Pregabalin may be triable.

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The investigation of common clinical and genetic indicators of migraine, episodic tension type headache and irritable bowel syndrome

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Migraine is a chronic disorder characterized by disabling, unilateral and throbbing headache, accompanied by autonomic dysfunction, gastrointestinal and neurological symptoms. Episodic Tension type headache (ETTH) is sharing some common mechanism with migraine. Irritable Bowel Syndrome (IBS) is a common functional disorder possibly related to altered brain structure. The aim of this study is to evaluate the phenotypic and genotypic relation of these diseases (via clinical associates and serotonin transporter gene polymorphism). In this study 107 subjects with migraine, 107 subjects with IBS, 53 subjects with ETTH patients and 53 healthy controls were included to determine clinical variables and 5-HTT-VNTR, 5-HTT-LPR, 5-HT2A-T102C, 5-HT2A-1438 G/A polymorphisms.

In our study IBS prevalence in migraine and ETTH groups were 54.2% and 28.3% respectively. There was no statistically significant difference between headache characteristics of migraine patients and migraine plus IBS patients. Similarly there was no difference between ETTH patients and ETTH plus IBS patients. In IBS patient's, migraine and ETTH prevalence were 35.5% and 22.2% respectively.

The frequency of HTT VNTR 10/12 allele was significantly increased in our patients with migraine as compared with the

control group ($p = 0.0247$). The frequency of HTT VNTR 10/12 allele was significantly increased in our patients with ETTH as compared with the control group ($p = 0.0103$). And finally the frequency of 5-HT_{2a}-1438 AA allele 10/12 allele was significantly increased in our patients with IBS as compared with the control group ($p = 0.0005$).

Our study suggested a highly possible phenotypic and genotypic association between IBS and primary headache disorders (migraine and ETTH) supporting some shared pathophysiological basis.

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Low prevalence of chronic cluster headache and aura, and uncoupling of sense and behavior of restlessness in Japanese

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This study examined the clinical profile of cluster headaches in Japan and the presence of any features peculiar to Japan. A total of 86 consecutive new cluster headache patients (68 M/18F; mean age 38.4 ± 12.2 years) were enrolled in this study. The mean age of onset was 31.0 years and the gender ratio (males to females) was 3.8. Chronic cluster headache was observed in 3.5% patients and 2.3% of patients had aura. More than half of patients (68.9%) reported feelings of restlessness during the headache episodes and 42.9% reported restless behavior. Patients with uncoupling of feelings of restlessness and restless behavior forced themselves to keep still. Similar findings were reported in a Taiwanese study. Low prevalence of chronic cluster headaches and aura, and uncoupling of sense and behavior of restlessness may be common features in Japanese and Taiwanese.

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Blood flow distinctions in acute migraine attack and in intermission detected by MRI perfusion

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Brain blood flow in migraine attack MRI perfusion MRI perfusion study of brain blood flow during migraine attack was aim of research.

Methods MRI research was performed on GE MR tomograph 3.0 Tesla with Magnevist contrasting. MRI included T1 WI, T2 WI, T2FSE, T2 Flair, T2*GRE, Diffusion-tensor imaging (DTI), Diffusion-weighted imaging, Perfusion (flow rate 5 ml/s), T1 post contrast, 3D TOF angiography. Patient was 43 year old female suffering MO without aura during 25 years with migraine attack frequency 1-2 per month. During last 2 months before the research attack frequency increased up to 4-5 per month due to stress and high intensive work. MRI study was performed during severe attack of MO being in progress for 24 hours. Headache attack was evaluated as 8-9 points of VAS and was attended by vomiting, photophobia and phonophobia.

Results MRI study visualized five white matter lesions. Three lesions were visualized in frontal lobes in subcortical area, two lesions were in subinsular area of left hemisphere. The largest lesions (4-4,5 mm in diameter) were located in left frontal lobe and in subinsular areas of left hemisphere. The lesions were isointensive in DWI and didn't show enhancement in postcontrast imaging. There were no arterial stenosis and malformations observed in MRI angiography. Results of perfusion measuring in left hemisphere showed lowering of blood flow volume and regional perfusion rate at unchanged time of contrast bolus transmission.

Conclusions

1. Lowering of blood flow volume in frontal lobe at the side of headache location proves vascular component in pathogenesis of migraine attack.
2. High intensity MRI makes quality and quantity estimation of blood flow lowering in migraine attack feasible.

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Markers of endothelial activation in primary headache disorders

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Epidemiological studies show an association of migraine, especially with aura, with cardio- and cerebrovascular events. A dysfunction of the vascular endothelium is suggested to be the underlying pathology connecting these different disease entities. Ang-1 and Ang-2 are markers of endothelial activation, changes in their serum concentrations reflecting the state of the vascular endothelium. Our study aimed to analyze angiotensin serum levels in patients with migraine and other primary headache disorders further investigating the role of the endothelium in headache patients.

Bi-center prospective trial enrolling 4 groups of patients: episodic migraine with and without aura, episodic cluster headache (CH), episodic tension-type headache and healthy individuals (HC). In migraineurs, venipuncture was performed twice: outside attack and during typical migraine attacks prior to pain medication. In CH patients serum samples were collected in- and outside bout. Analysis of Ang-1 and Ang-2 was performed using enzyme-linked immunosorbent assay technique.

Ang-1 was significantly elevated in patients with migraine and CH during migraine attacks / cluster bouts ($p < 0.05$). In migraine patients Ang-2 levels were increased during attacks compared to the interval ($p < 0.05$). Further, Ang-2 serum concentrations were significantly higher in migraine patients outside attack compared to HC and TTH ($p < 0.05$). CH patients revealed higher levels of Ang-2 during cluster episodes but showed normal Ang-2 levels when comparing outside-bout concentrations with HC and TTH. Our results indicate that there is an imbalance of the Ang-1/Ang-2 ratio in favour of Ang-2 in migraine and CH patients inside attack/bout compared to pain-free intervals. Moreover, we found higher Ang-2 concentrations in migraine patients outside attacks compared to TTH and HC. Our findings of elevated Ang-2 serum levels might reflect endothelial activation in this patient population and further corroborate the hypothesis of an important affection of the vascular endothelium in migraine and CH pathogenesis.

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Levels of nitric oxide metabolites in cerebrospinal fluid in active cluster headacheA. Steinberg¹, N.P. Wiklund², L. Brundin³, A.I.M. Nilsson-Remahl⁴¹Department of Clinical Neuroscience, Karolinska Institute, Karolinska University Hospital Huddinge, Stockholm, Sweden;²Department of Urology, Karolinska Institute, Karolinska University Hospital Solna, Stockholm, Sweden;³Department of Clinical Neuroscience, Division of Neurology, Karolinska Institute, Karolinska University Hospital Solna, Stockholm, Sweden;⁴Department of Clinical Neuroscience, Division of Neurology, Karolinska Institute, Karolinska University Hospital Huddinge, Stockholm, Sweden

The pathophysiology of cluster headache (CH) is only partly understood. Nitric oxide (NO), a potent vasodilator, has been suggested to be involved and increased plasma levels of nitrite, a stable product on NO degradation, have been identified in both active period and remission. We studied the role of NO in CH by measuring its oxidation products, nitrite and nitrate, in the cerebrospinal fluid (CSF), a biological compartment closer to the supposed focus of the disorder. We collected CSF from 18 episodic CH patients in active period and from 4 patients with chronic CH as an extension of a previously published series of cases (1). The samples were collected between attacks, except in 2 cases when an attack started during the lumbar puncture. Eleven healthy headache free volunteers served as controls. We determined the levels of NO-oxidation end products (NOx), i.e. the sum of nitrite and nitrate, by using capillary electrophoresis. CH patients in active period had significantly increased NOx-levels (mean 8.1, 95% CI 7.1–8.9) compared to control subjects (mean 6.2, 95% CI 4.9–7.5; $p < 0.01$). Both nitrite and nitrate levels were significantly increased in episodic CH patients. A trend towards relatively lower NOx values was observed among the few chronic CH patients.

We interpret the results as an indication of a generally raised NO tonus during active CH, possibly as an expression of inflammatory activity, and causing sensitization of pain pathways. A trend towards a difference in NOx levels between episodic and chronic patients was observed. The results support NO involvement in the pathogenesis of CH.

Reference

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Efficacy and safety of telmisaltan in migraine-preventive therapy

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Objectives Preventive therapy for migraine is generally indicated in patients with failures of triptan therapy. Efficacy of angiotensinII-receptor blocker (ARB) for the prevention of migraine attacks has been

reported, however Japanese guideline has not yet recommended the use of ARBs as first-line drugs for migraine prevention. The aim of this study was to elucidate efficacy and safety of telmisaltan in migraine attacks.

Methods We prospectively enrolled 10 patients (average 44.7 ± 15.2 years) with frequent migraine attacks (≥ 4 times/month) under a prophylactic use of lomerizine over the last three months. Telmisaltan (20 mg daily) was administered for three months in all patients. Rescue treatment by triptan was allowed. The frequency of headache and drugs used were recorded using self recording sheets at monthly visits. The Headache Impact Test (HIT)-6 was also used for the evaluation of effectiveness of telmisaltan treatment and changes in HIT-6 score more than one point from the baseline after the observation period was considered significant.

Results There was no significant difference in blood pressure and pulse rate recorded at baseline and at the end of the observation period; $110.3 \pm 11.6 / 75.6 \pm 11.5$ mmHg and 75.4 ± 7.2 /min at baseline, and $106.0 \pm 10.0 / 69.1 \pm 9.3$ mmHg and 80.4 ± 6.9 /min at the end of the observation period. There were no adverse effects and drop-outs during the observation period. Overall the telmisaltan treatment was effective in 9 patients (90%). Significant decline in HIT-6 score was demonstrated before and after the telmisaltan treatment, 62.7 ± 2.1 and 52.0 ± 5.8 points, respectively ($p = 0.0002$). The frequency of attacks per month was also decreased from 9.8 ± 3.0 to 3.7 ± 2.7 times ($p = 0.0006$). The frequency of triptan use per month decreased from 8.8 ± 2.3 to 3.1 ± 3.0 times ($p = 0.0007$).

Conclusion Our study suggests further randomized controlled study should be warranted to explore the significance of telmisaltan as a migraine-preventive drug.

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Patterns of triptan use: results of a 2-year retrospective cohort study in 4 countriesW.M. Golden¹, T.W.-H. Ho², B.J. Katic¹, B. Stanford³, S. Rajagopalan⁴, Y.-T. Chen¹, D.S. Ng-Mak²¹Global Health Outcomes, Merck Sharp & Dohme Corp, Whitehouse Station, NJ, USA;²Merck Research Labs, Merck Sharp & Dohme Corp, North Wales, PA, USA;³Health Economics and Outcomes Research, IMS Health, London, UK;⁴Med Data Analytics, Inc., Williamsville, NY, USA

Aim We sought to describe patterns of triptan use in the UK, France, Germany, and the U.S.

Methods Using electronic medical records (UK, France, Germany: IMS Disease Analyzer) and pharmacy claims data (U.S: proprietary administrative claims database), we retrospectively identified migraineurs newly prescribed triptans. Included patients could not have received any prescription therapy for acute migraine for 1 year prior to the index triptan. Each patient was followed for 2 years from the index date to evaluate patterns of treatment (i.e. persistency, switches, and discontinuations). Persistency, evaluated at the time of each refill, was defined as sustained prescription of the index triptan.

Results A total of 3618 patients in the UK, 2051 in France, 954 in Germany, and 40,892 in the U.S. were included in the analysis. During the follow-up period, 53.9 - 65.8% of migraineurs did not persist with their initial triptan prescription (U.S: 53.9%; UK: 55.7%;

Germany: 63.3%; France: 65.8%). In the EU countries, the majority of those who did not receive further triptan prescriptions did not receive any other prescription for migraine (85.7%), while in the U.S. most filled prescriptions for non-triptans (67.0%), predominantly opioids (33.8%). In the EU, a smaller percentage switched to a different triptan (9.5%) and even fewer switched to a non-triptan (4.7%), whereas in the U.S. a smaller percentage discontinued prescription migraine treatment (26.5%) and the fewest switched to a different triptan (7.4%).

Conclusions We observed poor persistency in triptan prescription both in the U.S. and Europe. Our findings suggest potential unmet needs in the acute treatment of migraine. The reasons for the lack of continuing prescription of triptans warrants further investigation.

Conflict of interest Daisy S. Ng-Mak is a full time Merck & Co., Inc. employee, received stock options of the company. The study was sponsored by Merck & Co., Inc.

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Cardiovascular risk factors in migraine without aura

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Introduction Several studies have revealed that cardiovascular risk factors are more commonly seen in migraineurs with aura. However, limited studies on this issue in migraineurs without aura have been conducted. We performed a study to evaluate cardiovascular risk factors in patients suffering from migraine without aura.

Methods One hundred and thirty migraineurs and 80 matched controls from the similar age, sex and social group were selected. The evaluated cardiac risk factors were hypertension, lipid profile, diabetes mellitus, obesity, cigarette smoking, past medical and family history of ischemic cardiac and cerebral events. Chi square test was used to compare the frequency of these factors between the cases and the controls.

Results Comparing cardiac risk factors, no significant difference was noted between the cases and the controls in the presence of diabetes mellitus, hypertension, obesity, cigarette smoking, past medical and family history of ischemic cardiac and cerebral events. Low HDL cholesterol (lower than 40 mg/dl) was significantly more frequent in migraineurs without aura ($P = 0.023$).

Conclusion The result may suggest that migraine without aura is not accompanied by ischemic cardiac and cerebral events risk.

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The TRPV-1 agonist olvanil inhibits nociceptive trigeminovascular activation *in vivo* in rat

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Transient receptor potential vanilloid receptor subtype 1 (TRPV-1) are located in trigeminal fibers innervating the dura mater. While they co-localize with calcitonin gene-related peptide (CGRP) the relevance of the TRPV-1 receptor in migraine is unclear. Olvanil is a weak TRPV-1 agonist that desensitizes neuronal fibers. In comparison to capsaicin it induces almost no CGRP release, lacks pungency and has anti-emetic effects. We hypothesized, that olvanil leads to an inhibition of stimulus-evoked neuronal transmission in the trigeminal ganglion.

In male Sprague-Dawley rats, anesthetized with propofol (20 mg kg^{-1}), the middle meningeal artery (MMA) was stimulated and electrophysiological recordings of second order neurons were collected in the trigeminocervical complex (TCC). Experimental groups received either olvanil in a dosage of 0.1, 1 or 5 mg kg^{-1} dissolved in intralipid or intralipid alone as the respective control group. The effects of olvanil on trigeminovascular activity in response to MMA stimulation were recorded following the drug infusion.

Olvanil significantly reduced cell firing in response to trigeminovascular activation within the TCC ($P < 0.05$). This effect was dose-dependent and immediate, reaching maximum inhibition at 25 minutes post infusion of olvanil at 5 mg kg^{-1} ($61.66 \pm 6.29\%$; $P < 0.05$). Cell firing was not fully recovered at 60 minutes post-application ($49.07 \pm 12.22\%$; $P < 0.05$). Infusion of intralipid alone had no significant effect on MMA stimulation-evoked firing.

The results show that the TRPV-1 agonist olvanil inhibits stimulus-evoked trigeminal activity, thereby functionally acting like an inverse agonist. The high efficacy of olvanil combined with the lack of pungency due to its slower depolarization deserve further investigation as these results might provide the basis for a novel antinociceptive mechanism relevant to migraine.

Conflict of interest Oliver Summ received a fellowship by the European Federation of Neurological Societies and fellowship by MSD.

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Regulatory systems impairment as factors contributing to primary headache chronicity

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Comparison of episodic and chronic forms of primary headache to reveal the possible factors and mechanisms contributing to the disease chronicity has been performed.

Clinical and laboratory examination of 237 patients with primary headache was performed, 158 of them suffered from migraine and 79 patients from tension type headache. The control group consisted of 89 healthy subjects. The total number of leucocytes, leukocytic formula, content of subpopulations, indices of neutrophils and monocytes functional activity, content of immunoglobulins of A, M and G class, complement components, circulating immune complexes, concentration of cytokines, serotonin, β -endorphin, P substance and cortisol were examined in the peripheral blood.

High incidence of somatic diseases has been found in patients with primary headache, clinical manifestations of immune disorders was quite prevalent among them. Significant differences in the rates of chronic inflammatory and allergic diseases in patients with episodic and chronic primary headache allow consider these conditions as a factor unfavorably affecting the cephalalgia course.

Leucopenia, lymphopenia, lymphocyte subpopulation imbalance, disorders of neutrophil functional activity, and alteration of cytokine status and decrease of cortisol level were found in patients with

episodic and chronic course of migraine and those with chronic tension type headache. The content of serotonin and β -endorphin was found to be decreased in the peripheral blood of patients with chronic forms of migraine and tension type headache. The results of laboratory tests in patients with episodic tension type headache do not virtually differ from those in the group of healthy subjects. In patients with chronic cephalalgia the revealed changes were similar to their direction and intensity of alterations, what was the evidence of existence of universal pathogenetic mechanisms of primary headache transforming into chronic ones.

These results suggested that some factors of immune, neural and endocrine regulation might contribute to primary headache chronicity.

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Real-world usage patterns in self-medication of pain. Pooled analysis of five pharmacy-based non-interventional studies with aspirin

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Objective Analysis of usage patterns of a very commonly used analgesic (Aspirin) under daily life conditions and compliance with leaflet instructions.

Methods The individual data of 9444 patients from five pharmacy-based non-interventional studies performed in Germany, Switzerland and Spain respectively were analyzed. In all studies Aspirin was used for the treatment of different pain states, mainly headache, pain associated with common cold and migraine. Patients who purchased the drug in a pharmacy were provided with a questionnaire to be filled in at home during/after the treatment.

Results About 90% of the patients rated their pain as moderate to severe before treatment. Severe pain at baseline led to a higher percentage of intake of 2 tablets (1000 mg, 50.1%) at the first dose than mild to moderate pain (27.7%). Mean daily dose was 2.2 ± 1.8 tablets and mean treatment duration was 2.2 ± 4.4 days. The total amount of tablets taken during the treatment course was 4.6 ± 5.7 tablets, thus far below leaflet recommendations. Severe pain at baseline caused an increase in daily dose and total amount of tablets taken. In total, 38.9% of the patients only used one tablet, the remaining multiple doses.

Conclusions While the indication for OTC-analgesics is mild to moderate pain the perceived pain severity of many patients is moderate to severe and they adapt their self-treatment accordingly, taking higher dosages for stronger pain and lower dosages for milder symptoms. Overall treatment duration is short (approx. 2 days) and the total amount of tablets taken (approx. 5) below the recommendation given in the package insert. Thus patients show a high degree of compliance when treating themselves. It might though be worth considering to rephrase the indication for OTC-analgesics from "mild to moderate pain" to "pain" to better reflect perceived efficacy and usage.

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Neurophysiological evaluation of trigemino-cervical system in patients with chronic daily headaches: age peculiarities

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Objective To elucidate neurophysiological mechanisms of chronic headaches in consideration with age and to evaluate functional activity of trigemino-cervical system in patients of different age with chronic daily headaches (CDH).

Methods 222 patients were divided into 5 groups: 1st - children and adolescents - 61 patients, 2nd - 55 patients aged 18-44 years old, 3rd - 44 patients aged 45-59 years old, 4th - 47 patients aged 60-74 years old and 5th - 15 patients aged 75-82 years old. 44 healthy subjects aged 14-76 years old presented the control group. Neurophysiological investigations were performed with the use of standard techniques and included somatosensory evoked potentials (SEP), trigeminal evoked potentials (TEP), blink reflex (BR) and EMG of masticatory muscles. Statistical methods included Fisher's exact test and correlation analysis.

Results The statistical analysis revealed increase of SEP interpeak intervals N9-N11 ($p < 0,01$), N9-N13 ($p < 0,01$), N9-N20 ($p < 0,05$) in the 1st group of patients. In the 2nd group of patients we observed TEP latencies decrease ($p < 0,05$). In patients aged 45-59 years old statistical analysis showed increase of N13-N20 ($p < 0,05$) and P23 latency ($p < 0,05$) and the tendency to TEP latencies increase. In the 4th and the 5th groups we revealed increase of N11 and P23 latencies ($p < 0,05$ and $p < 0,01$, correspondingly), increase of N9-N11 ($p < 0,001$), N9-N20 ($p < 0,01$) and N20-P23 ($p < 0,05$) and TEP latencies decrease ($p < 0,05$).

Conclusion The present study demonstrated age peculiarities of functional activity of trigemino-cervical system in patients with CDH which should be taken into account in treatment: conduction delay in somatosensory pathway on spinal and brainstem level in children and adolescents, increase of reflex irritability of trigeminal system in young age, dysfunction of supraspinal level in middle age, conduction delay in somatosensory pathways and increased irritability of trigeminal system in elderly patients.

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Genome-wide association study for migraine in a dutch genetically isolated population

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Aim Migraine is a neurovascular disorder with a genetically complex and heterogeneous background. Many linkage and association studies have been performed, but so far with limited success. The aim of this study was to identify novel genetic factors for common migraine by performing a genome-wide association study (GWAS) in the genetically isolated Dutch Erasmus Rucphen Family (ERF) population.

Methods For each of approximately 2.5 million SNPs, logistic regression was performed using an additive genetic model, while adjusting for age and gender. Uncertainty in the inferred genotype from the imputation was accounted for by utilizing the estimated genotype probabilities (implemented in ProbABEL). Data were filtered for rare variants and low LD (MAF < 0.05 were excluded; SNPs with r^2 below 0.3 were excluded). We accounted for relatedness between study participants of the isolate by correcting for genomic control inflation factor.

Results We performed a GWA with 330 migraine cases and 1216 non-migraine controls from the ERF population. Although none of the SNPs reached the threshold for genome-wide significance (5.0×10^{-8}),

22 SNPs showed highly suggestive associations with P -values below 10^{-5} . No less than 221 SNPs had a P -value below 10^{-4} . The most significant SNP in this study showed association with a P -value of 1.34×10^{-7} , and is an intergenic SNP. In a sub-analysis, we investigated the SNPs that were located in the FHM genes; SNPs in the FHM2 gene *ATP1A2* showed best signal for association.

Conclusions This is the first genome-wide association study for migraine in a population-based cohort. Replication efforts are needed to evaluate how relevant the present association findings are.

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Interaction between prolactine, estrogen and dopamine. chronic hemicranial migraine in association with hyperprolactinemia in subsequent pregnancies: a case report

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A 24-year old female is suffering a daily pressing and stabbing strictly unilateral headache, most prominent above the right eye in association with mild autonomic features, i.e. partial ipsilateral ptosis and eyelid oedema during 5 subsequent pregnancies.

The headache forced her to stay in bed. Physical activity was provocative. After the 3rd pregnancy analysis of irregular menstruation and galactorrhea revealed a hyperprolactinemia (HPL) (1.2 u/l; normal < 0.5/l). MRI showed a pituitary microadenoma. Endocrinological analysis did not reveal other abnormalities. On a dopamine receptoragonist, cabergoline, these complaints disappeared and treatment was stopped. During the next two pregnancies (one with HPL of 1.22 u/l) the headache disappeared on cabergoline after initial increase.

Between the pregnancies she was headache free. Cabergoline treatment was continued by the patient (0.25 mgr/week) and later on stopped with recurrence of the same headaches now without pregnancy. Her mother was known with migraine.

We examined the patient during her last pregnancy. A diagnosis of hemicranial chronic migraine (CCM) with mild autonomic features was made. Hemicrania continua could not be excluded totally because of non-performance of the indotest. The association of HPL with CM during pregnancies has not been reported before. A dopamine receptoragonist stopped the migraine totally. HPL may lead to the occurrence of migraine and TACs which may disappear on dopamine agonists as in our patient. The initial headache increase on cabergoline has been reported before. The mode of action of dopamine and prolactine has not fully been clarified. Dopamine agonists may induce both antinociception as well as hyperalgesia. We have no explanation for the homolaterality of the headache.

The occurrence in pregnancies suggests a causal interaction between prolactine and estrogen. Estrogen may stimulate prolactine with subsequent inhibition of dopamine leading to headaches as in our patient.

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Orbital myositis posing as cluster headache

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Introduction The headache is a reason for daily consultations in neurology. Cluster headache, a disorder of unknown cause and pathogenesis, can be mimicked by other disorders. Clinical exam and investigations allowed rectifying diagnosis.

Objective To describe the case of a patient with recurrent orbital myositis who was thought to have cluster headache for 2 years

Case report A 20-year-old woman, without family history developed paroxysmal headache in the left orbital and supraorbital region with lacrimation, conjunctival hyperemia, moderate ptosis, and painful eye movements. The headache was severe and not preceded by an aura. It fluctuated in intensity over the course of the day and lasted approximately ten days. This patient had previously another attack two years ago in the same period of the year, which was treated successfully by prednisone as a cluster headache. Neurological examination revealed paralysis of extrinsic pathway in the third left cranial nerve. MRI of the brain and orbits demonstrated enlargement of the left medial rectus muscle. The clinical improvement was obtained after 3 days IV corticosteroid. After few weeks oral treatment we note remission of all signs.

Conclusion This case behooves neurologists to consider obtaining computed scan tomography or magnetic resonance images of the orbits in cases of cluster headache especially in which eyelid edema, ptosis, and conjunctival hyperemia are prominent features.

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Botulinum toxin treatment of cervicogenic headache: a randomized, double-blind, placebo-controlled cross-over study

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Objective Cervicogenic headache (CeH) is pain referred to the head from a source in the cervical spine. Good and reliable treatment is lacking.

Methods In the present randomized, placebo-controlled, patient-, injector- and evaluator-blinded cross-over study, 29 adult patients (mean age 46.2 years, 59% women) with a disabling, long-standing and treatment-resistant strictly unilateral cervicogenic headache were included. The diagnosis was based on clinical criteria and anesthetic blockades. After a 4 week baseline period, injections of either botulinum toxin or placebo were given in m. trapezius, m. splenius capitis and m. semispinalis. The second injections were given after a minimum of 8 weeks, or when the patient had reached $\geq 50\%$ of days with moderate to severe headache compared to baseline. Patients were thereafter followed for another 8 weeks. Throughout the study, a detailed headache calendar was filled in, and patients were followed with algometry and neck mobility measurements.

Results With regard to the reduction of days with moderate to severe headache during 3-8 weeks after injection, there was no significant difference between verum and placebo in a mixed linear model analysis ($p = 0.084$). The mean frequency of moderate to severe headache was 4.48 days/week during baseline, and the mean changes were -0.72 ± 0.20 days/week after botulinum toxin and -0.40 ± 0.20 days/week after placebo. More patients experienced a $\geq 30\%$ improvement with botulinum toxin ($n = 11$) than placebo ($n = 7$) ($p = 0.25$). Four patients withdrew from the study before the second injections, and an intention-to-treat analysis using the last observations carried forward revealed no significant effect

($p = 0.27$). Side-effects of botulinum toxin were minor and short-lasting.

Conclusions Botulinum toxin is probably not beneficial in CeH, but the study may be underpowered. We are presently analysing the secondary endpoints of the study.

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Medication use in patients with migraine and medication-overuse headache: on the role of problem solving and attitudes about pain medication

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Introduction and aims Excessive medication intake is believed to be a major risk factor of developing Medication-Overuse Headache (MOH), a condition characterized by an increase of headache attacks to a daily or near-daily pattern. Research focusing on the underlying psychological mechanisms of the disorder is still in its infancy and it is hardly known why some patients overuse their medication. In this study, we examined the value of attitudes about pain medication, especially perceived need and concerns, and problem solving style in accounting for MOH. We also sought to examine the relation of problem solving style with need for and concerns about medication. **Methods** Patients with migraine (N = 133) and MOH (N = 42) were recruited from a tertiary headache referral center and completed a range of questionnaires measuring problem solving style and attitudes about pain medication.

Results A problem solving style aimed at controlling pain was associated with a higher need for and concerns about medication intake. Interestingly, in a model accounting for demographic factors and pain intensity, controlling pain (OR = 1.28, 95% CI 1.1 to 1.5), need for medication (OR = 1.24, 95% CI 1.1 to 1.4) and concerns about scrutiny by others (OR = 1.12, 95% CI 1 to 1.2) all had unique value in accounting for MOH.

Discussion Results are discussed in terms of how a persistence in attempts at controlling pain may trigger overuse of medication, even in the presence of clear negative consequences.

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Progression of infratentorial hyperintense lesions in migraine: the population-based camera-2 nine year follow-up MRI study

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Background We previously demonstrated an increased prevalence of brainstem (mainly pons) and cerebellar T2 hyperintense lesions on

brain MRI in migraineurs from the general population. These infratentorial hyperintense lesions (IHLs) are reported to be strongly associated with cardiovascular risk factors, and their development has been suggested to reflect small vessel disease. Based on the follow-up CAMERA MRI study we evaluated prevalence and progression of IHLs in population-based migraineurs and controls.

Methods IHLs were hyperintense on T2 and proton density weighted images, and not hypointense on FLAIR images (infarcts and Virchow-Robin spaces were excluded). Progression was defined as an increase in number or size of the IHL. Baseline and 9 yr follow-up brain MR images were acquired in 203/295 (69%) migraineurs with and without aura (mean age 57 y, SD 8) and 83/140 (60%) controls (mean age 55 y, SD 7) with same MRI protocols/scanners as baseline. Blinded for diagnosis, IHLs were scored if present and progression was assessed. Analyses were adjusted for age, gender, diabetes and hypertension.

Results After 9 years follow-up, there was no decrease in IHL number or size. In the follow-up scans, IHLs were found in 39/203 (19%) of migraineurs vs. 5/83 (6%) of controls (adjusted OR 3.4 [1.3-9.2]). Progression of IHL was found in 26/203 (13%) of migraineurs vs. 2/83 (2%) of controls (adjusted OR 5.0 [1.1-21.9]). Prevalence and progression of IHL were even more pronounced among women with migraine, especially those without aura. In addition, an association between the presence of IHL and attack frequency was found, with the highest odds in female migraineurs without aura with ≥ 1 attack per month (adjusted OR 11.4 [2.2-58.3]).

Conclusion Migraine is, notably in women, associated with presence and progression of infratentorial hyperintensities.

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Open-label, multicenter study of the efficacy and outcome of onabotulinumtoxin-a treatment in patients with chronic migraine and comorbid depressive disorders

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Objectives To prospectively assess the efficacy of onabotulinumtoxinA as a prophylactic treatment in patients with chronic migraine (CM) and comorbid depressive disorders and to evaluate the potential of onabotulinumtoxinA in reducing the severity of depressive symptoms as a consequence of reduced headache episode frequency.

Background Depression and anxiety are common migraine comorbidities and occur at even greater rates in CM. Some studies suggest that migraine may provoke depression.

Design and methods Thirty-two outpatients (age > 18 years) at 3 centers with CM (defined by ICHD-2R: ≥ 15 mean headache days/month) and comorbid depressive disorders (classified by DSM-IV) participated. No changes were made from patients' baseline medication regimens. Participants met criteria, gave consent, kept diaries, and were seen by a physician and psychologist at 4 visits (weeks -4, 0, 12, and 24). Participants were treated with onabotulinumtoxinA at baseline and week 12 according to the PREEMPT protocol.

Questionnaires assessed headache-related disability (MIDAS), depression (PHQ-9 and BDI-II), anxiety (GAD-7), headache impact (HIT-6), and health-related quality of life (SF-36). A Wilcoxon signed-rank test and Paired t-test were used for data analysis.

Results At 24 weeks headache diaries demonstrated $\geq 50\%$ reduction in headache/migraine days (-8.2 , $P < 0.0001$), more headache/migraine-free days ($+8.20$, $P < 0.0001$), and reduced days with migraine (-6.71 , $P < 0.0001$). Positive change was observed on the following measures: PHQ-9 (-4.3 , $P < 0.0001$), GAD-7 (-3.5 , $P = 0.0002$), SF-36 ($+15.1$, $P < 0.0001$), BDI-II (-7.89 , $P < 0.0001$), HIT-6 (-6.32 , $P < 0.0001$), Pain VAS (-2.51 , $P < 0.0001$), and MIDAS score (-44.18 , $P = 0.0058$).

Conclusion Open-label treatment of CM with onabotulinumtoxinA was associated with reductions in headache and migraine frequency, depression, anxiety and disability and improvement in quality of life. As onabotulinumtoxinA has no known direct effect on mood, we suggest that the reduction in depression and anxiety may be attributable to improvement in headache. Additional blinded studies with larger samples are required.

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Conflict of interest Dr. Boudreau received research support from Allergan Pharmaceuticals.

Dr. Buse has acted as a consultant or received research support from Allergan Pharmaceuticals, MAP Pharmaceuticals, Merck Inc., and Iroko Pharmaceuticals.

Dr. Grosberg serves on a scientific advisory board for Kowa Pharmaceuticals American Inc. and Merz Pharmaceuticals; has received honoraria for speaking engagements or educational activities from Merck and Nautilus Pharmaceuticals; and received institutional research support from Allergan Inc., Merck, GlaxoSmithKline, Endo Pharmaceuticals, Boston Scientific, Neuralieve Inc., Advanced Biomics, ProEthics, Minster Pharmaceuticals, and Capnia.

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Migraine in emergency department: a study on indirect costs

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Background Migraine is a frequent chief complaint in the Emergency Department (ED). Migraine entails an average annual indirect costs of € 554 per patient in Western European Countries. No data on indirect costs of migraineurs referring the ED are available.

Objective To determine indirect costs in employees with migraine referring to ED.

Methods We performed a six-months prospective analysis of all consecutive patients referring to ED for headache and afterwards evaluated in the Acute Headache Centre (AHC) of the University of

Trieste. Employees with an AHC diagnosis of migraine (ICHD-II criteria) were enrolled. Patients were properly treated in the AHC and were re-evaluated in a three-month follow-up visit. Absenteeism (missed workdays [MW]) and pre-absenteeism (workdays with reduction in work effectiveness [RWEW]) over the preceding three months (MIDAS scale), the daily costs of migraine-related absenteeism and pre-absenteeism of each professional employee (quantified by mean daily wage, National Statistical Institute wage data) were analyzed with SPSS 14.0.

Results We enrolled 69 patients, 58 F (84.1%) and 11 M (15.9%), mean age 38 ± 8 years. Most frequent AHC diagnosis was migraine without aura (42 patients, 60.9%). MW and RWEW over the preceding three months were 404 (median 5 days per person) and 658 (median 9 days per person), respectively. The indirect costs estimated per year due to migraine-related absenteeism and pre-absenteeism were €346,211 (€2,508 per patient). At three-month follow-up visit a reduction of 70.4% of MW and 45.1% of RPCW was found. The estimated annual wage costs saved due to the proper AHC therapy was €235,740.

Conclusions Indirect costs in migraineurs referring to ED are about five-time higher than in migraineurs in general population. An Acute Headache Centre dedicated to Emergency Department is effective in reducing about 2/3 of indirect costs due to the productivity loss caused by migraine.

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Trigeminal nociceptive system and quality of life in migraine in dependence on thyrotropin-stimulating hormone levels

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Purpose To study hormonal axis hypophysis - thyroid in migraine and its influence on trigeminal system and patients' quality of life.

Patients and methods 123 migraine patients of tertiary care headache center aged 16-57 years (mean age 38,08 years) and 10 healthy subjects were investigated. Thyroid-stimulating hormone (TSH), trigeminal somatosensory evoked potentials (TSEPs) and quality of life (QoL) by means of general Goetheborg questionnaire and migraine-specific QVM questionnaire were studied.

Results Latencies of TSEPs were significantly enlarged in migraine patients compared with control group. Asymmetries of P1 latency and N1P1 amplitude were enlarged in migraine as well ($p = 0,005-0,016$). TSEPs didn't correlate with age of patients. TSH values didn't differ in migraineurs and healthy controls. TSH in migraine patients correlated with attacks' duration ($R = -0,344$; $p = 0,014$). Patients with TSH values $< 2,0$ mkME/ml showed significantly enlarged duration of attacks compared with those who had TSH $> 2,0$ mkME/ml ($53,14 \pm 27,52$ hours vs $37,34 \pm 27,29$ hours, $p = 0,047$). Statistically significant direct correlation between TSH on one hand and Goetheborg QoL score ($R = 0,355$; $p = 0,033$), functional QVM index ($p = 0,046$), social QVM index ($p = 0,017$) on the other hand was found. Asymmetries of latencies P1 and N2 were significantly higher in patients with TSH values $< 2,0$ mkME/ml ($p = 0,031$; $p = 0,048$).

Discussion Up to now there is no evidence concerning TSH influence on trigeminal system. But changes of heart conducting system in patients with low TSH values have been described: spontaneous atrial fibrillation (Wilson GR et al. 2005), shortened interventricular conduction time, premature heart beats, atrial arrhythmias (Boelaert K,

Franklyn JA, 2005; Biondi B et al. 2008). We suppose that the influence of thyroid system on conducting structures is universal, not restricted to the heart conducting circuits. It could explain correlations between the state of hypophysis - thyroid axis and electrophysiological changes in trigeminal system in migraine patients.

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More antisaccade errors in migraine patients

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Aim Recent voxel-based morphometry studies in migraine patients have shown subtle but significant reductions in grey matter in cortical areas involved in pain processing (including the prefrontal and cingulate cortices), which are related to migraine frequency. (1-5) We hypothesized these changes would be reflected in the control of saccadic eye movements.

Methods Saccades were recorded by infrared-oculography. Three tasks were performed: a prosaccade gap and overlap task during which the subject was instructed to look at the stimulus, and an antisaccade gap task during which the subject had to look in the opposite direction of the stimulus. Latency and direction were analyzed. These parameters were compared between patients with migraine (n = 80) and controls (n = 87).

Results Our results suggested a greater latency variability in migraine patients (pro-gap P = 0.002 and pro-overlap P = 0.004). The latency of the prosaccades with gap was borderline increased in migraine (P = 0.042). Migraine patients on prophylactic therapy made significantly more directional errors than controls in the antisaccade gap task (P = 0.001). The group on prophylaxis had on average 10.66 days migraine per month, those who did not take prophylactic medication had on average 3.85 migraine days a month. No significant differences were found between migraine patients with and without aura for all parameters studied.

Conclusion We found abnormal saccade behaviour in migraine patients, especially more antisaccade errors in patients on prophylactic drugs, suggesting it is related to migraine frequency. We hypothesize that grey matter changes in the prefrontal and cingulate cortex account for this abnormal antisaccade behaviour.

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The pupils of migraine patients: preliminary results

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Aim To date there is no consensus whether there is a sympathetic or a parasympathetic disturbance in migraine; most pupillometric studies point towards a sympathetic hypofunction. (1-4) By testing migraine

patients both during an attack and in the headache free interval, we wanted to compare whether a potential sympathetic dysfunction increases during an attack by using apraclonidine 1%, an alpha adrenergic agonist.

Methods We used infrared pupillometry to measure the dark adapted and light adapted pupil diameter. The minimal diameter, latency, amplitude, constriction and redilatation velocity of the light reflex were measured as well. We studied 31 controls and 42 migraine patients interictally, after a migraine-free period of at least 15 days. None of the migraine patients took prophylactic medication. Fourteen migraine patients were also studied ictally; they were not allowed to take any attack-aborting medication before or during the test.

Results We found no differences between migraine patients with and without aura. None of the parameters correlated with the headache side in patients with unilateral migraine. We found no significant difference between migraine patients and controls, neither interictally, nor ictally. The pupil parameters of migraine patients did not differ significantly between and during the attack. However after administration of apraclonidine 1%, migraine patients had a longer latency compared to controls. This increase in latency was more pronounced ictally (right: P = 0.046, left: P = 0.023) than interictally (right: P = 0.075, left: P = 0.021).

Conclusion We assume there is a subtle pupillary sympathetic hypofunction in migraine patients which is unmasked after administration of apraclonidine 1%. The sympathetic hypofunction creates a sympathetic hypersensitivity that causes the prolonged latency.

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Intracerebral aneurysm revealed by chronic daily headache

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Introduction Headache is a common complaint among patients seeking care at neurology. Fortunately, chronic headache associated with significant morbidity and mortality, occurs infrequently.

Objective We describe the case of a woman with a chronic headaches found to be a result of an intracranial aneurysm.

Case report A 39-year-old woman was received frequently in the psychiatric department, for a chronic daily headaches diagnosed as a tension-type headaches. It was generally reported to occur in relation with emotional conflict and psychosocial stress. She was treated during 5 years with Amytriptyline. When severe acute and sudden headaches appear, she was hospitalized in neurologic department. The neurologic examination was normal. The MRI showed a right bleeding intracranial aneurysm. The patient was transferred to the neurovascular hospital for intracranial medial carotid embolization. After intervention, headaches disappeared and the control examination revealed complete third right nerve palsy and painful hypoesthesia in the right fifth nerve. The evolution was favorable and the patient hasn't any neurological abnormality since 8 years.

Conclusion Physicians need to be aware of the signs and symptoms that indicate whether a headache may be a result of serious problems such as an aneurysm.

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Healthcare resource use and costs among chronic and episodic migraine in five European countries

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Background Migraine is a common, disabling neurological disorder imposing a significant burden on patients and healthcare systems.

Objective Evaluate resource use (RU) and associated costs in chronic migraine (CM) and episodic migraine (EM) patients in France, Germany, Italy, Spain, UK.

Methods Cross-sectional data collected via web-based survey, February to April 2009. Respondents classified as CM or EM (ICHD-2 diagnosis of migraine and ≥ 15 headache days/month or ≤ 14 headache days/month, respectively). Data collection included baseline demographics, headache frequency and symptomology, and medical RU for headache treatment (clinician and emergency department [ED] visits, medical procedures, and hospitalizations over the preceding 3 months and medications used over the preceding 4 weeks). Unit cost data collected for each country using public sources and applied to RU profiles. Cost estimates were annualized and presented in 2010 €. Cost calculations included imputation of missing RU data using mean values of the non-missing participants. Group comparisons of medical RU made using Fisher's Exact test.

Results 5,657 participants with migraine evaluated. CM were more likely to have a primary care provider or neurologist/headache specialist visit compared to EM ($p < 0.0001$). 11.9% of CM and 5.8% of EM were treated either in an ED or hospital for headache ($p < 0.001$). 75.1% of CM and 64.2% of EM reported headache-related medication use over the last 4 weeks ($p < 0.001$). Mean incremental difference in total costs between CM and EM patients was €1,129 in France (CM €1,650 vs. EM €521, $p < 0.0001$), €392 in Germany (CM €965 vs. EM €573, $p = 0.08$), €1,800 in Italy (CM €2,631 vs. EM €831, $p < 0.0001$), €6,310 in Spain (CM €8,162 vs. EM €1,852, $p < 0.0001$), and €2,329 in the UK (CM €3,204 vs. EM €875, $p < 0.0001$).

Conclusions CM was associated with higher medical RU and total costs compared to EM.

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Conflict of interest Dr. Blumenfeld has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

Dr. Buse has acted as a consultant or received research support from Allergan Pharmaceuticals, MAP Pharmaceuticals, Merck Inc., and Iroko Pharmaceuticals.

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Mr. Stokes is a full time employee of United Biosource Corporation which conducted the data collection and statistical analysis on behalf Allergan Pharmaceuticals.

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Dilatation by CGRP of middle meningeal artery and reversal by sumatriptan in normal volunteers

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Background The neurotransmitter Calcitonin gene related peptide (CGRP) is a strong vasodilator present in the perivascular nerve fibers. CGRP plays a fundamental role in the pathophysiology of neurovascular headaches. CGRP infusion causes headache and dilatation of cranial vessels. However, it is unknown to what extent CGRP induced dilatation of extra- and intracranial arteries contributes to immediate head pain and whether the migraine specific abortive drug sumatriptan (a 5-HT_{1B/D} agonist) inhibits CGRP induced immediate vasodilatation and headache.

Method To address these issues we performed a double-blind, randomized, placebo-controlled crossover study in 18 healthy volunteers. We directly recorded circumference changes of the extra cerebral artery; the middle meningeal artery (MMA) and the intra-cerebral artery; the middle cerebral artery (MCA) using 3 Tesla MR-angiography before and after 1.5 $\mu\text{g}/\text{min}$ human αCGRP or placebo (isotonic saline) as well as after 6 mg sumatriptan subcutaneous injection.

Results CGRP caused significant headache ($P = 0.003$) and dilatation of MMA ($P = 0.006$) but no dilatation of MCA ($P = 0.69$). Sumatriptan administration resulted in a marked contraction of MMA (15% to 25.2%) and only a marginal contraction of MCA (3.9% to 5.3%). Explorative analysis revealed that sumatriptan had a more selective action on MMA compared to MCA on both study days; the CGRP day ($P < 0.0001$) and on the placebo day ($P = 0.007$).

Conclusion These data suggest that in exogenous CGRP only dilates extra cerebral arteries. Furthermore, the present data suggests that sumatriptan exerts part of its anti-nociceptive action by constricting MMA (extracerebral artery) and not MCA (intra cerebral artery). We suggest that sensory afferent input from extra cerebral arteries may play a crucial role in the pathophysiology of neurovascular headaches.

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Impact of chronic and episodic migraine on work patterns in five European countries

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Background Migraine is a prevalent and disabling condition, impacting the ability of migraineurs to work and perform daily activities.

Objectives This study compared the impact of chronic (CM) and episodic migraine (EM) on work patterns and productivity across five European countries.

Methods Web-based survey data were collected from migraineurs in France, Germany, Italy, Spain and the United Kingdom (UK). Respondents were classified as CM or EM (ICHD-2 diagnosis of migraine and ≥ 15 headache days/month or ≤ 14 headache days/month, respectively). Questions on attendance (absenteeism) and reduced productivity (presenteeism) in the preceding four weeks assessed headache impact on work or school. Analysis of covariance (ANCOVA) models predicted absenteeism by migraine group and examined impact of adjusting for sociodemographic characteristics (age, gender, race, education), and comorbidities (pain, vascular disease [VD] risk factors, VD events, psychiatric disorders, and other conditions).

Results Of 42,187 panelists contacted, 12,264 (29.1%) responded and 5,657 (13.4%) completers met migraine criteria ($n = 1,461$ France, 1,449 Germany, 976 Italy, 701 Spain, 1,070 UK). Participants were 4.9% ($n = 277$) CM and 95.1% ($n = 5,380$) EM. Respondents were largely female (83.9%), with an average age of 39 (SD = 10.8 years). CM reported more absenteeism due to headache symptoms than EM (adjusted mean \pm SE = 8.6 ± 0.9 vs. 3.9 ± 0.7 , $P < 0.0001$) and working more days with headache symptoms (15.9 ± 0.7 vs. 5.3 ± 0.6 , $P < 0.0001$). Nearly three-quarters of CM and EM participants reported that work was negatively affected by headache symptoms (73.3% vs. 71.5%, $P > 0.05$), with a similar number of hours affected (5.0 ± 0.7 vs. 5.0 ± 0.6 , $P > 0.05$). Furthermore, CM and EM both reported working at approximately half of their full effectiveness with headache symptoms (51.7 ± 2.4 vs. 55.3 ± 1.7 , $P > 0.05$).

Conclusions Migraine adversely affected attendance and increased absenteeism among migraine sufferers, particularly those with CM, who missed more days and had more days with reduced productivity due to headache than EM.

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Sepideh Varon, PhD is full time employee of Allergan Inc., Irvine, California, USA.

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Zonisamide in the preventive treatment of frequent refractory migraine: focus on patients with intolerance to topiramate

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Background Chronic migraine refractory to preventive treatment is a common clinical situation in general neurology clinics.

Objective To analyse our experience with zonisamide in the preventive treatment of patients with frequent refractory migraine.

Patients and methods Those patients with no response or intolerance to topiramate and at least two more preventatives received zonisamide. All but 5 patients met chronic migraine criteria with or without analgesic overuse. This drug was increased 25 mg per week up to 200 mg/day. The efficacy of zonisamide was evaluated in terms of “response” (reduction in attack frequency below 50%) at the third month of treatment. The use of zonisamide in this indication was allowed by our ethics committee.

Results Our series comprises a total of 172 patients, with ages ranging from 22 to 69 years. 85% were women. The final dosage of zonisamide was 50-200 mg/day, with the 100-150 mg/day being the most frequently administered dose. Zonisamide was efficacious (response) in 76 (44%) patients; response being excellent in only 22 (13%). MIDAS score was reduced by 43.2% in responders. Zonisamide was not tolerated by 27% of the patients, mainly due to subjective mental slowness and/or digestive symptoms. Two cases stopped the drug due to nephrolithiasis, one due to cutaneous allergy and one because of diffuse joint pain.

Conclusions These results, obtained in a big sample of patients refractory or intolerant to topiramate and other preventatives, indicate

that, at least in conditions of daily clinical practice, zonisamide, at relatively low dosages, is an option to be considered for the preventive treatment of desperate patients with frequent migraine.

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Occipital nerve stimulation for treatment of migraine headache

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Introduction Migraine is a primary headache disorder affecting 18% of women and 6% of men in US. Control of migraine headache can be difficult to achieve in the group of patients who do not respond to accepted medical treatment or cannot tolerate side effects of medications used to treat migraine. Occipital nerve stimulation (ONS) has been used to treat patients with occipital neuralgia but recently this type of treatment is utilized to control different headaches including migraine and cluster headaches.

Methods The patient is a 42 year old female with 15 years history of migraine who failed conservative medical treatment and had short lasting pain relief after right occipital nerves block. She underwent a successful trial of percutaneous placement of an 8-electrode subcutaneous lead in right occipital region. During the 3 day ONS trial, the patient had good control of headaches. Two weeks later the patient underwent subdermal implantation of a permanent lead and RestoreULTRA (Medtronic Inc.) rechargeable generator.

Results After ONS implantation, the headaches were well controlled. The patient reported over 50% decrease in headache days per month and 4 to 5 point drop on VAS score during migraine attacks. The patient was able to suppress the migraine in 30-40 minutes after initiating of ONS. She discontinued the all medications for preventive and acute therapy of migraine. The patient also reported other positive outcomes including the opportunity to start school and improved relations with friends and family. At 18 months post-implant, the patient continued to report good control of the migraine headache.

Conclusion ONS can be a new therapeutic option for patients with intractable migraine headache who did not responded to currently established treatments. This neuromodulation technique decreases the intensity of pain during migraine attacks and can lead to reduction in the number of headache days per month.

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An analysis of out-patient characteristics of headache in a general neurology department of China

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Objective Categorize neurological headache outpatient visits in a general neurology department, and analyze the demographic characteristics and clinical features.

Background Headache is a common neurological disorder, limited data, based on out-patient visits to general neurology department, are available, and more studies in this area are warranted.

Methods From March to May 2010, we conducted face-to-face consultations and investigations with patients claiming suffering headache as the chief reason for visiting our general neurology outpatient department. A self-administered headache questionnaire was used, and headache diagnoses were made according to ICHD-II of the International Headache diagnosis and treatment standards.

Results Patients with chief complaint of headache accounted for 19.5% of the total general neurology clinic out-patients. A total of 1683 cases of headache patients were investigated, the average age was 46.14 ± 14.61 , female-dominated, accounting for 68.1%.

56.1% patients were diagnosed with primary headache, the largest population; 21.0% with secondary headache, and 22.9% with undiagnosed headache. Among the primary headache group, 40% were diagnosed with migraine, the average age was 41.80 ± 13.28 , women account for 80.9%; 26.0% with tension-type headache; 19.0% with chronic headache; and 15.0% with other types of primary headache. In the primary headache group, 67.1% patients had received medical diagnosis and consultation previously; however, 48.2% of them cited the purpose of visits to be seeking definitive diagnosis.

Conclusion One fifth of out-patient visits to a general neurology department are headache patients. The majority is patients suffering primary headache, and among them, the No1 diagnosis is migraine. Improve the diagnosis and treatment of primary headache, will effectively reduce the headache patient clinic visits, and reduce the economic and social burden.

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Alice in wonderland syndrome among juvenile headache patients

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Background and purpose The Alice in Wonderland syndrome (AWS) is characterized by 4 specific symptoms including

- (1) bizarre disturbances of body images,
- (2) illusions concerning size, position, and distance of objects,
- (3) feeling of levitation, and
- (4) alteration in the sense of passage of time, is considered as one of the specific symptoms seen in migraineurs although the mechanism and prevalence of AWS still remain unknown.

The purpose of the present study is to investigate the correlation between AWS in childhood and prevalence of migraine headache in adulthood.

Subjects and method We conducted a surveillance using headache questionnaire sheet to 2289 students (599 elementary, 1123 junior high and 567 high school). The questionnaire includes the feature, frequency and concomitant symptoms of headache, and the experience of AWS. The prevalence of AWS among students are compared with those of 267 adults migraineurs (15 to 70 years old) who are visiting our outpatient clinic regularly from 2006 to 2009.

Results The questionnaire revealed that 59% of elementary and junior high and 52% of high school students experienced headache, and 8.7% of elementary, 8.3% of junior high and 8.8% of high school students experienced migraine headache. Among those who have headache, 16 out of 159 (10.1%) elementary school students and 13 out of 293 (4.4%) high school students had experienced AWS compared to 3 (1.1%) in 267 adult migraineurs. Among students with AWS, 8 elementary (50%) and 8 high school students (61.5%) had familial history of migraine headache.

Conclusions The above data suggests higher prevalence of AWS among school children although their experience fade out as they grow up. It is important to ask about the experience of AWS for early diagnosis and treatment for juvenile patients with migraine headache.

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Multi-pulses transcranial magnetic stimulation (TMS) and recurrent limb pain (RLP) in children with migraine

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Rationale RLP have been reported in children with migraine and are sometimes associated with motor weakness. The symptoms may mimic functional (i.e. psychogenic or conversion) limb weakness (FMW) which are commonly associated with pain and headache. We have demonstrated the immediate efficiency of multi-pulses TMS in functional limb weakness (in press, movement disorders). Because of the similarities between RLP and FMW, we have studied the effect of multi-pulse TMS on RLP

Patients and methods Nine children (8F/1H, mean age: 11.7 ± 2.2 ys), with migraine presented one ($n = 4$) or several ($n = 5$) pain limb episodes with weakness or disturbance of motor control. The symptoms were localized in both lower limbs ($n = 5$), in one limb ($n = 2$) or variable localisation ($n = 2$). A precipitating event was observed in 4 patients, a head minor injury ($n = 2$) and a unusual physical effort ($n = 2$). An average of 30 stimuli over the sensitivo-motor cortex, contralateral to the corresponding affected limb, was delivered with a circular coil.

Results TMS was delivered once for 5 patients, and was effective in all cases, with a total recovery immediately after TMS ($n = 2$) or quasi-immediately (within a few minutes, $n = 3$). TMS was delivered several times for 4 patients during recurrent episodes, with, each time, an immediate recovery after TMS. Video of patients before and after TMS will be presented.

Conclusion Multi-pulses TMS are effective in RLP as in FMW. These two entities are probably linked by a partially common physiopathology.

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Rapid initial absorption rate cannot alone explain the high efficacy in migraine of sumatriptan nasal powder delivered with novel device

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Objectives Sumatriptan is marketed as SC injection (6 mg), conventional and RADIS tablets (25–100 mg), rectal suppositories (25 mg) and nasal liquid spray (10–20 mg). Onset of pain relief is thought to be a function of the initial rate of absorption to the blood, rather than the extent. However, recent studies of sumatriptan oral spray (20 mg), transdermal patch (6 mg) and nasal powder

(7.5/15 mg) offer new insights into the mechanism of action of sumatriptan.

Methods Published data on the pharmacokinetics and efficacy of sumatriptan administered by the various routes were compared with published data on intranasal sumatriptan powder. Doses of 7.5 mg (ON7.5 mg) to the side of the migraine or 15 mg (ON15 mg) split between nostrils were delivered using the novel breath actuated device, offering optimized drug deposition.

Results The C_{max} and $AUC_{0-\infty}$ for ON7.5 mg/ON15 mg are similar to 20 mg nasal spray and 20 mg oral spray, but substantially lower than 100 mg tablets, 6 mg SC, 20 mg oral spray and 6 mg transdermal patch. The initial rate of absorption (first 15 minutes) is faster for ON 15 mg than all other treatments except for 6 mg SC. Interestingly, the oral spray displays a similar bi-phasic absorption pattern as the nasal formulations, with fast initial absorption across the oral/nasal mucosa and a delayed GI absorption phase. However, despite an initial absorption rate similar to ON15/ON7.5 mg sumatriptan powder, the onset of pain relief of 20 mg oral spray is substantially slower than ON15/ON7.5 mg and other delivery routes/formulations.

Conclusions Comparison of PK and efficacy data for the various delivery routes and formulations suggest that rapid initial absorption alone cannot explain the high efficacy of sumatriptan nasal powder delivered with the novel device. We speculate that improved nasal deposition of sumatriptan powder offers a unique combination of rapid absorption and blocking of pain signalling in the 1st & 2nd trigeminal nerve branches directly involved in the pathophysiology of migraine.

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Repetitive transcranial magnetic stimulation over the visual cortex modulates trigeminal nociceptive pathways

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Background Bright light can cause visual discomfort, referred as photophobia; however, the mechanisms linking luminance to the trigeminal nociceptive system probably mediating this discomfort, are unknown. Neural connections between the visual cortex and the spinal trigeminal nucleus (STN) were observed in animal experiments. We address this issue in healthy subjects (HS) by studying the modulatory effects of repetitive transcranial magnetic stimulation (rTMS) applied over visual cortex on the nociceptive-specific blink reflex (nBR), reflecting STN activity.

Subjects and methods Fifteen bilateral consecutive nBR responses were recorded by stimulating the right supraorbital nerve (1.5x pain threshold) in 16 HS before and after rTMS over the visual cortex (phosphene or 110% motor threshold). Nine hundred pulses were delivered at 1 Hz (15 minutes train) or 10 Hz (20 trains of 4 seconds, inter-train interval of 15 seconds) frequency. We measured sensory and pain thresholds, and R2 area under the curve (AUC) on 3 blocks of 5 responses. Habituation was defined as the slope of the linear regression line for 3 successive blocks.

Results 1 Hz rTMS which has an inhibitory effect on the underlying cortex, significantly increased sensory ($p = 0.03$), but decreased pain threshold ($p = 0.02$). 10 Hz rTMS, supposed to have activating

effect, had no effect on these thresholds. Low frequency rTMS increased nBR R2 AUC and potentiated habituation, whereas high frequency rTMS decreased R2 AUC and left habituation unchanged ($p = 0.03$ for AUC; $p = 0.05$ for the slope). These effects were significant contralaterally to the stimulated side only, while effects were negligible in the ipsilateral recordings.

Conclusions Our data show for the first time in humans that there are functional connections between visual cortex and second order nociceptors in the STN. Interestingly, inhibitory rTMS modifies pain threshold (decrease), nBR area and habituation (increase) in the same direction as does the migraine attack, known to be associated with photophobia.

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Psychophysiological syndrome-specific descriptor profiling in migraine patients: electrodermal responses to pain and emotional descriptors among migraine patients and healthy controls

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Background and aims Individuals with migraine may present a syndrome-specific descriptor profiling and demonstrate greater skin conductance responsivity to descriptors that describe migraine due to the additional significance that these terms have acquired from their repeated association with the migraineurs' internal pain experience (Jamner and Tursky, 1987). Enhanced autonomic reactivity in chronic pain patients to words descriptive of their pain problem has been substantiated (Flor et al., 1997). Chronic pain may be linked to an increased reactivity to a wide range of stimuli, such as pain-related words (Flor et al., 1997) or emotional words (Bonnet and Naveteur, 2006). The objective of this study is to gather specific information about the reactions of migraineurs to emotional and pain-related words, and compare them with those from healthy persons.

Methods 15 migraineurs and 15 nonmigraineurs observed a series of 20 pain descriptors and 20 emotional descriptors, each presented twice, 12 sec each time. 80 trials were conducted and the skin conductance responses were recorded during each presentation. After the experiment, participants selected pain descriptors from the McGill Pain Questionnaire that described migraine headaches.

Results Our hypothesis is that migraineurs will demonstrate greater skin conductance responsivity to the visual presentation of pain descriptors, confirming a syndrome-specific use of pain language. Migraineurs may be conditioned or sensitized to particular sets of verbal pain descriptors, but also to emotional descriptors.

Conclusions If confirmed, this would imply that migraineurs have a syndrome-specific descriptor profile, which differentiates them from pain-free individuals regarding the electrodermal responses to pain and emotional words. There are important clinical and empirical implications to this study. The psychophysiological syndrome-specific profiling could be used as an adjunct in diagnostic procedures. Similarly, interventions could be tailored at interfering with the learning process underlying the acquired additional meaning and significance of specific stimuli for the migraine patient.

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Cortical silent period duration in medication overuse headache changes according to the drug overused

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Background Episodic migraineurs recorded interictally have shortened cortical silent period (SP), as a result of reduced activation of GABAB-ergic circuits in the motor cortex. In episodic migraine cortical activation fluctuates depending on the migraine cycle, whereas in chronic daily headache due to medication overuse (MOH) it seems locked in a pre-ictal state, it is of interest thus to study the cortical SP in patients with MOH.

Material and methods We recorded the transcranial magnetic stimulation (TMS) induced SP in perioral muscle in 36 MOH patients, 12 migraine without aura patients studied interictally (MO), and 13 controls. MOH patients were sub-grouped in patients who overused triptans ($n = 9$), nonsteroidal anti-inflammatory drugs (NSAIDs) ($n = 12$), and combination of both ($n = 15$) drugs. We delivered high intensity magnetic stimuli through a figure-of-eight coil over the hot-spot for the perioral muscles, while subjects maximally activated target muscles, and recorded the electromyographic responses with surface electrodes placed bilaterally.

Results MO patients had shorter SP than controls ($p = 0.021$). Despite as a whole group patients with MOH had normal SP duration ($p = 0.314$), the subgroup of triptan overusers had significantly shorter SP than controls ($p = 0.005$) and NSAIDs overusers ($p = 0.119$) or both medications combined ($p = 0.847$). Monthly tablets intake, but not disease history, correlated positively with SP duration ($r = 0.476$, $p = 0.003$) in the whole group of MOH.

Discussion In patients with MOH the activation of motor cortical inhibitory interneurons is greater than in episodic migraineurs studied interictally, and it is similar to that observed in controls. SP normalisation takes place in the MOH subgroup who overuse NSAIDs, whereas SP duration remains short in patients who overuse triptans alone. This finding confirms that in chronic migraineurs the overuse of NSAIDs or triptans changes the cortical physiology distinctly, and it shows that such distinctive effect is also exerted on cortical inhibitory circuits.

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Impairment of temporal development of the visual system short-range lateral inhibition in migraine without aura patients

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Background Migraineurs lack of habituation to repetitive visual stimulation during the pain free period, which was currently explained as due to cortical hyper-excitability, or to low cortical pre-activation levels. The latter should be affect both excitatory and inhibitory cortical neurons. Which of the former or the latter contributes more to the habituation deficit cannot be determined with the methods commonly used to evoke transient visual responses. Here we have used differential temporal modulation of adjacent regions of radial windmill-dartboard (W-D) or partial-windmill (P-W) visual patterns, since they accentuate the relative contributions that arise from short- and long- range lateral inhibition between neurons of the visual cortex.

Methods Steady-state visual-evoked potentials (4 Hz) were recorded in 42 migraine without aura (MO) patients (22 interictally [MOii] and 20 ictally [MOi]) and in 21 healthy volunteers (HV). Two visual stimuli were used: W-D and P-W. For each stimulus session, 600 sweeps were acquired and 6 blocks partitioned. Fourier analysis was performed to extract the amplitude of the fundamental (F1) and the second harmonic (2H) components reflecting respectively short- (W-D, F1) and long- range (P-W, 2H) lateral interaction.

Results Repeated ANOVA testing W-D F1 amplitude disclosed a group by block interaction ($p = 0.01$). In MOii patients the F1 harmonic block amplitude starts higher than HV ($p = 0.01$) and MOi ($p < 0.001$), and decreases with time, instead of increase like in HV and MOi. There were no significant between groups difference in the temporal development of the P-W 2H amplitude.

Discussion From our data emerges that interictally migraineurs visual cortex seems basically overinhibited since early F1 W-D amplitude is higher than HV and MOi. We hypothesize that hypofunctioning serotonergic pathways in migraine may cause a functional disconnection of thalamus leading to a decreased intracortical short-range lateral inhibition, which could contribute to induce interictal lack of habituation.

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Trends over time in the prevalence of headache disorders. The Nord-Trøndelag health studies (HUNT 2 AND 3)

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Objective Earlier reports regarding secular trends of migraine are conflicting, and there is a lack of long-term follow-up studies of other headache syndromes among adults. The aim of the present study was to assess any changes in the prevalence of the major headache types according to the diagnostic criteria of the International Headache Society (IHS) in a large adult population during an 11-year period.

Methods This study involved two cross-sectional surveys of all inhabitants aged ≥ 20 years in the Norwegian county of Nord-Trøndelag, from 1995 to 1997 ($n = 92\,566$) and from 2006 to 2008 ($n = 94\,194$). Attendance rates were 56% and 42%, respectively. Main outcome measures were the age-adjusted 1-year prevalences of all headaches combined, migraine, probable migraine, tension-type headache (TTH), chronic daily headache (CDH) and

medication overuse headache (MOH). Attack frequencies and sex-ratios were assessed.

Results In the second cross-sectional study, the 1-year prevalence of 'headache suffering' was 37.4%, for CDH 2.5% and MOH (1%). Compared to the first survey, this remained stable. The prevalence of migraine overall increased (12.1% versus 13.6%, $p < 0.001$), but the sex ratio did not change over time. The prevalence of definite migraine in the second survey according to the IHS criteria was 12.0% (women 14.9% and men 7.4%). The prevalence of non-migrainous headache overall decreased (26.0% versus 23.8%, $p < 0.001$), and the prevalence of TTH in the second survey was 16.5% and for chronic TTH 0.6%.

Conclusions The main finding was a significant increase in migraine prevalence, but no change over time in the prevalence of all headaches combined, nor in CDH. Together with earlier findings from Denmark, this may suggest a recent increase of migraine among adults in the Nordic countries.

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Is subcutaneous stimulation of the greater occipital nerve the invasive treatment of choice in patients with chronic headache syndromes?

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Objective In patients with chronic headache syndromes (CHS) which are refractory to any pharmacological treatment invasive techniques can be offered. In specific headache syndromes a dysfunction of the trigeminovascular system and hyperactivity in the hypothalamic area are supposed. Different invasive procedures are performed despite there is no evidence for each of these methods.

Methods The greater occipital nerve is stimulated (ONS) using subcutaneously placed leads at the level of C1/C2. ONS is suprathreshold with pleasant paraesthesias in the distribution of the greater occipital nerve. In ten patients (7 female, 3 male, mean age: 45 years; 4 pat. with chronic cluster headache (CCH), 2 pat. with chronic migraine (CM), 1 pat. with CCH and CM, 3 patients with occipital neuralgia (ON)) ipsi- or bilateral ONS was initiated and a test trial performed.

Results After implantation a testing phase of 7–14 days was performed. In all patients a positive effect with pain reduction was correlated with active and suprathreshold stimulation. Patients reported a decrease in attack frequency, intensity and duration with active ONS. In all patients a reduction of the pain medication was possible and a neurostimulation device was implanted. No periprocedural complications were observed. During the mean follow up of 22 months (range: 6–54 months) two technical problems needed to be revised operatively (one lead dislocation, one wound infection).

Conclusion ONS of the greater occipital nerve offers an effective, simple and low-risk treatment option for patients with specific CHS like CCH, CM or ON. Despite no pain-free status can be achieved a significant pain reduction and therefore an improved quality of life can be observed. Therefore ONS should be offered to those patients as the first invasive treatment option. There is an urgent need for better evidence and a prospective randomized trial comparing ONS with best medical and conservative treatment.

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Cessation of migraine after thalamic infarction

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The thalamus, a key centre in migraine, is activated during the attack, in the contralateral side to pain. Some drugs (triptans, propranolol) elicit pain-relief by acting on locally activated thalamic neurons. In similar terms, structural lesions in the thalamus could potentially modify the course of this disorder. We support this possibility, by providing a case with sustained cessation of chronic migraine after a thalamic infarction. The patient is a 65 year-old hypertensive woman, under candesartan. Since her twenties, she suffered from headache, as many other members of her family. The pain was preceded by aura symptoms in about a half of the episodes: they consisted of bilateral positive and negative visual manifestations, followed by ascending paresthesias from her left fingers to the shoulder, and later on to her left facial side; shortly afterwards, dysarthria and some difficulties finding words ensued. All of them receded about 15 minutes later. Aura never appeared without cephalalgia. Under different symptomatic (acetaminophen, nonsteroidal anti-inflammatory drugs, and four triptans) and preventive drugs (amytriptilin, flunarizin, propranolol, valproic acid and topiramate) she had got poor relief. She had abandoned medical follow-up, although she never abused drugs. During the last year she developed chronic migraine. Five days after her last cephalalgia, she suffered from an acute episode of right hemiparesis and paresthesias. In hospital, CT and MRI disclosed an acute left thalamic infarction, in its anteromedial area. Paresis and paresthesias vanished in a week. She remains headache and aura free 15 months after the stroke. As a unique cessation of chronic migraine followed the thalamic infarction, a causal link seems plausible. The involved nuclei, anterior and anteromedial, connect with the cingular, medial temporal and prefrontal cortex. Therefore, their deafferentation might render unperceived the emotional and rational aspects of headache, accounting for the final cessation of pain in this patient.

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The prevalence and characteristics of headaches in schoolchildren in the Czech RepublicM. Muchova¹, E. Janousova², L. Danis³, H. Andrlouva³, D. Schwarz², H. Oslejskova¹¹Department of Paediatric Neurology, Masaryk University and University Hospital Brno, Brno, Czech Republic;²Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic;³School of Medicine Masaryk University Brno, Brno, Czech Republic

Objectives The goal of this study was to estimate the prevalence of headache and primary headache like migraine and tension-type headache among children and adolescents and examine the possible differences in headache prevalence and type by gender and age. The characteristics of headache in children was also explored. This is the first study about epidemiological parameters of paediatric headaches in the Czech Republic.

Methods A population school-based study was conducted between November 2009 and April 2010 in the primary and high schools of Moravian region in the Czech Republic. The method use in this research was a questionnaire, which was based on the modified 2004

International Headache Society criteria for paediatric headaches. The questionnaire was completed by 1086 pupils (635 girls and 450 boys) aged 8-18 years and consequently processed statistically.

Results According to the questionnaires 95.5% students reported having had headache during their life. The prevalence rates of tension-type headache were 36.3% and migraine 27% (21.6% migraine without aura, 5.4% migraine with aura). Tension-type headache was found to be more common than migraine in both genders and in all age groups. 40.7% boys suffered from tension-type headache, 17.5% migraine without aura and 4.1% migraine with aura. 36.5% girls had tension-type headache, 25.9% migraine without aura and 6.8% migraine with aura. The onset of headache and especially migraine headache begins at an earlier age among males than among females. There was a high occurrence of headache in family history predominantly in mothers.

Conclusions The prevalence of headache in schoolchildren is high. Tension-type headache and migraine were found to be the most frequent types of headaches. It is very important and necessary to use modified IHS criteria in the diagnosis of childhood migraine.

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Epidemiology of headaches in Tehran—Iran in 2010, “Face-to-Face, in-door” studyS. Shahbeigi¹, M. Fereshtenejad², N. Mohammadi³, S. Tadayon⁴, G. Jalilzadeh⁵, M. Golmakani⁶, M. Heydari⁴, H. Pakdam⁴¹Neurology, Shahid Beheshti Medical University, Tehran, Iran;²Iran University of Medical Sciences, Department of Neurology, Tehran, Iran;³Iran University of Medical Sciences, Department of Epidemiology, Tehran, Iran;⁴Shahid Beheshti Medical University, Tehran, Iran;⁵Jondishapur Neurology Clinic, Tehran, Iran;⁶Tehran Municipality, Tehran, Iran

Headaches are one of the most common symptoms during life with high impacts on individuals and societies. A few studies were performed to evaluate different types of headache as face to face in door study. Therefore, this study was performed to evaluate the prevalence rates of different types of headache among people of Tehran urban area.

In this cross-sectional survey performed in collaboration with Tehran Municipality, a “face-to-face, in-door” structured interview was developed and studied a population of 378725 people (census 2006) as a pilot study of “Tehran Headache Study” in the year 2010. Using the random residential block numbers, the forms were applied to the family members with more than 10 years old age and finally 3655 individuals were enrolled. Subjects were diagnosed in accordance to the most frequent type of headache experienced in the last 1 year, using ICDH-2 criteria (revision 2004).

Of 3655 recruited individuals of the 8th district of Tehran urban area, 67% were female and 33% were male with the mean age of 35.87 (SD = 14.90) yr ranged between 10 to 95 years old. Overall number of 2778 (76%) people have experienced headache within last year. Tension and migraine headaches were the most common types with the prevalence of 48.6% (n = 1777) and 18.2% (n = 665), while, drug-induced, chronic daily (CDH) and cluster headaches were presented in 4.9% (n = 180), 3.3% (n = 122) and 0.1% (n = 3), respectively. This is the first population-based epidemiological studies of headache in Tehran general population which was performed in 8th district as the pilot survey. Our results show that the prevalence of

primary headaches in Tehran population is significant, particularly in females. We showed that impact of headaches in Tehran were very high and this emphasised that we should perform the better programs for headache prophylaxis and control in Iran.

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Prevalence of diabetes, hypercholesterolemia and clinical stroke in migraine patients after 9 years follow-up: results of the population-based camera-2 study

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Migraine is associated with subclinical ischaemic lesions as well as with ischaemic stroke, coronary disease and venous thrombo-embolism. Previous studies also suggested a higher prevalence of risk factors associated with cardiovascular disease (CVD) like hypertension, diabetes, hyperlipidemia and livedo reticularis among migraineurs. Here we investigate the presence of cardiovascular risk factors and events after 9 years follow-up in our population based cohort.

Methods Data are from the CAMERA-1 study (1999-2000), we re-examined 75% of the original cohort including 229 migraineurs (102 migraine with aura; 72% female; mean age 57 y.) and 95 controls (70% female; mean age 55 y). Participants underwent a structured computer guided telephone interview and a general physical and neurological examination, blinded for diagnosis. Presence of (cardiovascular) co-morbidities was self-reported, but had to be doctor diagnosed. Multivariate models adjusted for age were used to test differences in CVD related factors.

Results Alcohol use and smoking habits did not differ between groups. Physical examination revealed no differences for neurological deficits, systolic or diastolic blood pressure and body mass index, nor for presence of livedo reticularis. However, diabetes was reported by 9% of migraineurs vs. 2% of controls (OR 4.0 [0.9–17.7]), hypercholesterolemia was reported by 29% of migraineurs vs. 18% of controls (OR 1.8 [1.0–3.3]). Prevalence of reported cardiac arrhythmia, coagulation disorder, deep vein thrombosis, pulmonary embolism, myocardial infarction, angina pectoris, and TIA was similar in both groups. However, strokes of any type were reported more frequently by migraineurs (5%) vs. none of the controls ($p = 0.04$). We found no differences between migraineurs with or without aura.

Conclusion Migraineurs from the general population have more often diabetes (trend), hypercholesterolemia and clinical stroke, these differences were not present at baseline nine years earlier. Obesity, livedo reticularis, hypertension, or venous thrombo-embolism were not more prevalent in migraineurs.

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Clinical profile of children below 5 years of age with early onset recurrent headaches

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Objective Recurrent headache in children under 5 years of age is less common than in older children and adolescents. The clinical profile of headache is understudied in this group. It can be different from those with onset of symptoms at a later age.

Methods A retrospective study was undertaken into children who presented to a tertiary paediatric headache clinic over a 9-year period (1997-2005). All children with recurrent headache who had onset of headache symptoms before five years of age were included.

Results During the study period 815 children were seen in the headache clinic. 123(15%) children had headache symptom onset before five years of age. 74(60%) were boys and 49(40%) were girls. The diagnoses made according to IHS classification were migraine without aura in 64(52%), migraine with aura in 7(6%), migraine variants in 4(3%), non-specific headache in 15(12%), mixed in 12(10%) and other types in 21(17%).

Children with migraine (71/123) were the predominant group. They were studied in more detail. The site of maximal pain was frontal (66%), with other sites being holocranial (10%) and vertex (4%). Only 7 (10%) children had unilateral headache. The common associated symptoms were Anorexia (87%), Nausea (78%), Vomiting (67%), Photophobia (60%) and Phonophobia (72%). Imaging was done in 20 (16%) children and was normal in all but one. For acute treatment all were advised lifestyle changes and 109 (87%) were given routine analgesics (paracetamol and or Ibruofen). In children with migraine, for acute migraine attacks 10 (14%) needed sumatriptan and only 11 (15%) were advised prophylaxis.

Conclusions Migraine without aura is the most common headache in children with symptom onset before 5 years of age. In this age group, migraine without aura rarely lateralizes. Most of the children had benefited with advice on lifestyle changes and simple analgesics for severe headaches and were rarely prescribed prophylaxis.

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Headache as the sole presentation of cerebral venous thrombosis: a prospective study

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Introduction Headache is the most frequent presenting symptom of cerebral venous thrombosis (CVT), most commonly associated with other manifestations. It has been described as its only clinical presentation in 15% of patients. There is no typical pattern of headache in CVT.

Objectives To study the characteristics of headache as the sole symptom of CVT at presentation.

Methods From a prospective study of 26 consecutive patients diagnosed with CVT over 16 months, we selected those who presented with headache only: they had a normal neurological examination, no papilloedema and no blood or any parenchymal lesion on CT scan. All were submitted to a systematic aetiological work-up and a structured questionnaire about the characteristics of headache was applied.

Results Headache was the sole manifestation of CVT in 12 patients. Onset was progressive in 10 patients and thunderclap in 2. Headache was diffuse in 4, bilateral (frontal or posterior) in 7 and unilateral in 1. It was constrictive in 10 patients and pulsating in 2. Seven patients referred worsening with sleep, Valsalva manoeuvres or straining. There was no association between the characteristics of headache and extension of CVT. The mean delay between onset of symptoms and diagnosis in this group was 9 days; in those patients presenting with other symptoms/ signs was 4 days. Five patients had previously been evaluated because of the headache and were discharged from hospital diagnosed with “primary headache”.

Conclusions In our series, 46.2% of patients presented only with headache. There was no uniform pattern of headache apart from being bilateral. There was a significant delay of diagnosis in these patients. Some characteristics of headache should raise the suspicion of CVT: recent persistent headache, thunderclap headache or symptoms suggesting intracranial hypertension even in the absence of papilloedema or focal signs.

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The impact of a migraine attack and its after-effects on perceptual organization, attention, and working memory

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Introduction Many migraine patients report mild to moderate cognitive complaints during the first hours to days following a migraine attack, like slowing of reaction and memory problems.

Goal The aim of this study was to assess whether cognitive (perceptual, attentional, or memory) processes are impaired during the first 48 hours after a migraine attack.

Methods Three different cognitive tasks (Global-Local task, the Attentional Network Task and N-back task) were applied to 16 migraine patients (81% migraine without aura; mean age 58 yrs, 94% female) and 18 healthy controls (59 yrs, 83% F), matched to age, gender, and educational level. Cognitive test data were obtained at three time points; during the first headache free day following a migraine attack (1st session), after 24 hours (2nd session) and 12 days after the attack (3rd session).

Results The attentional network (ANT) and N-back tasks showed no significant differences between migraineurs and controls. For the Global-Local task subjects were presented visual figures, in which a larger (global) letter was composed of smaller (local) letters, and subjects were asked to respond which letter was either the local or the global one. Controls showed faster reaction times, when responding to global than to local stimuli, which is the standard global precedence effect. This effect was absent in the migraineurs. [$F(1,28) = 4.99$, $p = 0.034$]. The found (migraine vs control with global vs local) interaction was strongest when comparing prophylaxis using migraineurs with controls ($p = 0.06$). The impact of migraine however was roughly comparable across sessions.

Conclusion No evidence for temporary changes in cognitive performance was found during the post-attack phase in migraineurs on attentional function, working memory, or perceptual organization capabilities. Surprisingly, we found that the normal global precedence effect (making responses to global stimuli fastest), was absent in migraineurs, especially in those on prophylactic medication.

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The ‘trigger avoidance model of headaches’ and ‘learning to cope with triggers’

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We have argued in three recent publications that the standard clinical advice that headache management should involve avoidance of triggers is open to criticism as it has minimal empirical support and problems with implementation. In addition, the literatures on anxiety, stress and chronic pain would suggest that avoidance is generally a maladaptive strategy. We have proposed the ‘Trigger Avoidance Model of Headaches’, which suggests that fear of the experience of headache drives susceptible individuals to try to avoid headache triggers, and this natural tendency is encouraged by clinicians and advice on the internet. Attempts to avoid triggers will result either in no exposure, or short exposure, to the triggers. This may lead to the capacity of the trigger to precipitate headaches being maintained or increased, through a process of sensitisation, failed habituation/adaptation, or lack of opportunity for learning to cope with the trigger. Hence, whilst attempts to avoid triggers may lead to fewer headaches in the short-term, it may result in more headaches in the long-term as tolerance for triggers decreases. We have argued that counselling avoidance should be replaced with a philosophy of ‘Learning to Cope with Triggers’. The stress literature demonstrates that no one coping strategy can be selected as the best way of coping with stress for all situations and across time, but approach strategies generally are more adaptive than avoidance strategies. We have argued that in parallel with the stress literature, no one strategy can be singled out as the best way of managing all headache triggers. Sometimes avoidance will be the strategy of choice but more often, approach/engagement/exposure strategies will be the strategies of choice. This presentation will focus on the practicalities of our approach to management of triggers - that is, how it works for the diverse range of factors that can precipitate headaches.

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Body mass index (BMI) and headache days in Japanese migraineurs

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Chronification of migraine headache is one of the most urgent issues in headache management. Obesity is regarded as a risk factor for chronification of migraine. To clarify possible association of migraine chronification and obesity, we analyzed headache days and BMI in Japanese migraineurs.

Subjects and method Four hundred and sixty five headache sufferers have visited our headache center from February 2010 to April 2010. We interviewed all patients with structured questionnaires. Full neurological examination was performed to all subjects. Brain imaging was carried out if necessary. Type of headache was determined in accordance with ICHD-II. Two hundred thirty one subjects had migraine headache, the other 234 s had tension-type headache, cluster headache or other primary headache. Height and body weight were measured in the clinic. According to BMI, subjects were categorized to five ranks, i.e., underweight (BMI < 18.5), normal (18.5–24.9), overweight (25–29.9), obese (30–34.9), and morbid obese (>35). Average headache days and migraine days of recent three months were recorded. Frequency of acute medication use was also recorded. The data were analyzed with chi-square test and one way ANOVA.

Results Thirteen out of 38 underweight migraineurs (34.2%), 70 of 160 normal-weight ones (43.8%), 11 of 26 overweight ones (42.3%) and 6 of 7 obese ones (85.7%) had more than 15 headache days ($p = 0.91$, Pearson's chi-square test). There was no morbid obese migraineur in this series. Mean headache days were 10.9 ± 1.5 (SE), 13.4 ± 0.9 , 14.0 ± 2.2 , and 22.4 ± 2.4 days/month in underweight, normal, overweight, and obese migraineurs, respectively ($p = 0.013$, ANOVA). Mean migraine days were 5.3 ± 0.7 , 5.5 ± 0.4 , 6.9 ± 0.9 and 10.8 ± 1.9 , respectively ($p = 0.002$, ANOVA).

Conclusion Obese migraineurs tended to have more headache and migraine days than normal or underweight migraineurs in a Japanese series.

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Multimodal visual functions (visual field, contrast sensitivity, visual evoked potential) and cerebrovascular reactivity in migraine patients between attacks

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Background Migraineurs have significantly interictal altered visual field and contrast sensitivity (CS), and it has long been thought that these changes are related to vascular origin.

Objectives To investigate the relationship between visual functions (visual field, spatial-contrast function, visual evoked potential) and cerebral flow velocities and vasoreactivity in migraineurs between attacks.

Methods The study included 27 migraineurs (23 females and 4 males) are matched to 18 healthy volunteers. They were subjected to severity grading by migraine disability assessment score (MIDAS); transcranial doppler sonography (TCD) with vasoreactivity testing for MCA and PCA; pattern reversal visual evoked potential (PRVEP); CS assessment and visual field study using standard and short wavelength automated perimetry (SAP and SWAP).

Results Compared to controls, patients had significantly impaired response of MCA to hyperventilation (HV) ($P = 0.018$) and a highly significant lower vasoreactivity index ($P = 0.0014$); significantly lower mean P100 amplitude of both eyes in all ($P = 0.03$); significantly prolonged mean P100 latency of both eyes ($P < 0.05$); and significantly lower CS ($P \leq 0.01$). None of visual fields in the migraine group had homonymous defects. SAP and SWAP detected total field deficits in patients (63% and 74% respectively); bilateral minimal criteria of glaucomatous damage (37%, 40.7% respectively) and unilateral changes (26% and 33.3% respectively). There was statistically significant negative correlation between VEP P100 latency, and mean MCA flow velocity, mean MCA flow velocity after HV and percentage of vasoreactivity. There was positive correlation between cerebral blood flow velocity and reactivity index and CS; however this was not statistically significant.

Conclusions Migraineurs had significant interictal changes of visual functions, VEP and cerebrovascular reactivity, suggesting the underlying vascular etiology of visual function deficits and that glaucoma and migraine may share a common vascular etiology.

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Prevalence and burden of headache disorders: comparative study in same latitude region of China

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Background Over the past 20 years, no investigation on the prevalence and burden of headache disorders on the suffered population was carried out in China.

Objective We aimed to conduct a one-year survey on the prevalence and burden of primary headache in Chinese in Guangdong and Guangxi provinces. Also evaluated are the factors of similarity and dissimilarity affecting the sufferers' burden between the two regions.

Methods Random samples of local residents in Guangdong and Guangxi aged 18–65 years were invited to a face-to-face interview.

Results The 1-year prevalence of primary headache was consistent with the previous studies in that Asian. The total cost of headache treatment in one year would be close to 1.44% of national GDP in 2008. Migraine had more impact on patients than tension-type headaches (TTH), while TTH had higher prevalence than migraine among population. There was significant difference of life quality score between headache and non-headache populations in the two regions.

Conclusion Headache had higher prevalence in low income regions and ethnic minority areas and the financial burden on headache population in the low income region also relatively increased. Although the impact caused by migraine was much more serious than that of TTH among the population, taking the high prevalence of TTH into account, both migraine and TTH caused similar burden on the suffered population. The impact of headache is potential high and may cause the psychological burden on patients.

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Memantine for prevention of cluster headache: a possible new treatment?

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Introduction Cluster headache (CH) is the most common type of TAC and although effective therapies exist, there remain a significant number of patients for whom current treatments are either ineffective or poorly tolerated. Memantine (MEM), is an activity dependent blocker of NMDA receptors. Since glutamatergic signalling has been implicated in primary headache disorders, we investigated the possibility that MEM may be an effective therapy for patients with CH who had failed current standard therapies.

Methods Patients were evaluated in the outpatient headache clinic of an academic medical center. Patients were diagnosed according to the ICHD-2 classification for *episodic CH* and *chronic CH*. All patients had failed first-line preventive therapy. MEM was added to other preventive treatments in 5 CH patients, and MEM alone was used as preventive treatment in 5 patients. A retrospective descriptive analysis of the data was performed.

Results Patient ages ranged from 26 to 78 years (mean age 53.3); 9 M and 1 F, 5 episodic CH and 5 chronic CH. Patients used MEM for a duration of between 1 month and 12 months (20 mg/day). The headache frequency prior to MEM was daily with a daily frequency of attacks ranged from 1 to 5 (mean 2.1). Out of 10 patients, 6 (60% of all patients) reported remission, 4 episodic CH and 1 chronic CH patients, 2 patients reported remission after only one month of treatment. Four chronic CH patients (40% of total patients) reported a greater than 50% reduction in estimated monthly headache frequency. No patients discontinued MEM for side effects.

Conclusions This study, although clearly limited by its retrospective approach, lack of blinding, and lack of a controls, suggests that MEM may be treatment option for CH patients who do not respond to or do not tolerate conventional therapies. Prospective placebo controlled studies are warranted.

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Chronic pain, use of mixed analgesics/opioids and medication overuse are associated with chronic daily headache: results of german headache study

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Objective To estimate the 1-year prevalence of headache ≥ 15 days/month (chronic daily headache, CDH) and identify its principal risk factors in the general population in Germany.

Methods A random sample of 18.000 participants (6.000 each in Essen and Münster, a large and mid-sized city in North Rhine-Westphalia, and Sigmaringen, a rural area in the southern part of Germany) were screened by using a previously validated questionnaire.

Results The response rate was 54% (9.665/18000), 5.088 (52.6%) were female; mean age was 43 ± 13.1 . CDH was reported by 248

respondents hence resulting in the prevalence of 2.6% [95% CI 2.3-2.9%]. Of those, 136 individuals had medication overuse. Risk factors for CDH were smoking (OR 1.1 95% CI 1.0-1.9), chronic low back pain (OR 4.4 95% CI 3.3-6.0), chronic facial pain (OR 26.4 95% CI 13.0-53.4) and medication overuse (OR 13.4 95% CI 9.8-18.4).

We furthermore analyzed a subgroup of people who reported headache in the previous year (N = 5779). People using mixed analgesics (OR 2.3 95% CI 1.5-3.5) and opioids (OR 4.1 95% CI 1.4-12.3) were at higher risk for CDH compared to those with headache, who reported not to take any acute headache drug. In contrast, the risk for CDH was not increased in respondents who reported to use single analgesics (OR 1.1 95% CI 0.8-1.5) or triptans (OR 1.4 95% CI 0.7-2.6).

Conclusions

- (1) The prevalence of CDH is in line with previous studies in Europe and US.
- (2) In addition to the well known risk factors such as medication overuse we were able to show that concomitant chronic pain is strongly associated with CDH
- (3) The association of use (not overuse) of combination analgesics and opioids with CDH is of clinical importance and should be further studied prospectively.

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Prevalence of episodic primary headaches and associated risk factors in Germany: results of the German headache study

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Objective To estimate the 1-year prevalence of migraine (MIG) and tension-type headache (TTH) and identify their principal risk factors in the general population in Germany.

Methods A random sample of 18.000 participants (6.000 each in Essen and Münster, a large and mid-sized city in North Rhine-Westphalia, and Sigmaringen, a rural area in the southern part of Germany) were screened by using a previously validated questionnaire.

Results The response rate was 54% (9.665/18000), 5.088 (52.6%) were female; mean age was 43 ± 13.1 . Headache on < 15 days/month was reported by 5531 subjects. The 1-year prevalences among these participants were as follows: definite MIG 12.7% [95% CI 12.1-13.4%], Prob-MIG 4.2% [95% CI 3.82-4.62%], definite TTH 3.6% [95% CI 3.1-3.9%], Prob-TTH 9.4% [95% CI 8.8-9.7%], MIG + TTH 4.6% [95% CI 4.2-5.0%], and Prob-MIG + Prob-TTH 7.5% [95% CI 7.0-8.1%] and 15.3% of cases were unclassifiable.

People with definite MIG were predominantly female (OR 3.1, 95% CI 2.7-3.6), were more likely to smoke (OR 1.2, 95% CI 1.1-1.4) and less likely to drink alcohol (OR 0.64, 95% CI 0.5-0.8).

People with definite TTH were less educated (OR 1.3, 95% CI 1.1-1.6) and were less likely to drink alcohol (OR 0.52, 95% CI 0.3-0.8).

Conclusions

- (1) Prevalences of migraine and tension-type headache are comparable with those in Europe and the USA.
- (2) The study reveals different risk factors for the two biologically different disorders.

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From the migraine to the brain, and back. Neuropsychology of medication overuse headache

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Objective 30% to 50% of chronic migraineurs fall into a self-perpetuating cycle of daily headache and overuse of analgesics, experiencing pharmacological tolerance and dependence and developing Medication Overuse Headache (MOH). We investigate causal relations among disability, addiction, anxious and depressive symptoms, neurocognitive performance.

Methods This cross-sectional study shows datasets of 50 patients suffering from MOH, diagnosed by International Headache Classification Criteria, before withdrawal. Patients completed self-administered scales (MIDAS, SDS, Subs-SR, ScI90-R) to determine disability, dependence, substance use, psychopathological dimensions. Anxiety and depression were evaluated by Hamilton Scales. Neuropsychological assessment of prefrontal cortex and frontal-striatal circuits has been investigated by Probabilistic Reversal Learning Task and Iowa Gambling Task.

Results Statistical analyses identified that disability correlates with frequency of attacks, dependence-like behaviours, anxiety and depressive symptoms. Moreover, psychopathological variables are associated with deficits in reversal learning. A separate model involves decision making functions, duration of migraine and overuse.

Conclusions Medication overuse is a complex phenomenon, where prefrontal cortex dysfunction may play a key role, as seen in addicts of other substances. Decision making deficit is linked with duration of overuse and migraine, while deficits in relearning of stimulus-reward associations and perceiving negative feedback could be in relation with dependency behaviours and psychopathological symptoms. Dependence seems pervasive in determining disability and should be the first target of treatment. Anxiety and depressive symptoms are more likely a consequence of disability than a predisposition. More research is required focusing on underlying neuronal substrates of dependence and decision-making.

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Related research in the polymorphism of CACNA1A of migraine in the southerners of China

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Background During the 1990 s, owing to the development of molecular biology and hereditary statistical analysis, there was a breakthrough about the study of Familial hemiplegic migraine (FHM) which had the most evident hereditary tendency in all kinds of migraine. The researches indicated that many genes like a gene of $\alpha 1A$ subunit of brain-specific P/Q calcium channel might participate the pathogenesis of FHM.

Objective To determine the connection between mutations in CACNA1A gene and the patients with familial hemiplegic migraine

(FHM) in the southerners (Han people) of China, through the method that detected the three most frequent mutable points in CACNA1A gene from the peripheral blood of patients with FHM.

Design Adopted single-strand conformation polymorphism (SSCP) method to detect the peripheral blood samples of 10 patients and their 12 normal relatives in tow families with FHM and 53 migraineur with aura but without FHM and 10 people for control.

Results Sequence variants in chromosomes were detected from neither the 2 families with FHM nor the sample with aura but without FHM and we also didn't detect the sequence variants of chromosomes in the control group.

Conclusions None of the three most frequent mutations (T666 M, R583Q and D715E) was detected in chromosomes from the patients with FHM or the patients without FHM among the southerners (HAN people) of China. The connections between FHM and CACNA1A gene or migraine with aura and CACNA1A gene still need to be further investigated in more cases.

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Post-radiosurgery headache: does it exist?

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Post gamma knife headache was first described by Rozen in 1997. This diagnosis is included in the International headache Classification in the Appendix (A7.9.1) and is defined as a headache developing within 7 days after radiosurgery.

We conduct a retrospective study in Marseille Timone Hospital (France) to determine if *de novo* headache can occur after radiosurgery and if post-radiosurgery headache is related to the location of the lesion and the dosage and radiation field employed.

During five months, patients coming back to the follow-up consultation after radiosurgery were included in a study and ask to answer to a specific questionnaire. The goal of this questionnaire was to determine if the patient had headaches before surgery and if he developed a *de novo* headache or a modification of a previous headache after radiosurgery.

Between February 2009 and July 2009, 82 patients were included in this study. Twenty -one patients had no headache before and after radiosurgery. Twenty-three patients had a headache before the radiosurgery and no headache after. Twenty-eight patients complain of headache before and after radiosurgery with no modification of the presentation of the headache for 21 patients. Finally, headache appears after radiosurgery for 10 patients and a diagnosis of post radiosurgery headache was proposed for one patient. A 65-year-old male patient, without previous personal and familial history of headache, was treated with radiosurgery in 2006 and in 2008 for a geniculate ganglion schwannoma.

He developed six months after the second radiosurgical treatment a permanent, retro-auricular headache ipsilateral to the tumour. Two years after, and despite a reduction of the tumour volume, the headache persists. We suggest that post-radiosurgery headache does exist and that the pathophysiology of this headache is related to dura mater inflammation.

Conflict of interest Dr. Donnet has perceived personal compensation for activities (consulting, clinical research) with Almirall SAS, Merck, Pfizer Inc.

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Current progress of a study to explore putative links between migraine, appetite behaviours and obesity in childrenS. Singh¹, S. Ray¹, A. Curran², J. Halford³, J. Harold³, R. Kumar²

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Aim To discuss the progress of an ongoing pilot study of migraine and appetite behaviours in children.

Background Recent research has highlighted an association between migraine and obesity, including in children. A causal relationship, and its direction, is not established. There are overlapping neurobiological mechanisms in migraine, appetite behaviour and obesity. Migraine has been noted to affect appetite behaviours, but this has not been formally studied previously. We wish to explore the biologically plausible hypothesis that migraine may lead to obesity, via alterations of appetite and food intake.

Method A single-centre, cross-sectional, questionnaire-based, clinical migraine population pilot study was designed. The primary outcome measures are migraine severity and eating behaviour using validated tools. Secondary outcomes are to classify, describe and quantify appetite behaviour in paediatric migraineurs including food cravings. Specific tools used are the PedMIDAS, Dutch Eating Behaviour Questionnaire, Child Eating Behaviour Questionnaire, Child Behaviour Checklist, Food Cravings Inventory and the food intake questionnaire. Body mass index z scores will be used as a measure of adiposity. The sample size appropriate for a pilot study is 60 children with migraine, and 30 non-migraine headache controls. The main exclusion criterion is current treatment with migraine prophylaxis medications due to their adverse weight altering effects. Local Research Ethics and Trust R&D approvals were granted in June 2009.

Results The total of 60 migraine cases have been recruited as previously intended from general paediatric and neurology outpatient clinics. Participants enrolled in the study are aged between 5 to 16 years. The primary focus will be to examine the relationship between migraine severity, appetite behaviours and BMI z-scores. Pending collaboration with the longitudinal ALSPAC study for data on migraine and obesity may provide findings that can establish causality. The analysis and discussion of results should be complete by early August 2010.

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Serial polysomnography in hypnic headache shows no association with REM sleepM. Obermann¹, D. Holle¹, T. Wessendorf², S. Zaremba¹, M.-S. Yoon¹, C. Gaul¹, H.-C. Diener¹, Z. Katsarava¹

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Objective To identify associations of REM sleep with the occurrence of headache in patients with hypnic headache.

Background Hypnic headache is a rare primary headache disorder exclusively related to sleep. Patients wake up every night with typical

headache lasting between 15 min and several hours. Early case reports and small case series suspected a strong association with REM sleep, as it was observed, that patients always woke up in REM sleep. However, recent polysomnographic investigations reported patients with headache onset in Non-REM sleep.

Design/ methods We performed polysomnography in 6 patients with hypnic headache according to the diagnostic criteria of the International Headache Society (ICHD-II) in four consecutive nights. An independent, experienced sleep medicine specialist blinded to the diagnosis evaluated a total of 22 nights where typical headache occurred.

Results We found no association of the occurrence of headache in patients with hypnic headache with a particular sleep phase. Headache onset was arbitrarily distributed to REM and Non-REM sleep. Two patients had two headache attacks in one night and had one attack in REM and the other one in Non-REM sleep. Headache occurred most often in sleep phase 2, which also is the most likely finding as this is the most common sleep phase. One patient had obstructive sleep apnoea syndrome where headache resolved after CPAP mask therapy.

Conclusion/ relevance The occurrence of hypnic headache attacks is not associated with a particular sleep phase, neither REM nor Non-REM sleep. The underlying pathophysiology remains uncertain, but is obviously not dependent on REM sleep.

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The role of eletriptan in migraine-acute attack therapy in patients with somatic pathology

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Headache is one of the most frequent complaints, imposed patients for therapists. There are several types of headache, but migraine studied more than others. The aim of our study was to determine the frequency of migraine in the practice of therapist and efficiency of pain therapy. 284 patients were included in our prospective study. Of these, 225 (79%) patients complained of headache. These were 133 (59%) women and 92 (41%) men. The average age of patients was 69 ± 14 years. We found that headache occurs most frequently in patients with essential hypertension (97; 43%) and coronary artery disease (CAD) (70; 31%). Also, the headache was observed in 34 (15%) patients with chronic obstructive pulmonary disease and 18 (8%) patients with malignant neoplasms. These types of headache were regarded as migraine in 17% of cases (38 patients). The average age of these patients was 43 ± 7 years. Therapists and neurologists have identified migraine in 29% and 71% of cases (11 and 27 patients), respectively. Migraine is testimony to the appointment of selective 5-hydroxytryptamine 1B/1D receptor agonists (selective 5-hydroxytryptamine 1B/1D receptor agonist (eletriptan). But 20 patients had contraindications (for example, CAD) to eletriptan (Relpax®). So, non-steroidal anti-inflammatory drugs (NSAIDs) were assigned for these 20 patients (group A). Relpax was assigned for 18 patients who did not have these contraindications (group B). We used the scale of MIDAS (Migraine Disability Assessment) to evaluate the characteristics of headache. Average score of the scale in these groups was 17 and 19, respectively. The intensity of headache decreased in both groups after drug treatment. After 2 hours the average score of the scale in groups was 10 and 13 and after 4 hours - 4 and 9, respectively. Thus, the intensity of headache decreased by 76,5% in group A and 52,6% in group B.

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Osteopathic management of an adult patient suffering from trigeminal neuralgia after an arnold chiari type I decompression surgeryR. Zegarri-Parodi^{1,2}, P. Allamand², L. Fabre^{1,2}¹CEESO, Lyon, France;²Private Practice, Paris, France

Introduction Herniation of the cerebellar tonsils through the foramen magnum into the cervical spinal canal with obliteration of the cerebellomedullary cistern is the primary feature of Arnold-Chiari type I (AC1) malformation. Posterior cranio-cervical decompression by opening foramen magnum and atlas lamina usually with corresponding dural and arachnoid opening is the surgical procedure most frequently used. Postoperative pain impairing functional activity and quality of life is common and it is possible that manual treatments such as osteopathy may bring relief.

Objectives To describe the examination, intervention, and outcomes for a patient suffering from trigeminal neuralgia after an AC1 decompression surgery with osteopathic treatment.

Methods A case report of a 29 year old man who presented with trigeminal neuralgia 5 years after decompression surgery. Encephalon and cervico-thoracic medulla MRIs were normal, describing only scar tissue following surgery. The trigeminocervical nucleus receives nociceptive inputs from both the trigeminal nerve and the first three cervical nerve roots which innervate the anatomical structures most affected during the surgery. Musculoskeletal scar tissue was targeted for osteopathic manipulative treatment based on its hypothesized influence on a sensitization state of the central nervous system. Manual desensitization techniques devised to reduce patient pain perception were proposed.

Results A clinically significant decrease in overall pain as measured with a VAS occurred after the second treatment. Throughout the treatment period, an increase in cervical function was also described by the patient.

Conclusions Pain perception in some patients suffering from trigeminal neuralgia following cranio-cervical decompression could be triggered by scar tissue and reduced by appropriate manual treatment.

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An open study on the polymorphism gene apolipoprotein e in migraine and cardiovascular diseaseV. Pizza¹, F. Infante², G. Schiavo³, A. Agresta¹, A. Capasso⁴, A. Bisogno⁴, C. Colucci d'Amato⁵¹Neurophysiopathology Unit, S. Luca Hospital, Vallo della Lucania, Italy;²Molecular Biology Unit, S. Luca Hospital, Vallo della Lucania, Italy;³Biochemistry Unit, S. Luca Hospital, Vallo della Lucania, Italy;⁴Faculty of Pharmacology, Salerno University, Salerno, Italy;⁵Neuroscience Department, Second University of Naples, Napoli, Italy

Introduction Nitric oxide plays an important role in the pathogenesis of migraine. Studies suggest that the expression of molecules involved in the pathogenesis of headache (i.e., nitric oxide-interleukin) is influenced by apolipoprotein E (APOE) and is gene specific. Hence, we hypothesized that APOE polymorphism may be associated with migraine.

Aim Our study analysed the incidence of genetic polymorphism Apolipoprotein E in a sample of migraineurs and a control group of the patients with ischemic cardiopathy.

Materials and methods In this study 103 consecutive patients aged 18-64 years (mean age 33.4 years), suffering from migraine

(1) (81 migraine without aura, 22 migraine with aura, ICHD-II criteria) and 90 patients aged 36-74 years (mean age 46.5 years), with ischemic cardiopathy

(2) were studied with Polymerase Chain Reaction (PCR) for genetic polymorphism Apolipoprotein E.

Results ApoE: 72 patients (70%) [1] and 63 (70%) [2] had an E3/E3 genotype; 16 (15.5%) [1] and 14 (15.5%) [2] had a E3/E4 genotype; 7 (6.8%) [1] and 9 (10%) [2] had a E2/E3 genotype; 2 (2%) [1] and 4 (4.4%) [2] had a E4/E4 genotype; 3 (3%) [1] and 0 [2] had a E2/E4 genotype; 0 [1] and 0 [2] had a E2/E2 genotype.

Conclusions Our results highlighted a more or less equivalent prevalence of apolipoprotein E gene polymorphisms in migraineurs and in subjects suffering from ischemic cardiopathy. Further research is required to confirm the findings of the present study in a larger sample and to elucidate the role of APOE polymorphism in headache.

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Interventional pain management procedures for refractory trigeminal neuralgiaA.R. Cooper¹, Z. Elchami²¹Pain Relief Clinic, Causeway Hospital, Coleraine, UK,²Pain & Headache Management Center, International Medical Center, Jeddah, Saudi Arabia

The authors report their experience in managing refractory trigeminal neuralgia (TN) referred for interventional pain relief therapy. The population etiology was mixed (idiopathic n = 66, Demyelinating Disease n = 38, post traumatic n = 7 and vascular anomalies n = 3) and duration of symptoms ranged from 6 months to 20 years. All had undergone extensive medical therapy and were receiving polypharmacy at referral. Mean age was 59 yrs (range 24-94 yr) and M:F = 32:82 A single procedure often sufficed but in 26 cases additional procedures were required. Techniques included Radiofrequency thermocoagulation (n = 105), balloon compression (n = 5) and glycerol injection (n = 4). Mean radiation exposure times were 2.25 min ranging from 0.25 - 9.6 minutes. Most treatments were for V2 & V3 pain (n = 98) with V1 & V2 being least commonly targeted (n = 16). Good to excellent pain relief was achieved in 109 procedures, with > 40 - 100% relief being obtained, while in only 5 procedures was this inadequate with < 40% relief being attained. Demyelinating Disease was more refractory to intervention than with idiopathic aetiology. Facial numbness was the most commonly experienced side effect but was well tolerated. Interventional pain relief procedures offer a safe and effective option in refractory TN when other methods have failed or produce intolerable side effects.

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Lifestyle redesign[®] for chronic headaches: prevention of chronic migraines through lifestyle modificationS. McNulty¹, S. Sahai²¹Occupational Therapy and Occupational Science, University of Southern California, Los Angeles, CA, USA;²Neurology, University of Southern California, Los Angeles, CA, USA

Lifestyle Redesign[®] for Chronic Headaches is a program implemented at the University of Southern California through a collaboration between Occupational Therapy and Neurology. People with chronic headaches have an underlying genetic vulnerability to headaches and lifestyle factors, called triggers, which can cause headaches. Traditional treatment includes medication management; more recently some multidisciplinary teams have developed to address the numerous needs of patients, which have been successful in decreasing headache frequency. Occupational Therapy (OT) is a health care profession aimed at improving performance, preventing illness and disability, and promoting adaptation to life changes through participation in meaningful occupations. OT would address the application of headache prevention into the person's actual routine and activity choices with a particular focus on lifestyle balance. Lifestyle Redesign[®] is an approach within OT that is uniquely suited for the headache population due to its focus on occupational self-analysis and the health promoting effects of occupation. Constructs applied to the headache population from occupational science include lifestyle balance, habits, and perceived control. This program applies occupational science research and address lifestyle factors such as stress, physical activity, sleep routine, and diet in order to decrease headache occurrence.

The three goals of the program are:

- (1) To increase patient's knowledge of lifestyle habits and factors related to headaches.
- (2) To improve the patient's ability to adapt behaviors through tools and strategies from a Lifestyle Redesign[®] perspective, and
- (3) To decrease the overall number of headaches that patients experience.

Outcome measures used include: Migraine Disability Assessment Scale (MIDAS), Migraine Specific Quality of Life Questionnaire (MSQ v.2.1), The Headache Management Self-Efficacy Questionnaire (HMSE), Headache Impact Test (HIT-6), and the Canadian Occupational Performance Measure (COPM). Initial outcomes from 4 patients result in a significant positive improvement in their quality of life as measured by the MSQ v 2.1.

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An open study on factor XIII VAL 34 LEU polymorphism gene in migraine and cardiovascular disease

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Introduction At present, it is contradictory to determine if the combination of certain prothrombotic polymorphisms and migraine and also the risk to develop ischaemic vascular disease. Recently, the common Val34Leu polymorphism of the A-chain factor XIII gene, associated with variations in factor XIII activity, has been suggested to play a significant role in the development of arterial and venous thrombotic disorders.

Aim Our study analysed the incidence of genetic polymorphism Factor XIII (V34L) in a sample of migraineurs and a control group of the patients with ischemic cardiopathy.

Materials and methods In this study 103 consecutive patients aged 18-64 years (mean age 33.4 years), suffering from migraine [1] (81 migraine without aura, 22 migraine with aura, ICHD-II criteria) and 90 patients aged 36-74 years (mean age 46.5 years), with ischemic cardiopathy [2] were studied with Polymerase Chain Reaction (PCR) for genetic polymorphism Factor XIII (V34L).

Results Factor XIII (V34L): 63 subjects (61.2%) [1] and 40 (44.4%) [2] were heterozygous; 7 subjects (6.8 %) [1] and 5 (5.5%) [2] were mutated.

Conclusion These data evidenced that the incidence the factor XIII Leu 34 allele in two population studied not evidenced meaningful differences. Therefore a role in the pathogenesis of such disturbances is hypothetical and deserves ulterior deepening in more important casuistries.

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Investigating the molecular basis underlying the increased CSD susceptibility in transgenic familial hemiplegic migraine type 1 mice

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Aim We generated transgenic knock-in mice bearing pathogenic FHM1 mutations in the orthologous *Cacnala* gene to study mechanisms and pathways involved in migraine pathophysiology. Previous investigations had shown that FHM1 mutant mice had an increased susceptibility to cortical spreading depression (CSD), a wave of glial and neuronal depolarization that spreads slowly across the cerebral cortex and that is generally believed to underlie the migraine aura. Here we investigated whether the visual (occipital) cortex is more susceptible to CSD and whether basal molecular profiles in this brain region differ between mutant and wild type mice.

Methods CSD induction thresholds were measured by topical KCl application to occipital and frontal cortices of mutant mice bearing the FHM1 R192Q mutation as well as wild type mice. Basal molecular profiles were determined in occipital cortices (the more susceptible brain region) of mutant and wild type mice. RNA expression profiles were studied using Illumina mouse-6 Bead Chips microarrays. Synaptosome proteome profiles of occipital cortices were obtained by an iTRAQ-based LC-LC MS/MS approach.

Results The CSD induction threshold was lowest in the occipital cortex, but only in mutant mice. This increased susceptibility to CSD was not accompanied by profound differences in molecular profiles of RNA and protein in this brain region between mice of both genotypes. The proteomic profile did reveal a subtle up-regulation of certain proteins involved in neurotransmitter-relevant mechanisms.

Conclusion Our results indicated that the increased susceptibility to CSD in the occipital cortex of FHM1 mice apparently is not due to major differences in molecular profiles between mutant and wild type

mice. Studies are ongoing to investigate whether molecular profiles are different after CSD.

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Magnesium, L-tryptophan and niacin: a new therapeutic options in prophylaxis of pediatric migraine?

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Aim To evaluate the efficacy and tolerability of magnesium, l-tryptophan and niacin in prophylaxis therapy of pediatric migraine.

Methods 35 outpatients, (19 F, 16 M) mean age 8.5 years (SD 2.1), range 5-14 years, suffering from migraine without aura (ICDH '04 criteria) were enrolled. The mean duration of disease was 2.0 (SD 1.1) years, range 1-6 years. At baseline the mean frequency of attacks was 6.3/month (SD 2.2), range 4-12; the mean number of drugs intaking for acute attacks was 5.1 tablets/month (SD 2). During the six month evaluation period magnesium, l-tryptophan and niacin was administered (starting dose mg/die, target dose 1000 mg/die). All patients filled a headache-diary card during the evaluation.

Results The basal frequency of attack was 6,3 (SD 2.2) and 3,6 (SD 1.9), 2,6 (SD 1.7), 1,8 (SD 1.9), after 1, 3 and 6 months respectively [$P = 0.003$; $P < 0.0001$; $P < 0.0001$]. The basal value of intaking drugs for acute attacks was 5,1 (SD 2) and 2,9 (SD 1.6), 2 (SD 1.5), 1,2 (SD 1.4) after 1, 3 and six months respectively [$P = 0.0001$; $P < 0.0001$; $P < 0.0001$](T-test analysis). magnesium, l-tryptophan and niacin was well tolerated (8 patients complained somnolence, asthenia, lack of concentration and gastralgia but none patient withdrew the study).

Conclusions These data showed a good efficacy in reduction of frequency and intensity of headache attack, a good tolerability and a very good reduction of drugs intaking for acute attacks. Our study suggests that magnesium, l-tryptophan and niacin could be an alternative therapy for pediatric migraine prophylaxis.

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Two cases of cluster-like headache secondary to surgical intervention

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We report two cases of cluster-like headache (CLH) related to surgical interventions. Both patients were previously well. They had not

familiar history of headache. The first one, a 31 years old woman, had a plastic intervention for nose septum deviation followed by left maxillary sinusitis at 29 years. Fever and face oedema remitted after antibiotic therapy. Severe left maxillary pain attacks persisted with increasing frequency. It was accompanied by ipsilateral tearing, conjunctival injection, and rhinorrhea. Physical examination showed anaesthesia in the left maxillary nerve area. Brain MRI was normal. All pharmacological therapies were ineffective, but parenteral sumatriptan. She completely recovered after percutaneous glycerol trigeminal gangliorhizolysis. The second one was a 44 years old woman. She had a right maxillary sinusitis after teeth implant at superior right dental arch, one year before. While fever and purulent secretions remitted with antibiotics, right maxillary pain did not. It recurred daily, with conjunctival injection and, many hours length. It was relieved by triptans. Physical examination showed right maxillary nerve anesthesia. MRI was unremarkable. To our knowledge, these are the firsts described CLH secondary to nasal septum surgery as well as to dental implants. Both surgical interventions were followed by infections. In a recent literature review (1) of pathologies associated with CLH, inflammatory infections were 13.5% (n = 20). Maxillary nerve involvement emphasizes the trigeminal nerve role. Tearing, conjunctival injection and, rhinorrhea show parasympathetic hyperactivity. Although a CNS (posterior hypothalamus) locus for the dysfunction is largely accepted, extracerebral activation of the trigeminal-autonomic reflex (2) is also possible.

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Prophylaxis therapy of the episodic and chronic cluster headache with zonisamide: an open study

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Introduction The prophylactic therapy of the episodic (ECH) and chronic cluster headache (CCH) is based on verapamil and carbolothium. Besides several patients are not responders at this drugs. In these cases the use of antiepileptic drug has been proposed. Recent clinical experience indicates a place for zonisamide in the management of headache disorders.

Aim To evaluate the efficacy and tolerability of zonisamide in prophylaxis therapy of ECH and CCH.

Methods 17 patients (pz), (3 F, 8 M) mean age 43.7 years (SD 5.9), range 34-56 years, suffering from ECH (11pz) and CCH (6 pz) (ICDH '04 criteria) were studied. In all patients with ECH prophylaxis therapy with verapamil, carbolothium and valproic acid was failed in the past and patients with CCH continued therapy with carbolothium (2 pz) and verapamil (2 pz). During the three months evaluation period zonisamide was administered (starting dose 25 mg/die, target dose 100 mg/die). All patients filled a headache-diary card during the evaluation.

Results In patients with ECH the basal frequency of attack/days and 1, 2, 3 months respectively was 4.5 (SD 1.8): 2.5 (SD 0.8), 1.5 (SD

0.8), 0.6 (SD 1) [$P < 0.0001$]. In patients with chronic CH the basal frequency of attack/days and 1, 3, 6 months respectively was 2.6 (SD 1.2), 0.5 (SD 0.3), 0.2 (SD 0.2), 0.1 (SD 0.1) [$P < 0.005$] (T-test analysis). In all patients zonisamide was well tolerated (5 patients complained somnolence, lack of concentration, vertigo and nausea but not withdrew the study).

Conclusions These data showed a good efficacy in reduction of frequency of attacks. Still, the drug is tolerable, in fact none patients withdrew the study. Our study suggests that zonisamide could be an alternative or complementary prophylaxis therapy for ECH and CCH. Controlled studies are warranted to determine the efficacy of zonisamide in prophylaxis therapy for ECH and CCH.

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Variants in the human potassium channel gene (KCNN3) are associated with migraine in a high risk genetic isolate

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Ion channel genes have been implicated in familial hemiplegic migraine and may also play a role in the more common types of migraine. The calcium-activated potassium ion channel gene, KCNN3 is located on chromosome 1q21.3, expressed in the central nervous system and plays a role in neural excitability. Previous association studies have provided some evidence for involvement of this gene in migraine susceptibility. To elucidate KCNN3 involvement in migraine we performed gene-wide SNP genotyping in a genetic isolate from Norfolk Island, a population descended from a small number of 18th Century Isle of Man ‘Bounty Mutineers’ and Tahitian founders.

Phenotype information was available for 377 individuals who are related through the single, well-defined 11-generational Norfolk pedigree, with 96 (25.5%) affected by International Headache Society criteria. A total of 85 SNPs spanning the KCNN3 gene were genotyped in a sub-sample of 285 related individuals (76 affected), all core members of the extensive Norfolk Island ‘Bounty Mutineer’ genealogy. Genotyping was performed using the Illumina BeadArray platform and analysis performed using the statistical program SOLAR v4.0.6 assuming an additive model of allelic effect adjusted for the effects of age and sex. Haplotype analysis was undertaken using the program HAPLOVIEW v4.0.

A total of 4 intronic SNPs in the KCNN3 gene displayed nominal-level significant association ($P < 0.05$) with migraine. Two SNPs, rs73532286 and rs6426929, separated by approximately 0.1 kb, displayed complete LD ($r^2 = 1.00$, $D' = 1.00$, D' 95% CI = 0.96–1.00). In all cases the minor allele led to a decrease in migraine risk (Beta Coefficient = 0.286–0.315), suggesting that common gene variants confer an increased risk of migraine, possibly related to founder effect, in the Norfolk pedigree. This study provides evidence for association of variants in the KCNN3 ion channel gene with migraine in the Norfolk genetic isolate with the rarer haplotypes conferring a possible protective role.

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Evidence for a vascular factor in migraine

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Background A vascular hypothesis of vasodilatation and a neuronal hypothesis have alternately been followed to explain migraine pathogenesis. Lately the prevailing theory has been that migraine is caused by neural dysfunction without involvement of vasodilatation. Because dismissal of vascular mechanisms seemed premature we examined diameter of extra- and intracranial vessels in migraine without aura patients before, during and after treatment of a migraine attack.

Method A novel high-resolution direct magnetic resonance angiography imaging technique was used to measure arterial circumference of the extra cranial middle meningeal artery (MMA) and the intracranial artery middle cerebral artery (MCA). Data was obtained at baseline, during migraine attack and after treatment with the migraine abortive drug sumatriptan (a 5-HT_{1B/D} agonist).

Results We found dilatation of both MMA and MCA during migraine attack ($P = 0.001$). Sumatriptan administration caused amelioration of headache ($P < 0.001$) and contraction of MMA ($P < 0.001$) but MCA remained unchanged ($P = 0.16$). Explorative analysis revealed that in migraine attacks with half sided headache there was only dilatation on the headache side of MMA of 12.49% (CI: 4.16% to 20.83%). and MCA of 12.88% (CI: 3.49% to 22.27%) and *no* dilatation on the non-headache side of MMA (CI: -4.27 % to 11.53%) and MCA (CI: -6.7% to 14.28%). While in double-sided headache we found bilateral vasodilatation of both MMA and MCA ($P < 0.001$).

Conclusion These data show that migraine without aura attacks are associated with dilatation of extra- and intra cerebral arteries and that the headache location is associated with the location of the vasodilatation. Furthermore, contraction of extra cerebral and *not* intracerebral arteries is associated with amelioration of headache. Collectively these data suggests that vasodilatation and perivascular release of vasoactive substances is an integral mechanism migraine pathophysiology.

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Abnormal cortical venous enhancement in RCVS: a precursor to radiographically significant arterial vasoconstriction?

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Objectives To hypothesize the implications of the novel finding of abnormal venous enhancement in the contrast-enhanced brain MRI of a man with reversible cerebral vasoconstriction syndrome (RCVS).

Background Vasoconstriction in RCVS is postulated to initially involve distal intracranial arteries with delayed involvement of proximal vessels which may account for the false negative MRAs seen early in this syndrome. This case illustrates the first description of abnormal venous dilation in RCVS preceding marked proximal arterial vasoconstriction by several days.

Methods A 25-year-old right-handed man with no significant past medical history presented to the emergency department after a severe thunderclap headache. Head CT and lumbar puncture were both normal and he was discharged home. A constant headache persisted with severe exacerbations upon Valsalva. Two days later, hypertensive and tachycardic, he was admitted for further evaluation. Repeat head CT was negative and he was eventually discharged with a diagnosis of muscle tension. He later presented to another emergency department after a severe exacerbation while having a bowel movement.

Results Except for a blood pressure of 145/112, the patient's physical examination was normal. Post-contrast MRI (now one week after headache onset) demonstrated prominent venous enhancement and intracranial MRA showed segmental narrowing within several arterial distributions. He was treated with verapamil and discharged the following day with reduced headache. Repeat imaging nine days later demonstrated unchanged venous enhancement but worsened vasoconstriction on intracranial MRA. Despite symptomatic improvement, the MRA findings warranted treatment with parenteral nicardipine.

Conclusions Cortical venous dilation in RCVS has never been described, may represent compensatory dilation of veins in response to distal arterial vasoconstriction. It may be an early imaging feature in RCVS and may precede proximal arterial vasoconstriction. Contrast-enhanced MRI should be obtained in patients suspected of having RCVS. This case also illustrates dissociation between improving symptoms and worsening MRA findings.

Conflict of interest Dr. Dodick has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

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GC/MS analysis of cerebrospinal fluid of familial hemiplegic migraine patients and a transgenic FHM mouse model; report from lumina

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Introduction Familial hemiplegic migraine (FHM) is a rare, monogenetic, subtype of migraine, characterized by hemiparesis during the aura phase. It is hypothesized that FHM in humans and a transgenic migraine mouse model with pathogenic FHM mutations (R192Q CACNA1A) can function as a good monogenetic model for the common forms of migraine. Using a non-hypothesis driven, translational approach, the aim of our study was to identify biochemical markers in cerebral spinal fluid (CSF) and decipher the neurobiological pathways for triggering and onset of migraine attacks.

Methods After obtaining informed consent, 4,8 mL CSF was obtained from 17 FHM patients (M:F, 8:9) and 15 healthy controls (M:F, 8:7) by lumbar puncture. A small amount of CSF (~2 µL) was sampled via the cisterna magna of 10 wildtype and 10 mutant mice (R192Q). CSF was sampled and stored at -80 °C. Metabolites were oxidized and silylated and subsequently analysed by gas chromatography coupled to mass spectrometry (GC/MS). For statistical analysis of the metabolite profiles principal component analysis (PCA) and partial least squares discriminant analysis (PLSDA) was used.

Results In human CSF 104 and in mice 106 different metabolites were detected. Separation between FHM patients and controls and mutant and wildtype mice could be made with PCA and PLSDA. Corresponding loadings show several, not yet identified, metabolites being important for separation. Approximately 95% of all metabolites measured in human CSF, were also found in the mouse CSF profiles.

Conclusions Results indicate that a translational approach in migraine comparing CSF from migraine patients and mice is feasible. Distinction could be made between metabolite profiles of FHM patients and controls, mutant and wildtype mice. Further analysis will clarify which biomarkers and pathways are implicated in this difference.

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Plasma levels of nociceptin in medication overuse headache

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Objective The purpose of the study is to determine the plasma levels of nociceptin and the cerebral dural vasodilatation in the paracetamol or paracetamol combined caffeine related medication overuse headache (MOH) patients in headache and headache-free periods.

The mechanisms of the MOH is unclear. The transformation of episodic to chronic headache probably is a result of sensitization in the trigeminal neurons. Activation of the trigeminovascular system allows the release of vasoactive peptides such as calcitonine gene-related peptide (CGRP) and substance P. The major cerebral arteries and pial arterioles of the cortical surface are invested with nerve fibers that contain CGRP, substance P and nociceptin. Nociceptin is a marker of trigeminovascular system with CGRP and substance P. Behavior of nociceptin variates according to the pain model.

Methods In the study, we enrolled 30 MOH patients diagnosed according to the International Headache Society II (IHS-II) revised criteria and 20 healthy, volunteers. In patients, the level of the plasma nociceptin is measured in the daily headache period while analgesic overusing and after two months in headache free period and the cerebral blood volume is measured in the proximal portion of the middle meningeal artery using perfusion magnetic resonance imaging. These measurements are made once in the control group.

Results The patients have significantly lower plasma nociceptin levels according to the control group, in both headache and headache-free periods. Although the cerebral blood volume was higher than healthy volunteers, it was not statistically significant.

Conclusion These results may be interpreted as the disinhibition of the trigeminovascular system is related with low nociceptin levels.

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Outcome of psychological group treatment for chronic headache patients

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Background Psychological factors may contribute to the sustaining or worsening for some patients suffering from chronic headache, making psychological treatment relevant.

Aim Evaluation of outcome of psychological group-treatment focusing on stress- and pain management in a specialized headache center.

Material and methods Weekly psychoeducational group sessions within a cognitive framework including intensive relaxation training over a 9-weeks period, with 6-9 patients. Psychological treatment was given in addition to other multidisciplinary interventions.

A self reporting questionnaire was distributed at the last session, with evaluation of the effect on headache, general well-being, work capability and overall importance of the treatment.

Results 150 patients completed the treatment with an average attendance of 7.3 out of 9 sessions, and 125 completed the questionnaire. Hereof, 61% of the patients reported a positive effect on the headache. 13% reported great effect on intensity, frequency or length of attack, whereas 53% reported some effect on either of the same variables. On average, patients ascribed 58% of the change to the effect of the psychological treatment.

Regarding change of general wellbeing (n = 122) 9% reported great effect, 62% good effect, 27% some effect and 2 % no change.

Regarding change in work capability (n = 118) 3% reported great effect, 36% good effect, 50% some effect, 10 % no change and 1 patient a negative effect.

Considering the overall importance of the treatment (n = 117) the average evaluation on a scale from 0-10 (0 = least important, 10 = most important), the average evaluation was scored at 8.1 (range 3-10).

Conclusion Overall our findings indicate that psychological treatment has a positive effect on headache, general wellbeing as well as work capability. The effect on headache is present, but the effect on general wellbeing and work capability is notably larger. Controlled studies are needed to confirm our findings and monitor the long-term effect.

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Natriuretic propeptides in idiopathic intracranial hypertensionR. Jensen¹, M. Skau¹, J.P. Goetsche², J. Rehfeld²

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Idiopathic intracranial hypertension (IIH) is characterized by severe headache and pulsatile tinnitus as a consequence of increased intracranial pressure (ICP) in the absence of an identifiable neurological pathology and associated to increased risk of permanent visual defects. IIH is linked to obesity and may be more rapidly reversed if

weight-loss is achieved. A disturbed ICP autoregulation in IIH is likely, but pathophysiological mechanisms of IIH are still unknown. Natriuretic peptides may be involved in intracranial pressure regulation, but cerebrospinal fluid (CSF) and plasma concentrations in this disorder are unknown. We evaluated venous and intrathecal concentrations of ANP, BNP and CNP precursor peptides in 40 patients with idiopathic intracranial hypertension and in 20 controls. Natriuretic propeptides were quantitated using processing-independent assays. In CSF, no differences in peptide concentrations between patients and controls were found (proANP: 239 ± 23 vs 231 ± 22 pmol/L, proBNP: < 2 pmol/L in all, proCNP: 1079 ± 318 vs 1138 ± 323 pmol/L). In plasma, proCNP was lower in IIH compared with controls (35.3 ± 4.8 pmol/L vs 43.8 ± 5.9 pmol/L, $p < 0.0001$). Moreover, plasma proBNP was significantly lower in patients compared with controls (47.1 ± 21.4 pmol/L vs 59.2 ± 22.0 pmol/L, $p = 0.045$). There were no associations between peptide concentrations and ICP and BMI, respectively. Plasma proANP and proCNP increased during 3 months follow-up ($p = 0.01$ and $p = 0.006$), $n = 12$. We suggest that decreased plasma proCNP concentration in idiopathic intracranial hypertension may reflect endothelial dysregulation of vascular tone and may be a marker in this disease. Further studies of proCNP and endothelial function are needed to establish such role.

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Disease activity in idiopathic intracranial hypertension: a 3-month follow-up study

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Background Idiopathic intracranial hypertension (IIH) is a disorder of raised intracranial pressure (ICP) characterized by severe headache, visual disturbances and pulsatile tinnitus.

Aim To evaluate the initial 3-month course of conservatively treated IIH using frequent optical coherence tomography (OCT) evaluations, visual field testings and lumbar opening pressure measurements.

Methods A longitudinal study of 17 patients with newly diagnosed IIH. Peripapillary retinal nerve fiber layer thickness (RNFLT) and retinal thickness (RT) measurements (Stratus OCT-3, fast RNFL 3.4 protocol), and Humphrey visual field testing were evaluated at regular intervals in a 3-month period starting from diagnosis. Repeat lumbar puncture was performed at final visit (n = 13).

Results Total average RNFLT and RT decreased significantly during the follow-up period ($p < 0.0001$ and $p < 0.0001$, respectively). Changes in RNFLT and RT correlated with improvements in visual field mean deviation (MD) (RNFLT: $r = -0.77$, $p = 0.006$; RT: $r = -0.63$, $p = 0.03$) and pattern standard deviation (PSD) (RNFLT: $r = 0.83$, $p = 0.002$; RT: $r = 0.77$, $p = 0.003$). In patients with weight-loss $> 3.5\%$ of BMI, ICP decreased significantly ($p = 0.0003$). In patients with weight-loss $< 3.5\%$ of BMI, changes in ICP were insignificant ($p = 0.6$).

Conclusions OCT combined with visual field testing may be a valuable atraumatic tool to monitor IIH in patients with papilledema. Weight-loss may be the main predictor of a favorable outcome with respect to CSF pressure.

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Is a multidisciplinary treatment programme cost-effective in medication overuse headache? A register based follow-up study

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Medication Overuse Headache (MOH) is a chronic secondary headache disorder caused by overuse of acute headache medication, defined as intake of weak analgesics ≥ 15 days/month or of specific anti-migraine drugs (triptans) or combined analgesics ≥ 10 days/month. Discontinuation of medication overuse is very rewarding and lead to more than 50% decrease in headache frequency, but the relapse rate may exceed 30%. The cost-effectiveness of treatment has never been documented.

Aim To analyse the direct cost of medication in patients with MOH before and after treatment from the Danish Headache Centre (DHC). A register based follow-up study on 336 MOH patients treated and discharged from DHC over a 2 year period. By means of the comprehensive Danish Register of Medicinal Product Statistics the total use and costs of prescription-only medication one year before and one year after the treatment was calculated.

Results Mean age was 46.7 years and male/female ratio 1:2.5. Overall, the total annual costs decreased with 24% ($P = 0.003$) and the medication use with 15%, ($P = 0.14$) after the treatment. For patients overusing triptans, the annual costs decreased with 43% ($P < 0.001$) and the use with 38% ($P < 0.001$). For patients overusing opioids the annual medication costs and use decreased with 4% and 16% resp.(NS). The annual use of prophylactics increased with 40% ($P = 0.002$) and the costs with 51% ($P = 0.028$).

Discussion Overall our findings indicate for the first time that the treatment of MOH is very cost-effective and that detoxification in a tertiary headache centre as DHC has a lasting effect on the medication use and costs, and thus indirectly on the burden of MOH. In particular a marked effect on the use and costs among triptan overuse was identified. As expected the use of prophylactics increased, which further supplemented the positive effects of detoxification.

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Fibromyalgia -headache and heat-disorders associated cephalalgias : neurologic clinics and medical issues

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Introduction Considerations should be pinpointed around diagnostic clusters considering headache and general pain-myofascial disorders .Thus, it has been described an overlap between fibromyalgia, chronic fatigue syndromes, temporo-mandibular dysfunction and tension-type headache. Moreover, descriptive series describe the TMD pain in adolescence such as predisposing condition to general myalgic conditions.

Post Heat-Stroke (HS) pictures have been described (in classic and exertional types) resembling new daily persistent headache, added to water-deprivation headache and bath-related headache.

Methods Descriptive superposition-area boundaries in TTH and myalgic TMD .Linear correlation between area and distributive position in pain-drawings and active trigger-points.

Case-comparatives with heat-disorders associated cephalalgias, considering previous hypertonic saline injection model (masseter or splenius distribution).

Results ORs of prevalence between TTH and TTD and splenius pattern and scalp pattern, show a coefficient of 0.74.

Linear rank correlation between frontal pattern in Heat-headache and frontal distribution in TMD is $r = 0.70$.

Conclusions Significant correlations may be obtained between scalp distribution in TTH and TTD with, on the other hand, hypertonic saline injection in splenius distribution, with OR of prevalence = 0.74.

Moreover, distributional areas of heat-related disorders cephalalgia may be related to frontal appearances of TMD ($r = 0.74$) ($p < 0.05$). Such explanation may be obtained by release of substances in trigger-points (tumor necrosis factor alpha), such as new daily persistent headache (NDPH) and, acting as ethiological mechanism, heat stroke (HS).

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Cognitive factors of illness perception and affective factors of anger expression in migraine and tension type headache

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The role of emotional factors such as anger and anxiety has been widely investigated in individuals suffering from headaches. However, it is not clear to what extent these variables are associated with cognitive factors concerning the perception of illness. Therefore, the objective of the present study was to explore the relationship between affective parameters such as anger, and cognitive parameters such as illness representation and their manifestations in migraine and tension type headache. Our sample consisted of 60 outpatients (migraine $n = 38$, tension type $n = 22$) from Papageorgiou General Hospital of Thessaloniki with mean age 44 years. To assess anger expression (externalization, internalization, control) we used the 24-item State-Trait Anger Expression Inventory. The Brief Illness Perception Questionnaire a nine-item scale designed to rapidly assess the cognitive and emotional representations of illness, and the McGill Pain Questionnaire designed to describe pain symptoms, served as measures of cognitive illness representations. Results concerning the cognitive parameter showed that patients with migraine differed from patients with tension type headache in (a) making more emotional representations regarding both concern and emotions about their headache, and (b) using significantly more often words like “contracting”, “vomit inducing”, “of increasing intensity” to describe their headache. No significant difference was found concerning the affective parameter between the two diagnoses of headache. Women and men of our sample differed in that the later reported better control of anger. Finally, the only significant correlation observed was between anger externalization and emotional representation of illness. Those findings suggest that cognitive parameters of illness perception and pain description would be useful in discriminating patients with migraine from tension type patients and in “cognitively” treating their perception of pain.

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Influence of etiological factors on clinical transformation of migraine in Aral sea region of the Republic of Uzbekistan

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Total combination of adverse factors promote development of migraine which is marked not only by considerable clinical polymorphism, but also propensity to transformation.

Aim To study influence of etiological factors on clinical transformation of migraine in Aral Sea region.

Methods 639 women and 101 men out of 740 patients are observed. All participants of the research were representatives of a local nationality (Uzbek).

Results Out of the total number of patients addressed for medical aid 170 (23 %) patients had common migraine, 203 (27,4 %) had ophthalmic and 367 (49,6 %) patients had associated one. In 96 (12,8 %) cases were observed loss of consciousness, in 76 (79,2 %) patients - faints, in 20 (20,8 %) - epileptic attacks. 48 (6,5 %) patients experienced transition of common migraine to ophthalmic; 78 (9,8 %) - transition of common migraine to associated; 27 (3,6 %) - transition of ophthalmic migraine to associated. 143 (19,3%) patients are manifested with sharp increase of attacks with joining of thrilling and tachycardia. Terms of occurrence of these changes from the beginning of the disease were various from 3–4 to 10–15 years. The major factors defining transformation of migraine with joining of other vegetodystonic and astenoneurotic manifestations consists of chronic mental trauma, intellectual overstraining, the meteorological factors which have changed sharply continental climate in Aral Sea region in connection with drying of Aral Sea. On this account migraines attacks became extremely intense, proceeding in the form of typical simpatico-adrenalic crises.

Conclusions Migraine is a disease prone to rather considerable transformations depending on various factors, including meteorological. Developed critical ecologically adverse conditions in Aral Sea region and worsening indicators of health of the population, high death rate from cerebrovascular diseases demand urgent modern complex preventive action.

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General practitioners with migraine: perceptions, treatment and impact of migraine headaches

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Personal experience of migraine may influence prescribing practices of physicians treating patients with migraine. Little data is available on perceptions of migraine by GPs.

An observational, cross-sectional, pharmacoepidemiological survey was conducted in primary care in France to assess headache treatments and impact of migraine on daily activities in two groups: GPs who suffered from migraine themselves (GP-M; N = 277) and GPs

having a close family member with migraine (GP-CFM; N = 641). Most GPs completed one of two questionnaires, and GPs belonging to both groups (N = 85) could complete both. Data were collected on headache treatments used (GP-M) or prescribed (GP-CFM), and on self reported (GP-M) or described (GP-CFM) migraine features and impact on daily activities.

The most frequently reported acute headache treatments in both groups were triptans and non-steroidal anti-inflammatory drugs (> 75% of GPs); > 81% of GPs in both groups were satisfied with acute headache treatments. Only 6.9% of the GP-M group used and 17.2% of the GP-CFM group prescribed a prophylactic treatment, which was considered satisfactory by 46.2% and 56.1% respectively. In the preceding 3 months, 79.4% of the GP-M group reported handicap in daily activities due to migraine, 23.6% interruption of extraprofessional activities and 7.6% interruption of work. In the GP-CFM group, 32.6% described interruption of extraprofessional activities and 57.3% interference with daily activities or work.

In conclusion, acute headache treatment prescribed by French GPs for their own migraines or those of their relatives respect practice guidelines and is considered as effective and satisfactory. Use of prophylactic medication is low and its effectiveness perceived as limited. Better use of prophylactic treatments may attenuate the impact of migraine on daily activities.

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Acetylsalicylic acid inhibits purinergic facilitation of neck muscle nociception in mice - implications for acute treatment of tension-type headache

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Infusion of α,β -meATP (ATP) into semispinal neck muscles induces facilitation of brainstem nociception in anesthetized mice. This animal experimental model is suggested to be appropriate for investigating pathophysiological mechanisms in tension-type headache (TTH). Reversal of ATP-induced facilitation of neck muscle nociception by acetylsalicylic acid (ASA) was hypothesized.

Experiments were conducted in anesthetized C57BL/6 mice (n = 42, male, 23 to 33 g). Noxious input from semispinal neck muscles was evoked by intramuscular administration of 100 nM ATP (20 μ l). Brainstem nociception was monitored by the jaw-opening reflex (JOR) elicited via electrical tongue stimulation. Two different experiments were performed. One hour after ATP infusion and established reflex facilitation, different dosages of ASA (15, 30, 60 mg/kg) or saline were intraperitoneally (i.p.) administered in 7 mice each. JOR monitoring continued for 90 min. In the second experiment, either 60 mg/kg ASA or saline was injected one hour prior to ATP infusion. JOR monitoring continued for 90 min.

With subsequent ASA, ATP-induced reflex facilitation decreased dose-dependently (2-way ANOVA, interaction of drug \times time $p < 0.001$). With 60 mg/kg ASA, facilitation completely reversed back to baseline within 30 min. Within 90 min after i.p. injection, saline group significantly differed from all ASA dosages. Preceding administration of 60 mg/kg ASA prevented ATP-induced facilitation as compared to control experiments (2-way ANOVA, interaction of drug \times time $p < 0.05$).

Subsequent and preceding i.p. administration of ASA reverses and prevents increased neuronal excitability in the brainstem.

Cyclooxygenases are involved in nociceptive transmission. These enzymes are inhibited by ASA. Unspecific inhibition of cyclooxygenases by indometacin fails to prevent purinergic facilitation in this model suggesting a specific mode of action of ASA.

Due to known involvement of neck muscle nociception in TTH pathophysiology the objective proof of ASA effects in the experimental model may emphasize its major role in pharmacological treatment of TTH attacks.

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The effect of riboflavin and vitamin-E on brain total calcium and calcium-ATPase levels in rats with glyceryl trinitrate-induced headache

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Objective The prophylactic treatment of migraine remains challenging. Riboflavine is shown to be effective in migraine treatment. In this study we aimed to investigate the effect of riboflavine and vitamin E on total brain calcium and calcium-ATPase levels.

Methods Sixty rats were administered into 4 groups: Group I: sham control (saline), Group II: glyceryl trinitrate (GTN) administered, Group III: GTN and riboflavine (RBF); and Group IV: GTN, riboflavin and vitamin-E group (RBF + E). Group I and II were given no drugs. Group III was given riboflavin 100 mg/kg/d p.o and Group IV riboflavin 100 mg/kg/d p.o. and 100 mg/kg i.p on alternate days for a ten day course. Twenty-four hours after the last drug treatment, group I infused with saline and the remaining groups with GTN 10 mg/kg i.p. for 3 hours. After slowing of movements and reaction to tail test was observed, rats were decapitated under ketamin HCl (50 mg/kg) and xylacine (5 mg/kg) i.p. anesthesia. Calcium and Ca²⁺-ATPase (PMCA) activity was measured spectrophotometrically in isolated microsomes.

Results Total brain calcium level was significantly lower in GTN administered group (3.73 ± 0.14 mg/kg) compared to the control group (5.99 ± 0.24 mg/kg) ($p = 0.002$). Total brain calcium levels were significantly higher in RBF (4.09 ± 0.14 mg/kg) and RBF + E (6.66 ± 0.19 mg/kg) groups compared to GTN group (for both $p = 0.002$). Comparison of PMCA activity yielded a significantly lower level in GTN group (0.06 ± 0.01 IU/gr) than controls (0.14 ± 0.01 IU/gr) ($p = 0.001$). In RBF (0.09 ± 0.01 IU/gr) and RBF + E (0.12 ± 0.01 IU/gr) groups PMCA activity was higher than it was in GTN group, though was still lower than in control group ($p = 0.001$).

Conclusion It has been shown previously that during cortical spreading depression a derangement in calcium homeostasis takes place. Our results suggest that riboflavin and vitamin-E improves deranged calcium homeostasis in glyceryl trinitrate administered rats.

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Patients with thunderclap headache and no signs of subarachnoidal haemorrhage: examination of persistent neurological deficits

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Background Thunderclap headache is common and is sometimes a symptom of subarachnoidal haemorrhage. Benign cryptogenic thunderclap headache is however frequent and the causes are unknown. In our clinics we have encountered several patients with benign thunderclap headache who suffer from neurological deficit afterwards. These have been followed, see below.

Method Seven patients were found. They were initially investigated according to the clinical routine with an acute CT head and a lumbar puncture (cell count, absorbance) some patients were also later investigated with an MRI of the brain.

Results The patients had an initial investigation and clinical investigation that excluded subarachnoidal haemorrhage, and they were then followed up at our out patients clinic. All patients except two had a lumbar puncture. Neuroradiological investigations were completely negative (four patients have done MRI brain).

In neurological examination there were remaining neurological deficits in the form of for example speech difficulties, sensory and motor abnormalities, ataxia, and other neurological symptoms. Of interest is that: 4 / 7 (57% of our patients) have migraine, compared with the percent of migraine in the general population in Sweden where the incidence is approximately 20%, 5 / 7 patients had right-sided neurological defect (71%). Moreover, two patients had possible epileptic symptoms.

Discussion The mechanism behind benign thunderclap headache is unclear. It is a common condition and patients often come to the emergency department. Previously such deficits that remains after benign thunderclap headache has not been studied carefully. We are interested with the association between thunderclap headache and migraine. A possible relationship to cerebrovascular constrictions syndrome is also important to be discussed.

We want to continue to investigate the reason behind the benign thunderclap headache, and why a small group of patients suffer from neurological sequelae despite negative investigation.

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Illicit drug use in males with cluster headache compared with that in the general population: a cross sectional survey

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The aim of this study was to examine the rate of illicit drug use in a clinic sample of CH male patients, compared with that in the general population and in a sample of headache patients in the same period. **Methods.** One-hundred and sixty-two CH patients (85.8 % episodic form, 14.2% chronic form) attending two headache clinics were asked to fill in a questionnaire designed to gather information about the lifetime use (once or more in their life, LTU), the recent use (once or more in the last year, RU), the current use (once or more in the last 30 days, CU) of cannabis, cocaine, opioids, hallucinogen, amphetamine, ecstasy. In addition, for each drug, information was obtained about the age of first use, the frequency of use in the last 30 days and the frequency of use lifetime. The control groups were represented by a population of 170 headache patients matched for socio-demographic variables and with the Italian general population (drugs use, IPSAD@Italia2007-2008). **Results.** In the age group 25-34 years, LTU of amphetamines and ecstasy and CU of cannabis was significantly higher in CH patients than in control groups. In the age group

35-44 years LTU of cannabis, opioids, cocaine, amphetamine and ecstasy, RU and CU of cannabis and cocaine was significantly higher in CH than in control groups. In the age group 45-54 years LTU use of cocaine was significantly higher in CH patients than in headache patients and general population. Age of first use of cannabis, cocaine and opioids was significantly lower in CH than in control groups. Current intensive users of cannabis were more prevalent in CH than in control groups. CH. Conclusion. Our study indicate that CH patients are prone to overindulge in addictive behaviour, probably for a common biological susceptibility that predispose to CH and addiction.

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Does the presence of cutaneous allodynia in Hemicrania continua predict a favorable treatment response to indomethacin?

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Objective To test the following hypotheses

- (1) Patients with hemicrania continua (HC) may experience cutaneous allodynia (CA)
- (2) Patients with HC and CA are more likely to respond to indomethacin.

Background CA is best described in primary headache disorders including chronic migraine (CM); anecdotal reports suggest that CA may occur in HC. Indomethacin response as it pertains to the presence of CA in HC may help elucidate the etiology and pathogenesis of HC.

Design and methods A chart review of patients seen at the Montefiore Headache Center from 6/2008 to 1/2010 was conducted. Eligible patients had a putative diagnosis of HC, an indomethacin trial and received the validated Allodynia Symptom Checklist.

Results Of 18 patients, 12 (66.7%) had CA, classified in 3 as mild (25%), in 4 (33%) as moderate and in 5 (41.7%) as severe. Of the 6 patients with no CA, 4 (66.7%) responded to indomethacin, 1 (16.7%) had an indeterminate response and 1 (16.7%) had no response. Of the 3 patients with mild CA, 2 (66.7%) responded to indomethacin and 1 (33.3%) had no response. Of the 4 patients with moderate CA, 3 (75%) responded to indomethacin and 1 (25%) had an indeterminate response. Of the 5 patients with severe CA, 3 (60%) responded to indomethacin, 1 had an indeterminate response and 1 had no response. Of the patients with moderate to severe CA, 88.9% (8/9) had at least two of nausea/vomiting, photophobia and phonophobia; whereas, among the patients with no CA, 33% (2/6) had at least two of nausea/vomiting, photophobia and phonophobia. The indomethacin non-responder with severe CA had nausea/vomiting, photophobia and phonophobia.

Conclusions CA is common in patients with putative hemicrania continua, including those who respond to indomethacin. The patient with severe CA, prominent migraine features and no response to indomethacin may have chronic migraine.

Conflict of interest Dr. Buse has acted as a consultant or received research support from Allergan Pharmaceuticals, MAP Pharmaceuticals, Merck Inc., and Iroko Pharmaceuticals.

Dr. Grosberg serves on a scientific advisory board for Kowa Pharmaceuticals American Inc. and Merz Pharmaceuticals; has received

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Dr. Napchan serves in the Advisory Board Iroko Pharmaceuticals, Speakers Bureau: Zogenix.

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An audit in to the efficacy and tolerability of flunarizine in the treatment of childhood migraine

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Background Flunarizine is unlicensed in the UK. It is prescribed on a named basis in our headache clinic for children with migraine.

Methods Retrospective analysis of clinical records of all patients treated with flunarizine in a tertiary paediatric neurology unit between 1998 and 2010.

Results 102 patients were identified, 30 were excluded - outcome data not available (13), non-migraineurs (9), No records (4), inadequate duration of treatment (4). Of the 72 patients in the final cohort, 44 had migraine without aura, 16 migraine with aura and childhood migraine equivalents, 7 sporadic hemiplegic migraine and 5 familial hemiplegic migraine. Mean age of the cohort was 12 years (Range: 1.5 to 17 years) and the mean duration of migraine prior to starting flunarizine was 61 months. Usual starting dose was 5 mg and escalated in 43 patients up to 15 mg per day. Average treatment duration was 14 months. Effective treatment was defined as a reduction in the frequency of individual attacks by at least 50% and this was observed in 55.5% (40/72). There was < 50% reduction in 6 patients, while there was no change in 25 patients and worsening in 1 patient. On subgroup analysis, the reduction in frequency was highest among hemiplegic migraineurs (> 50% 10/12, > 30% 2/12). Flunarizine was discontinued in 16 patients (22%) after an average trial period of 9.5 months (range 3 to 24 months). In 5 patients (6.9%), flunarizine was withdrawn on remission of the attacks. Average duration of flunarizine use in this group was 14.6 months (Range 6 to 21 months). Adverse effects were noted in 15 (20.8%) patients: Depression (6), weight gain/increased appetite (5), tiredness/sedation (3), worsening headache (2). This led to discontinuation of the drug in 13 patients (18%).

Conclusion Flunarizine appears to be more effective in the hemiplegic migraine group.

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Greater occipital nerve injection (GONI) for chronic headache in childrenE. Renaudon-Smith¹, C. Toolis², P.J. Goadsby³, P. Prabhakar²¹University College London Medical School, London, UK;²Neurology, Great Ormond Street Hospital, London, UK;³Neurology, University of California, San Francisco, San Francisco, CA, USA

Background It has become increasingly clear that greater occipital nerve injection (GONI) is effective in treating several primary headache disorders including migraine and cluster headache. Its use in children is not well documented.

Aim GONI has been offered at the Childrens headache clinic at Great Ormond Street since 2008. We set out to analyse its efficacy and side effect profile in our practice.

Methods Children with chronic, medication refractory migraine were consented and underwent GONI at GOSH between October 2008 and April 2010. Feedback forms and clinic notes were used to obtain outcome data.

Results A total of 17 patients - 5 Male and 12 Female(2008-1, 2009-10, 2010-6), age range 14 to 18 years had 23 injections. The average duration of migraine in this cohort was 7 years. The number of adequate therapeutic trials with migraine prophylaxis varied from 4 to 10. All patients and caregivers were consented for the procedures. One patient had 4 and 3 patients had 2 injections. The authors PP (18) and PJG (5) undertook the procedure. A combination of Methylprednisolone and Lidocaine was injected as infiltration around the Greater Occipital Nerve on the most tender site, identified by palpation. The procedure was tolerated well in all. The left was injected in 15 and the right in 7.

Outcome Complete resolution of headache at 2 weeks which sustained up to 12 weeks in 16/23, partial response 2/23 and no response 5/23. 5 patients reported local soreness and tenderness (3 days to 1 week). Out of which 3 went on to have a second injection. 1 patient felt dizzy and unsteady which resolved. 3 patients reported increased headache up to 4 weeks. None had alopecia.

Conclusion GONI is a safe procedure which appears to be effective in this cohort of children with chronic migraine.

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Headache as the only neurological sign of cerebral venous thrombosis: a series of 11 cases

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Background Headache is the most frequent symptom in cerebral venous thrombosis (CVT), and usually the first. However, it has rarely been reported as the only symptom of CVT.

Objectives To study the characteristics of patients in whom headache was the only presentation of CVT in the absence of intracranial hypertension, subarachnoid hemorrhage or meningitis.

Methods From a prospective study of 73 consecutive patients with CVT, only 11 patients with isolated headache were included in the present study. Among whom, we identified 9 adults and 2 children. All patients underwent an extensive systematic etiological work-up and were given intravenous heparin followed by oral anticoagulants with the exception of two patients.

Results Headache was the only sign of CVT in 11 patients. The mean age was 33 years (13 to 51 years) and the female/male sex ratio was 1.2. Onset of headache was progressive in 7, acute in 2, and thunderclap in 2 patients. The location of headache was reported as localized (frontal, occipital, and neck) in 3 cases (27%), usually ipsilateral to the occluded lateral sinus and diffuse (whole head) in 8 cases (73%). Nine (82%) patients have abnormal findings on neurological examination including papilledema 8 (72%) patients, and focal neurological deficit 2 (18%) patients. The lateral sinus was the most frequently involved sinus (n = 7). Numerous causes or predisposing factors were identified: infectious causes in 36% and non infectious causes in 27%. Cause was unknown in 36 % of cases. Treatment consisted of anticoagulation in all but two patients. All had a favorable evolution.

Conclusion Headache is the most frequent symptom of cerebral venous thrombosis. They don't have particular characteristics and can mimic other numerous varieties of headache. They are sometimes isolated, so radiological investigations are justified in all recent and unusual headaches.

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Automatic thoughts in different headache groupsL. İnan¹, S. Üçler¹, O. Coskun¹, U. Meriçli²¹Ankara Research and Training Hospital Neurology, Ankara, Turkey;²Psychiatry, Ankara Oncology Research and Training Hospital, Ankara, Turkey

Cognitive processing may have a role in the etiology of headache. As a result, cognitive behavioral therapy may be helpful in the treatment. So we decided to search cognitive processing in different types of headache and control group. Automatic thoughts may give ideas about cognitive processing. So, automatic thoughts scale and Beck depression scale were given to migraine, tension type headache, medication overuse headache and control group. The diagnosis of headache type were given according to IHS-2004 classification. The study were conducted in Ankara Research and Training Hospital Headache Unit. Twenty migraine without aura, 20 tension type headache, 19 medication overused headache patients and 20 controls were given these scales. There were no significant difference in terms of age and gender among all patient groups and controls. There was no significant difference in automatic thoughts scale in patient's groups compared to the controls ($p > 0.05$). Beck depression scale was significantly higher in patients with tension type headache compared to the controls ($p < 0.05$). According to the results, tension type group were different than control group in terms of beck depression scale but not in automatic thoughts scale. This significant difference may not be related with cognitive processing pathology in tension type headache or automatic thoughts scale may not be useful in evaluating patients with headache.

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Acute cervical headache by puncturing regular and extra acupuncture pointsM. Cesar-Komar¹, Z. Turk²¹Department of Anaesthesiology and Intensive Care Medicine, General Hospital Slovenj Gradec, Slovenj Gradec, Slovenia;²Institute for Physical Medicine and Rehabilitation, University Clinical Centre Maribor, Maribor, Slovenia

Aims Acute cervical headache because of the sprain of the cervical spine is commonly seen in pain clinic. The authors of this paper has treated patients, a total 60, of acute cervical headache with regular acupuncture points. The points were mainly from Urinary Bladder, Du, Large intestine, Spleen, Sanjinjiao, Hart meridian, and in the other group, added points from the extra meridians. Satisfactory results were achieved in both groups.

Methods The patients were randomly divided in two groups;

- (A) 30 patients using regular points
- (B) 30 patients using regular and extra points.

Patients were treated ten times with acupuncture method .

Results

- (A) 15 were completely cured (50 %); 8 good improved (26,7 %); 6 improved (20,0 %) and only in 1 case there was no effect (3,3 %).
- (B) 19 cases completely cured (63,3 %); 8 good improved (26,7 %); 2 improved (6,7 %) and 1 (3,3) no effect.

The male number complaining acute cervical headache is larger than that of female (72 %). The better effect in male is higher than that in female (81,1 %, 73 %). The age of patients was 18-60 years. The duration of acute cervical headache was between 1-20 days. The history of cervical cephalgia was 6 months till 2 years. The complete cure in the group A covered 50 %, in the group B was 63,3 %. The group B produces a better therapeutic effect. The effect was better if the cervical headache occurred with the sprain on one side of the cervical spine (72 %), in the contrast to having sprain on both sides (60%).

Conclusion Combination of distal and local regular points was used for easing tendons and muscles, for activating blood circulation and ceasing pain. The better effect is using regular and extra points

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Utility of Levadex™ in situations where early intervention paradigm is impractical

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Background Several well-controlled studies have shown that the efficacy of triptans is reduced significantly when treatment is delayed well beyond the start of the migraine. Surveys have also shown that some patients are unable and unwilling to treat their migraine early, leading to treatment failure and dissatisfaction with their acute treatment. LEVADEX, a novel orally inhaled form of DHE in development, may reverse central sensitization and hence should work well even when used late in a migraine attack.

Methods Post-hoc analysis of a randomized, double-blind, placebo-controlled phase 3 study. Two-hour pain-relief (PR) and pain-free (PF) rates were compared between those who treated their migraine in less than 1 hr, within 1-4 hrs, within 4-8 hrs and more than 8 hrs of the start of their migraine.

Results 903 subjects randomized; 771 subjects treating a single attack included in efficacy analysis. When treated less than 1 hr after migraine start, the 2hr PR and 2hr PF rates were 66% and 38% for the LEVADEX group and 41% and 13% for placebo. When treated

1-4 hours after the start, the 2hr PR and PF rates were 60% and 28% for LEVADEX and 35% and 10% for placebo, respectively. When treated 4-8 hours after the start, the 2hr PR and PF rates were 53% and 22% for LEVADEX and 30% and 30% and 8% for placebo, respectively. When treated even after 8 hours, the 2 hr PR and PF rates were 49% and 19% for LEVADEX and 24% and 9% for placebo.

Conclusions In this post-hoc analysis, LEVADEX showed efficacy in treating a moderate or severe acute migraine attack even when it was administered as late as 8 hours after the start of a migraine. Thus, LEVADEX may help many migraineurs who are unable to treat their migraine early due to practical real life limitations.

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Migraine induced disability and migraine treatment

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Introduction Migraine is a public health problem that has an impact on both the individual sufferer and on the society. Migraine has been found to rank in the top 20 of the world's most disabling medical illnesses, based on the 2001 WHO's World Health Report.

Objective Evaluation on migraine induced disability in migraine patients.

Methods We evaluated 30 migraine patients in our outpatient clinic. A secondary cause of headache was rule out by clinical examination and appropriate diagnostic tests.

Demographic data were collected for each patient, as well as data regarding migraine characteristics. Patients were asked about migraine preventive treatment use in the last 3 months and also about specific antimigrainous acute therapy use (triptans).

We measured migraine disability by asking each patient to fill a MIDAS and HIT test.

Results MIDAS score revealed severe disability in 43% patients MIDAS \geq 21, moderate disability in 30 % patients, mild disability in 17% patients and little disability in 10% patients..

HIT test was modified in accordance with MIDAS (57% patients with HIT > 60 points; 23% patients had HIT 56-58; 13% patients had HIT of 50-54 and 7% patients had HIT scor < 48).

Conclusions In our study mostly the patients with high disability due to migraine were asking for a medical advise.

Although MIDAS score of III-IV was found in 75% patients, only 6% of patients used specific antimigrainous acute therapy (triptans). Only 13 % of patients had a preventive treatment, although most of our patients had a moderate-severe migraine induced disability.

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Headaches secondary to psychiatric disorders (HSPD): a retrospective study of 87 patients consulting at a headache emergency department

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The aim of this study was to review the medical record of all patients having received a diagnosis of headache secondary to psychiatric disorder (ICHD code 12 and A12) when consulting in a headache emergency department during 2009. Out of a total of 8479 patients seen during this year, 25 men and 62 women received this diagnosis (1.02 %), mean age 40.3 ± 14 years. The psychiatric disorders concerned were: depressive disorder ($n = 37$), generalized anxiety ($n = 25$), panic disorder ($n = 5$), psychotic disorder ($n = 5$) undifferentiated somatoform disorder ($n = 4$), somatisation disorder ($n = 1$) and post traumatic stress disorder ($n = 1$). Data was missing for 10 patients. The fact that headache had occurred only during the evolution of a psychiatric disorder was not recorded for any of the patients. Headache description was tension type ($n = 45$), atypical ($n = 23$), migraine ($n = 19$). One-fourth of the patients suffered from pain in other parts of the body ($n = 21$), 40% had already had complementary investigations and consulted for their headache. The most usual prescription proposed to the patients were antidepressants ($n = 45$), i.e. amitriptyline and tranquillizer ($n = 43$), i.e. clonazepam. Patients were sent to a psychiatrist in 45 cases and complementary investigations were ordered in 21 cases. This study shows that, in practice, ICHD code 12 and A12 are rarely used. When used, criteria are not strictly applied. The criterion "headache occurring only during the evolution of the psychiatric disorder" is not checked. Not only are atypical headaches considered but, in the majority of cases, code 12 or A12 is given with tension type or migraine type headache. Even though psychotic disorder and somatisation disorder are the only psychiatric disorders accepted for HSPD in the classification itself, in clinical practice they are not frequently involved whereas depression and generalized anxiety are. It calls for the removal of those appendix diagnoses in the classification itself.

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Idiopathic intracranial hypertension without papilledema

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Introduction Idiopathic intracranial hypertension (IIH) is characterized by high cerebrospinal fluid (CSF) pressure with no underlying structural or systemic cause. Papilledema is a cardinal feature of IIH, however in rare cases IIH may occur without papilledema.

Case report A 25 year old women, gravida 1, para 1, eight days post partum presented to the neurologic department with a chief complaint of headache. Past medical history was unremarkable. The pain was holocranienne. It was accompanied by nausea without vomiting, neurological examination and brain MRI was normal.

A lumbar puncture was performed which revealed: CSF opening pressure = 400 mmH₂O, white blood cells = 4, protein = 35 mg/100 dl and sugar = 55 mg/100 dl (concomitant blood sugar = 95 mg/dl)

The patient was diagnosed with IIH and received a lumbar puncture 2 days after. The headache was disappeared.

Discussion Headache is one of the most common symptoms that encountered in the post partum period. IIH, in its classic form present as headache and papilledema. Although papilledema is a cardinal feature of IIH, in rare case it may occur without papilledema. It is there for advised that in the presence of obesity, post partum headache

and, a spinal tap may be indicated to exclude the presence of IIH without papilledema.

Conclusion In post partum condition, the diagnosis of IIH should be considered even in the absence of papilledema. A lumbar puncture is helpful both diagnostically and therapeutically.

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Iowa gambling task (IGT) in medication overuse headache (MOH) patients: a neuropsychological study of the orbitofrontal cortex functioning

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It has been proposed that MOH could be related in some patients to dependence-related behaviours. Such behaviours are connected to the orbitofrontal cortex (OFC) which exerts an inhibitory control on substance craving. The aim of this study was to explore the functioning of the OFC of MOH patients through neuroimaging techniques (18FDG-PET and fMRI) and through neuropsychological assessment (IGT). The data presented here concerned the IGT results from 12 MOH patients compared with 8 episodic migraineurs without prior MOH. IGT is a test aiming to detect decision-making impairment as it is observed in patients with OFC damage and in drug-addicts. It is a test where the subject is confronted with a decision that involves a conflict between an immediate reward and a long term negative consequence. Six MOH patients were overusing triptans, 4 were overusing acute headache medications containing opiate-derivatives, one was overusing simple analgesics and one was overusing combinations. The mean number of acute headache medication taken per month was $91.9(+/-50)$ for the MOH group and $5(+/-2)$ for the migraine group ($p = 0.008$). MDH-Q is a questionnaire measuring dependence behaviours in headache patients. Mean MDH-Q score was significantly higher in the MOH group than in the migraine group ($86.9 +/- 20$ versus $35.1 +/- 4$, $p = 0.01$), whereas mean BIS score, a measure of impulsivity, is not different between the two groups ($58.4 +/- 5.7$ versus $62.7 +/- 10.2$). Mean ITG score did not allow differentiating MOH patients from episodic migraineurs, whereas it was significantly different between opiates abusers and other medication abusers ($45 +/- 5.7$ versus $57.1 +/- 8.2$, $p = 0.019$). Those results must be interpreted with caution due to the low number of subjects. They, nevertheless, are in favour of a deficit in decision making processes, underlying behavioural dependence in MOH patients who overuse medications that contain psychoactive substances like opiates.

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Management of pediatric migraine in primary care

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Migraine is the most common cause of recurrent acute headaches in childhood (5 to 10%). The study was conducted by the Migraine Center (MC) of Trousseau University Hospital in Paris and the pain management health care network LCD-Paris.

The aim was to assess the management of pediatric migraine before the first consultation at the Migraine Center.

Parents of cephalgic children had to answer a questionnaire before the first consultation at the MC. During the consultation, the physician classified the headache according to IHS classification ICHD-II.

177 questionnaires were analysed over a six month-period (September 2007- February 2008).

The mean age of the children was 9.91 years (\pm 2.8 years), 20.9% were under 7 years and 33.8% were over 12 years.

At the end of the consultation in MC, 171 children (96.6%) were diagnosed with migraine, isolated or associated with another headache.

The first physician consulted (before MC) for the headache was the general practitioner (56.5%), the pediatrician (28.8%) or another specialist (7.3%).

That first consultation in primary care was mainly motivated by the headache in 58.2%. In 34.4 % of case, headache was discussed during a consultation for another problem.

Migraine diagnosis had already been mentioned for 91% of children. In 41.8%, migraine was evocated by the parents.

31.6% of parents decided to consult by themselves at the MC.

In primary care, 66.1% of children consulted the ophthalmologist, 25.4% the neurologist and 21% the ENT specialist; 46% of children had a brain imaging: CT scan (29%) and MRI (24%).

Given the prevalence of migraine, physicians in primary care should be better trained to recognize and to treat pediatric migraine.

Specialist centers should be consulted in a second phase, for children resistant to the therapy prescribed by their family doctor, or for the most complex cases.

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Prolonged migraine auras

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Introduction Migraine with aura affects about 30% of all migraine patients. Prolonged auras are defined as those lasting more than 60 minutes in typical or basilar migraine, and more than 24 hours but less than one week in hemiplegic migraine (ICHD-II). Although rare they may pose a diagnostic challenge and its natural history is not completely understood.

Aims Clinical characterization and prognostic definition of prolonged migraine auras.

Methods Retrospective review of clinical files and prospective personal assessment according to a standardized form, of all patients admitted or followed in a headache outpatient clinic with the diagnosis of prolonged migraine aura, between January/1999 and May/2010. Structural lesion was excluded by brain MRI with DWI in all patients.

Results 30 patients included, 25 females, mean age 33.7 ± 9.3 years. 15 patients used to have migraine without aura (1.1 ICHD-II), 14 had migraine with aura (1.2 ICHD-II) and one patient had no previous history of migraine. Prolonged aura was sensitive in 11 patients, visual in 3 and mixed in 16 (7 with motor symptoms). In 18 patients the aura lasted less than 24 hours. Headache had the usual features in 25 patients. Prolonged aura symptoms were similar to the previous typical auras in 9 patients and different in 5. Recurrence occurred in 11 patients, 2 of these with distinctive characteristics.

Conclusions Prolonged aura was often the first aura episode, making diagnosis challenging. Moreover they were frequently complex and with motor symptoms, which are less frequently recognized as aura manifestations. However the frequent maintenance of previous headache and aura features may help in differential diagnosis. Recurrence of prolonged aura symptoms occurred in 36.7%, having thus a favorable outcome in most patients.

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The prevalence and burden of primary headaches in china: a population-based door-to-door survey

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Objective A population-based door-to-door survey on the prevalence and the burden of primary headaches in the mainland of China was initiated by Lifting the Burden: the Global Campaign to Reduce the Burden of Headache Worldwide.

Method The 5041 respondents were sampled based on population using random sampling software, according to EPI method established by WHO. The questionnaire was structured from English version of that developed by Lifting the Burden to be translated to Chinese and fitted to Chinese culture after pre-pilot study.

Results The 1-year prevalence of primary headaches is 23.8% in China. The 1-year prevalence of migraine is 9.3%, and that of tension-type headache is 10.77%. The heavy social and economic burden was caused by primary headache, which lose 121.4 billion yuan (RMB) per year, 3.9 % of GDP, according to population modified by age. 66.7 billion yuan per year was cost for migraine, which is 3% of annual income every family.

Conclusion Primary headaches are not only pain for patients, but also disable their work, study and daily activities. The 2nd edition International Classification of Headache Disorders (ICHD-2) formulated by International Headache Society. In accordance with the Lifting the Burden translation protocol for hybrid documents, the Chinese version of the questionnaire was first evaluated by the chief investigators of six regions, who are fluent in both languages, and then assessed for comprehensibility by 20 outpatients at every department of neurology of the hospital which the chief investigator of region worked.

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Countrywide population-based survey in Russia reveals high prevalence of chronic daily headache and its association with low socioeconomic status

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Objective To estimate the current (1-year) prevalence of chronic daily headache (CDH), defined as headache occurring on ≥ 15 days/month, and identify risk factors, in the general population of Russia.

Methods By door-to-door unannounced visits, and follow-up visits when necessary, trained lay interviewers randomly sampled biologically unrelated adults aged 18–65 years from 35 cities and nine rural areas of Russia. The sample was thus drawn from all but one of the seven federal districts of the country, and was representative of the population of Russia in terms of age, gender, socioeconomic status and settlement type. A previously validated structured diagnostic questionnaire based on ICHD-II criteria was applied. Quality of life (QoL) was assessed using WHOQoL-8.

Results Of 2,725 eligible adults contacted, 2,025 (74.3%) responded, of whom 1,065 (52.6%) were female and mean age was 39.5 ± 13.4 years. Episodic headache (< 15 days/month) was reported by 1,060 (52.3%; 95%CI50.2–54.5) respondents and CDH by 213 (10.5%; 95%CI9.2–11.9). Of the latter, 145 (7.2%; 95%CI6.0–8.3) were overusing acute headache medication and therefore had probable medication-overuse headache.

Female gender (OR2.7; 95%CI1.8–4.2), low income (OR2.4; 95%CI1.6–3.8), increasing age (OR2.1; 95%CI1.4–3.2) and obesity (OR1.8; 95%CI1.2–2.8) were risk factors for CDH. Average income was 36% lower in people with CDH than in those with episodic headache. QoL was lower in people with headache than in people without, and lowest in those with CDH.

Conclusion This first population-based countrywide study in Russia revealed a very high prevalence of CDH. Whilst this result is in line with our previous findings in the Republic of Georgia, another country of the former USSR, in that country there was much less MOH. The Georgian population is not Slavic, and is therefore genetically different. The survey unmask high unmet needs of people with headache in Russia and confirms the importance of poverty as a risk factor.

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Comorbidity of depression in a clinical population of migraine patients: report from lumina

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Objective To study the prevalence of depression in a clinical population of migraineurs.

Introduction There is a bidirectionally increased comorbidity of migraine and depression, suggesting shared pathophysiological mechanisms. This association, in particular for migraine with aura, can be partly explained by shared genetic factors. We studied the prevalence of depression in a large clinic based population of migraineurs with (MA) and without aura (MO).

Methods Migraineurs were identified as follows: patients were enrolled via the LUMINA (Leiden University MIgraine Neuro-Analysis) website and answered validated screenings questions. Screen-positives were automatically directed to an extended validated web-based questionnaire on headache and aura symptoms, and individual diagnoses were calculated using an algorithm based on criteria of the International Headache Society (ICHD-II). Depression was measured using a web-based validated questionnaire about current and lifetime mood status. Descriptive statistics were used to describe the demographic data for age, sex, and the prevalence of migraine and depression. To evaluate the difference in prevalence between the group of MA and MO, a χ^2 test and a logistic regression analysis were performed with adjustment for age, gender and current anxiety disorder.

Results For the depression questionnaire 2600 migraineurs were approached. The response rate was 89.2%. A number of 2313 patients (86.5% female) was suitable for analysis. MO was seen in 59.7% of these patients. In total, 44.0% of all migraine patients fulfilled the criteria for a lifetime diagnosis of depression. There was no significant difference between MA and MO for comorbidity of depression.

Discussion This is the first large study investigating the comorbidity of migraine and depression in a large clinic based population of migraineurs. It confirms findings from previous population-based studies, showing that a considerable number of migraine patients fulfil the criteria of a lifetime depression. Remarkably, we found no difference in prevalence between MA and MO.

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Central facilitation of trigeminal nociceptive processing in episodic and chronic cluster headache

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Background Central facilitation of trigeminal pain processing was demonstrated in different primary headache and facial pain disorders. Whether this overactivity is also part of the pathophysiology of cluster headache (CH) is intensively discussed due to inconsistent study results.

Objective To investigate the function of the trigeminal nociceptive system in patients with episodic and chronic CH.

Methods Sixty-six patients with CH (18 episodic CH inside bout, 28 episodic CH outside bout, 20 chronic CH) according to the IHS-classification, as well as 30 healthy controls were investigated using simultaneous recordings of a the nociceptive blink reflex (nBR) and pain related evoked potentials (PREP) following nociceptive electrical stimulation on both sides of the forehead (V1).

Results NBR latency ratio (headache side/non headache side) was decreased in all CH patients independently of CH subtype compared with healthy controls. Area-under-the-curve (AUC) ratio was

increased in patients with episodic CH inside bout only. PREPs showed decreased N latency ratio in patients with chronic CH.

Conclusion Side shift of trigeminal nociceptive processing can be detected in patients with CH predominantly on brainstem level and most pronounced in the acute pain phase of the disease, but appears to persist in remission periods. These data support the hypothesis of neuronal alteration of the trigeminal nociceptive system in CH. PREPs show central facilitation only in chronic CH prompting to additional supraspinal alterations of pain processing in regard to chronic pain that exceeds changes observed in episodic CH.

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Migraine true disease state estimates (MTDSE): improving sensitivity in migraine definition and drug-efficacy detection

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Background Migraine is defined by a constellation of inter-related symptoms which vary among and within individuals over time. For acute treatment trials the FDA requires separation from placebo on 4 co-primary measures of migraine pain intensity, nausea, photophobia, and phonophobia. This approach is inconsistent with true-disease-state theory, dramatically increases sample size requirements, and fails to measure the migraine symptom complex.

Objective To develop scoring procedures capturing estimates of the true disease state, thereby increasing precision and sensitivity in migraine definition and drug efficacy detection.

Methods In 2005, we assessed a representative sample of 14,936 respondents who met ICHD-2 criteria for episodic headache. Latent class models were employed to identify natural subclasses of headache sufferers with migraine-dominant symptom patterns. Item Response Theory (IRT) models were used for assessing item quality. IRT parameters were employed to obtain adjusted true-disease-state scores corresponding to all possible ICHD-2 sum scores.

Results A four class model revealed two migraine-dominant classes. A single-factor IRT model optimally fit the data. The ICHD-2 items strongly measured the underlying disease state, with loadings ranging from 0.28 to 1.2. The odds of endorsing the items given the MTDSE ranged from 1.32 to 3.32. These underlying disease state score estimates are model-based, free of measurement error and asymptotically normal. MTDSE scores were obtained by calculating the mean of the posterior distribution of the IRT model corresponding to each sum score. Scores were rescaled to have mean of 2 and SD of 1.22, yielding 21 scores ranging from 0 to 4.17.

Conclusions ICHD-2 migraine-defining features can be scaled to produce an MTDSE capturing severity of migraine pain and associated symptoms. MTDSE scores are normally distributed with fixed mean and SD. Statistical tests using this scoring method should more powerfully detect the benefits of migraine treatments both in clinical trials and clinical practice.

Conflict of interest Dr. Buse has acted as a consultant or received research support from Allergan Pharmaceuticals, MAP Pharmaceuticals, Merck Inc., and Iroko Pharmaceuticals.

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Daniel Serrano, PhD has worked on research grants as a consultant with the following companies: Allergan, Merck & Co., Endo Pharmaceuticals, Map Pharmaceuticals, GlaxoSmithKline, Ortho-McNeil-Janssen Pharmaceuticals, Ortho-McNeil Neurologics.

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Greater occipital nerve infiltration with cortivazol for cluster headache (CHCI): a double blind randomized controlled trial

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Cluster headache (CH) bouts are highly disabling. Greater occipital nerve infiltration (GONI) has been used for CH with different substances and protocols. This randomized placebo-controlled trial included 43 CH patients, 15 chronic and 28 episodic, all having > 2 attacks daily preceding inclusion. Patients had three GONI, 48 to 72 h apart, performed in a double-blinded fashion either with normal saline (PL, n = 22) or with cortivazol 3,75 mg (CVZ, n = 21). Patients were followed for 90 days after inclusion. The primary endpoint was the number of patients in each group with a mean of 2 attacks or less per day on the second, third and fourth day after the third injection (between day 9 and 12 following inclusion). All the patients (100%) of the CVZ group reached this endpoint, compared to 65% of the PL group (p 0,0045). Cortivazol also was superior to placebo on various secondary endpoints: the mean number of attacks over the first 15 days was 7,24 vs 23,3 for CVZ and PL respectively (p = 0,0005). The delay to remission was 9,1 vs 16,8 days (p < 0,0001). At day 15, a 50% decrease in attack frequency was seen in 94,7% vs 72,2% (p = 0,05). No severe side effects were reported. Minor side effects were reported by 90% of CVZ vs 66% of PL groups (p = 0,07), the commonest being neck pain (65% CVZ vs 47% PL, p = 0,26) Repeated GONI with cortivazol can shorten a CH bout or exacerbation rapidly, decreasing the daily frequency of attacks and inducing a lasting remission, both in episodic and chronic patients. It is safe and well-tolerated, can be added to the standard prophylaxis, and should be considered early in the treatment algorithm of a CH period or exacerbation.

This study has been registered on clinicaltrials.org under the number NCT00804895.

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Refractory migraine in an outpatient neurology headache unit

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Introduction Certain migraines are labeled as refractory, and operational criteria have been recently proposed. However, epidemiology is poorly characterized, and there is a lack of data on prevalence and incidence. In this study, we aimed to determine the prevalence of refractory migraine in patients attended on the Headache Unit in a tertiary care center.

Methods The study population consisted of a consecutive sample of 370 patients (60,8% females) with a mean age 43 years (range 14-86; SD: 15) evaluated for the first time in the Headache Unit over a 1-year period (between October 2008 and October 2009). We recorded information on clinical features, previous treatments, Migraine Disability Assessment Score (MIDAS), diagnosis and outcome.

Results Overall migraine (chronic and episodic) and tension-type headache (chronic and episodic) were respectively found in 54.6% and 21.8% of patients. Chronic migraine was found in 7.3% of patients (13.4% of all migraineurs). Refractory migraine was found in 7.1% of patients (62% of whom were chronic migraineurs) according to the proposed criteria by Schulman. The mean MIDAS score was 71.8 (range 15-180). 52% of refractory migraineurs were medication-overusers.

Conclusion Refractory migraine has a prevalence of 7.1% in our headache clinic. New therapeutic strategies are needed to improve the quality of life of these patients.

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Migraine associated with arterial hypertension: clinical features and difficulties of diagnosis

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Introduction Migraine and arterial hypertension are both well known entities in the general population and important cardiovascular risk factors. Association between headache and hypertension is old and contradictory issue.

Objectives Analysis of clinical features of migraine associated with arterial hypertension and estimation of cardiovascular risk.

Methods The study included 30 consecutive patients referred to the Headache Center with headache (according to ICHD-2004) and arterial hypertension (BP > 140/80 mmHg). Patients underwent a clinical interview, a physical and neurological examination including the assessment of BP. Data were analyzed by means of EpiInfo for Windows. For ten patients was calculated Systematic Coronary Risk Evaluation (SCORE).

Results Headache sample consist of chronic migraine (18p), episodic migraine (7p) and tension type(5p). Average age was 50.2, 50% of them in the 50-60 age interval. Was some common clinical features: the headache history 10-30 years (30%), headache before hypertension diagnosis (90%), bilateral (50%), phonophobia (90%), other pain 16p (55%). 11 patients (40%) reported another type of headache fulfilling the criteria for "Headache attributed to hypertensive crisis

without hypertensive encephalopathy". 18 patients(60%) did not fill when there blood pressure arise, 40% of the patients(12p) presented dyslipidemia, 26.7% (8p) obesity, 16.7% (5p) diabetes mellitus,14% of the patients presented stroke. For 10 patients was performed Systematic Coronary Risk Evaluation (SCORE): 2p (20%) = 1%, 4p (40%) = 2%, 3p (30%) = 3-4%, 1p (10%) = 5-9% risk for fatal cardiovascular event for 10 years.

Conclusion Patients with headache and hypertension raise problems in diagnosis and management. From the moment they were told about the hypertension they interpret every headache as due to raised blood pressure. Both diseases are important cardiovascular risk factors and can produce white matter changes.

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Preliminary clinical data from a new headache outpatients service in the Republic of Ireland

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A new headache out-patient clinic was established in January 2010 at the Dublin Neurological Institute in Dublin, Ireland. The goal is to manage headache patients in a specialist setting and minimise waiting time to first consultation. It is the third specialist headache clinic in the Republic of Ireland (total population of more than 4 million people). During the first five months, 70 new patients were seen. Of these, 63 patients had migraine (47 chronic/16 episodic). 34 of these patients fulfilled the criteria for medication overuse headache. Only 30% of the migraine patients (20/63) had previously been treated with a preventative agent, and in many cases with sub-optimal doses or for too short a period of time. The waiting time for the clinic was between 3 and 14 months. Our data strongly supports the need for further specialist headache services in the Republic of Ireland.

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Is there an effect of functional electrical stimulation for inhibition of muscle contractions during sleep?

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Background Temporomandibular disorders (TMD) and tension-type headache (TTH) are both characterized by increased tenderness in the pericranial muscles. Functional Electrical Stimulation (FES) is developed to cause local relaxation of specific muscles by means of low electrical stimulation but the effect on headache is not known.

Objectives To investigate the effect of biofeedback system based on FES during sleep on symptoms and signs of tension-type headache.

Methods 50 patients from a multidisciplinary headache center, who fulfilled the ICHD-2 criteria for frequent episodic or chronic TTH were included in a randomized, double-blind placebo-controlled study of FES. All patients used the biofeedback system during sleep over 11 weeks period and completed questionnaires regarding sleep, headache and quality of life three times. Examination of TTH, jaw

and muscles was examined by a blinded observer by means of The Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD), and, McGill Pain Questionnaires (MPQ) and Sleep quality questionnaire. Total tenderness scores (TTS) were evaluated at baseline, after 7 weeks and after 11 weeks.

Results At present, 32 patients (24F,8 M) with a mean age of 38 years have completed the study. So far the treatment with FES did not cause any changes in the total TTS-score as the total values are unchanged from baseline (693), after 7 weeks (730) and after 11 weeks (691).

Conclusion At present only patients who has completed the study have been analysed in total and the randomization code is protected. However, the total outcome of TTS is completely unchanged indicating that the possible effect of FES is not directly linked to muscle tenderness and other mechanisms must be searched. Detailed results will be presented as the last patient is expected to complete the study in august 2010.

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Patent foramen ovale (PFO) closure reverses abnormal habituation of early contingent negative variation (ECNV) in chronic migraine

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Purpose Retrospective studies have shown improvement in migraines after PFO closure. To date, no study has evaluated the role of PFO closure on neurophysiologic marker of migraine. Lack of habituation of evoked potentials to repetitive sensory stimuli procedures, such as CNV, is the main neurophysiological finding in migraine.

The aim of the study was to detect any change in habituation of eCNV after transcatheter PFO closure in chronic migraineurs that were positive for moderate-severe shunt at transcranial Doppler examination (TDe).

Materials and methods Fourteen chronic migraineurs (8 without aura; 8 females; mean age 37 ± 4.2 years; mean duration of illness: 10 ± 3.8 years; mean headache frequency: 18 ± 2.7 days/month) diagnosed according IHS-2004 criteria were recruited. They were all resulted positive for moderate-severe PFO at TDe in the previous 3 months; ten of them had assumed prophylactic drugs in the six previous months with moderate and inconstant efficacy. The eCNV habituation was assessed by Cz/A1-A2 derivation recordings, according to standard odd-boll acoustic paradigm, during inter-ictal phase, in the basal condition (T0) and after 2 months (T1) from PFO closure.

Results A significant reduction in migraine frequency ($p < 0,05$) and reversing of abnormal habituation pattern ($p < 0,01$) respect to T0 was observed in migraineurs at T1. There was a significant correlation between migraine frequency reduction and normal eCNV habituation at T1 ($p < 0,01$).

Discussion Our study suggests a possible link between moderate-severe PFO and reduced eCNV habituation in chronic migraine patients. The possible role of right to left shunting in predisposing to chronic migraine and consequently to eCNV habituation lack could be explained by paradoxical embolism. The persistent paradoxical embolism could led to abnormal cortical information processing that is considered the main neurophysiologic finding of reduced habituation migraineurs. Finally migraine relief after PFO closure could suggest to perform this technique in selected chronic migraine patients.

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Magnetic resonance imaging in medication overuse headache (MOH) a report in a tertiary center in Argentina

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Some reports have detected MRI brain changes in migraine and tension type headache. The objective of this presentation is to analyze and correlate the presence of white matter lesions in chronic headache patients with medication overuse.

Methods We had studied retrospectively brain MRI in a MOH group, correlating them with some clinical data.

Result We studied 100 consecutive chronic headache patients,74 of them had MOH, according to the IHS classification, mean age was 36 years, 87% were females. The medication used were ergotamine compounds : 58,11%, simple analgesics :29,73 %, . As vascular risk factor, 2 patients were smokers, 1 used oral contraceptive treatment. Mean period of chronification headache: 51 months Hypertension was not detected in the group. MRI studies that were done in 51 patients shown white matter abnormalities in 8 of them, 5 overusing AINES and 3 ergotamine in combination.

Conclusions Although a correlation between migraine and white matter lesions has been discussed, these preliminary data shows a low percentage of brain changes in chronic headache patients overusing medication. Including those patients overusing ergotamine. Analyzing more clinical and radiological data may give us the possibility to deeply study risk factors that may be related to this unresolved headache disorder.

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Gender and headache: no difference in the therapeutic efficacy of drugs in emergency department settings

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Introduction The aim of this study is to evaluate the effectiveness of pharmacological treatment for acute headache in Emergency Department (ED) settings, as well as the difference in the therapeutic outcome among the genders.

Methods Data were collected by the ED neurologists of all patients that reported headache in the ED for a period of 6 months. A variety of drugs were used for the acute treatment of headache in the ED such as analgesics, NSAIDs, acetylsalicylic acid, triptans and antiemetics. The intensity of the headache for both genders and for every subtype of headache was estimated on a Visual Analogue Scale before and 45-60 minutes after treatment.

Results A total of 419 headache patients were examined in the ED and 190 of them were given some kind of analgesic medication. 147 (77,4 %) of these patients were female and 43 (22,6%) male. The medication was well tolerated and effective for every headache subtype and there wasn't any statistically significant relation between the positive effect of any medical option and gender.

Discussion Our study confirms the efficacy of specific acute pharmacological treatment in ED settings. All the given medications were well tolerated and equally effective to both genders.

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Duloxetine prophylaxis in chronic tension type headache

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Objectives Duloxetine is a serotonin-norepinephrine reuptake inhibitor, effective for major depressive disorder and generalized anxiety disorder. As known, anxiety is frequently associated with tension type headache. The aim of this study is to evaluate the efficacy and tolerability of duloxetine for patients with refractory chronic tension type headache and anxiety.

Methods Thirty two patients with refractory chronic tension type headache according to International Headache Society criteria and anxiety were enrolled in this study. Headache frequency (days per month), headache severity (according to the Visual Analogical Scale) and anxiety (according to Hamilton Scale) associated before and after treatment initiation with duloxetine were compared. The patients had failed an average of 3.3 prophylactic drugs prior to duloxetine. The average duloxetine daily dose was 57 mg and the average duration of treatment was 121 days.

Results The average number of days with headache per month was reduced in the entire study population from 19.4 before duloxetine treatment to 15.1 after its initiation; headache severity was reduced from 7.3 to 5.4, and anxiety was reduced, from 22.3 to 17.6. Duloxetine was well tolerated, the principal adverse event was somnolence and none patient abandoned the treatment for that reason.

Conclusion Duloxetine has efficacy in tension type headache and anxiety reduction. According to our results, this drug may be a safe and effective agent in patients with tension type headache and anxiety. Double-blind studies are warranted to confirm these findings.

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Determining of migraine prognosis using latent growth mixture models

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This paper presents a retrospective study results to classify patients into subtypes of the treatment according to baseline and longitudinally observed values considering heterogeneous in migraine prognosis. Then, to identify risk factors affecting the success of treatment for each subgroup will be more appropriate. In the classical prospective clinical studies, participants are classified with respect to baseline status and followed within a certain time period. However, latent growth mixture models, for statistical analysis of this type of longitudinal data, consider variation on the response of the treatment. The study data has

been based on a 10-year computer-based follow-up data of Mersin University Headache Outpatient Department. The developmental trajectories within subgroups were described for the severity, frequency, and duration of headache separately and the probabilities of each subgroup were estimated by using latent growth mixture models. SAS PROC TRAJ procedures, semiparametric and group-based mixture modeling approach, were applied to define the developmental trajectories. Bayesian Information Criteria was used to determine the number of subgroups. While the three-group model for the severity (mild, moderate, severe) and the frequency (low, medium, high) of headache appears to be appropriate, the four-group model for the duration is more appropriate (low, medium, high, extremely high). As a result, nausea, vomiting and photophobia were the most significant factors to identify developmental trajectories and the recovery time was not the same for the severity, frequency, and duration of headache.

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Trigeminal sensory and neuroimaging findings in a case of Parry Romberg syndrome

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Background Parry-Romberg syndrome (PRS) is characterized by a slowly progressive atrophy of one side of the face. The cause of the syndrome is unknown. There have been reports of neurological complications, such as migraine, trigeminal neuralgia, facial palsy and epilepsy. Among these, facial pain is frequently reported.

Methods This is a case report with quantitative sensory testing characterizing the somatosensory phenotype and neuroimaging of a new patient with Parry Romberg syndrome and facial pain. We review the literature of cases where at least part of the somatosensory phenotype has been reported to identify possible shared mechanisms of pain generation.

Results We describe a 37 year-old African-American woman with progressive hemifacial atrophy and strictly left-sided facial pain starting about twelve years ago. There was continuous pain in V1 and V2, and intermittent sharp shooting pains in V3. The sensory exam showed areas of pinprick hyperalgesia, cold and heat hyperalgesia, as well as dynamic mechanical allodynia indicating peripheral as well as central sensitization. In the literature review, we found four case reports with a detailed clinical description of the facial pain. Similar to our case, a constant component of the pain was always part of the phenotype, positive or negative trigeminal sensory signs were frequently described.

Conclusions The phenotype of our patient is suggestive of trigeminal neuropathic pain involving all three branches of the trigeminal nerve and the patient fulfils newly defined stricter criteria for neuropathic pain. Similar to our case, the phenotype of the other published cases seems to be in line with trigeminal neuropathic pain rather than trigeminal neuralgia specifically. Electron microscopy findings suggest that PRS involves chronic cell-mediated vascular injury and incomplete endothelial regeneration along branches of the trigeminal nerve (lymphocytic neurovasculitis). This again supports the view that patients with PRS are suffering from trigeminal neuropathic pain.

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Pharmacological treatment of headache patients in the emergency department and effectiveness in relation with patient's age

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Introduction The aim of this study was to estimate the effectiveness of pharmacological treatment of headache in Emergency Department (ED) settings for patients younger and older than 50 years.

Methods Data were collected by the ED neurologists of all patients that reported headache in the ED for a period of 6 months. A variety of drugs were used for the acute treatment of headache such as analgesics, NSAIDs, acetylsalicylic acid, triptans and antiemetics. The intensity of the headache for both age groups and for every subtype of headache was estimated on a Visual Analogue Scale before and 45–60 minutes after treatment.

Results 419 headache patients were examined in the ED and 190 of them were given some kind of analgesic medication. 160 (84%) of these patients were younger than 50 years and 30 (16%) older. 46% from the younger group suffered from tension type headache (TTH), 41% from migraine and 13% from secondary headache. From the older group, 57% suffered from TTH, 27% from migraine and 16% from secondary headache. For both groups the medication, chosen by the ED neurologist, was well tolerated and effective for every headache subtype and there was no important relation between the positive effect of any medical option and age.

Discussion All the given acute medications for ED headache patients were well tolerated and equally effective to both age groups (younger than 50 years and older than 50 years).

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Tilt test results in patients with migraine associated with syncope

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Background and aims Migraine (M) is frequently associated with syncope (S). One of the clinical tests of cardiovascular autonomic function is the tilt-table test (TTT).

The aim of the study was to estimate the prevalence of positive response at TTT and the mechanism (vasodepressive, cardioinhibitory or mixed) by which syncope occurs.

Methods Ninety three patients were included in the study, being distributed into 3 groups: I group - 63 patients with M associated with S, II - 15 with M without S and the III group- 15 with S without M. All patients performed TTT.

Results A positive response at TTT was present in 36 (57.1%) subjects in the I group, in 3 (20%) in the II and 11 (73.3%) patients in the III group. The mixed mechanism of syncope was the most common: in 28 (77.8%) in the I group, 3 (100%) in the II and 0 patients in the III group ($p_{1-2} < 0.01$; $p_{1-3} < 0.001$; $p_{2-3} < 0.01$). The heart rate decreased during TTT by 8.82 bpm in the I group and 7.33 bpm in the III ($p_{1-2} < 0.05$; $p_{2-3} < 0.01$). Systolic blood pressure decreased at S

by 34.46 mm Hg in the I group, by 3 mm Hg in the II and by 37.8 mm Hg in the III group ($p_{1-2} < 0.05$; $p_{2-3} < 0.01$). Diastolic blood pressure decreased at S by 7 mm Hg in the II group and by 25 mm Hg in the III ($p_{2-3} < 0.05$).

Conclusion In two thirds of patients with migraine associated with syncope the TTT was positive, having a mixed mechanism. During the syncope migraine patients had a reduced heart rate and systolic blood pressure, thus indicating the presence of a sympathetic adrenergic dysfunction.

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Migraine with aura and TCD bubble test

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Background According to results of several studies in which Transcranial Doppler (TCD) ultrasound was used for detection of right-to-left shunt, its prevalence is higher in patients with migraine with aura (MA), comparing with migraine without aura patients and healthy subjects. There is no data about some clinical feature of headache or aura whose presence would suggest existence of right-to-left shunt. The aim of this study was to analyze clinical features in patients with MA, in those with positive or negative TCD bubble test.

Methods During the period of two years, TCD-Bubble test with agitated saline was performed in 62 consecutive patients with MA. Detection of microembolic signals in the spectra of medial cerebral artery in the period shorter than 20 seconds from the beginning of injection, was considered as positive result. The demographic features, the characteristics of aura and headache were collected in all patients and then compared between groups with and without positive TCD Bubble test.

Results In the group of 62 patients (83,9% female, $35,8 \pm 12,7$ years old), 46 (74,2%) of them had positive TCD bubble test. Differences between demographic features (age at the time of examination and headache onset, gender), characteristics of headache (frequency, localisation, intensity, pain quality, duration, accompanying symptoms) and aura (symptoms, duration, time - relation to headache), in these two groups were not significant.

Conclusion Three quarters of examined MA patients had positive TCD Bubble test. According to our results, clinical features of MA patients could not predict the result of TCD bubble test.

Keywords Migraine with aura, bubble test

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Cerebral hemodynamic parameters in patients with hemodialysis headache

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There are data implicating arterial blood pressure and/or equilibrium changes during hemodialysis (HD) session could be important for pathophysiology of dialysis headache (DH).

The aim of this study was to compare mean cerebral blood flow velocities and vasomotor reactivity in patients on HD with and without DH measured by transcranial ultrasound examination.

In the cohort of 318 patients undergoing chronic HD, the diagnosis of DH was established in 21 (6.6%) patients. Mean flow velocities (MFV) and vasomotor reactivity (VMR) were measured at the beginning and at the end of HD session on medial cerebral arteries on the right (R) and on the left (L) side in 10 HD patients with DH and 19 HD patients without DH, matched by age and gender.

A mild MFV decrease was recorded during HD session in all patients. No significant differences were recorded in MFV between patients with (MFV_R 47.2 ± 23.5; MFV_L 50.3 ± 18.2) and without DH (MFV_R 52.2 ± 16.0; MFV_L 55.6 ± 15.3) at the beginning of HD session ($p_R = 0.508$; $p_L = 0.419$). MFV were significantly lower in patients with DH (MFV_R 37.1 ± 11.2; MFV_L 35.9 ± 11.2) than in patients without DH (MFV_R 49.1 ± 11.4; MFV_L 49.0 ± 13.2) at the end of the HD treatment ($p_R = 0.012$; $p_L = 0.014$). There were no differences in VMR between the two groups neither at the beginning nor at the end of HD session. Hematological and biochemical parameters, values of systolic and diastolic blood pressure at the beginning and at the end of HD session, as well as dialysis adequacy were not significantly different between the two groups.

The results of our study indicate that significant cerebral flow decrease during the course of HD session could be important in pathophysiology of DH.

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Migraine in iranian children;which criteria are the best diagnostic criteria?

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Objective The aim of this study was to identify the best criteria for diagnosis of migraine in our pediatric population.

Materials and methods A total of 85 children aged below 14 years who had been referred to the pediatric neurology clinic of Mofid Children's Hospital with headache as their complaint, were enrolled. Validated questionnaires were completed by them. The patients were evaluated using five sets of diagnostic criteria including the Vahlquist, the Prensky, the International Headache Society (IHS), the IHS-Revised (IHS_R), and the Maytal criteria, the sensitivity of each set of criteria was assessed.

Results Of the 85 children, clinically diagnosed as having migraine, 61(72%), 73(86%), 75(88%), 76(89.5%), and 76(89.5%) met the criteria of IHS, Vahlquist, Prensky, IHS-R, and Maytal respectively. Both the IHS-R and Maytal criteria had the highest, while the IHS criteria had the lowest sensitivity. Fifty-four children (63.5%) were positive for all five sets of criteria. The application of HIS criteria for diagnosing pediatric migraine led to a smaller percentage of children with migraine being identified.

Conclusion Assessment of the sensitivity of the five sets of criteria for the diagnosis of migraine revealed the inadequacies and limitation of the IHS criteria in the diagnosis of pediatric migraine.

Keywords Migraine, Child, Headache

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Morning headaches in snorers and their bedpartners - preliminary results of a diary-based study

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Background Morning headache (MH) is common in the general population, in patients with obstructive sleep apnoea syndrome (OSAS) and in women living with heavy snorers. MH is poorly defined and was recorded by means of retrospective questionnaires in all previous studies. To provide more reliable data we performed a diary study to elucidate prevalence, characteristics and predictors of MH in snorers and non-snoring bedpartners.

Patients and methods Up to now, 62 volunteers completed the study. All subjects completed a 90-days headache and sleep diary, a structured questionnaire, the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Self-rating Depression Scale (SDS) and Self-rating Anxiety Scale (SAS). Snorers underwent ambulatory OSAS screening. MH was defined as headache present upon awakening and differentiated from nocturnal headache (NH) and diurnal headache (DH).

Results We analysed 5580 subject days of 41 snorers aged 46 ± 11 years (13 female) and 21 bedpartners aged 42 ± 12 years (5 female). The number of subjects reporting MH, DH, and NH was similar in snorers and bedpartners. The three headache types occurred on 8 %, 9 % and 5 % of all days in snorers and on 6 %, 14 % and 5 % of all days in bedpartners. MH was associated with poorer sleep quality in snorers ($p < 0.001$) and bedpartners ($p = 0.004$). Snorers and bedpartners without MH differed significantly regarding PSQI (4 ± 3 vs. 7 ± 3, $p = 0.004$) and ESS (10 ± 4 vs. 7 ± 3, $p = 0.009$). Occurrence of MH was predicted in snorers by consumption of alcohol before bedtime ($p = 0.003$) and in bedpartners by subjective disturbance due to nocturnal recurring leg movements of their snoring partner ($p = 0.01$).

Conclusion MH is associated with reduced sleep quality in snorers and in their bedpartners. In the first, it is related to alcohol consumption, in the latter to recurring leg movements of the bedpartner.

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Sleep in migraine and tension type headache: preliminary study

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Background A relationship between migraine headaches and sleep disturbances has been suggested in both children and adults. Clinical studies performed in adult populations indicate that certain headache types may be related to specific sleep stages, but there is a lack of research examining the relationship between primary headache and sleep in children. The aim of the study was to evaluate sleep in children with migraine and tension type headache (TTH).

Methods 450 children and adolescents with headache (16% of migraine and 84 % TTH) seen in the neurology clinic in 2 year were screening for sleep problems. Parents completed the sleep questionnaire and a standardized questionnaire regarding headache characteristics. Only 29 agreed to undergo nocturnal polysomnography (21 migraine and 8 TTH).

Results There were no significant differences between the sleep habits between children with TTH and migraine. Snoring was reported more frequently in children with TTH (24.9%) than in migraine patients (13.7%) ($p = 0.037$). The parents of children with migraine reported more frequent day time naps: 37% vs. 24.4% in TTH ($p = 0.026$); daytime sleepiness 26% vs. 11.7% ($p = 0.001$); learning difficulties 30.1% vs. 19.6% ($p = 0.045$). On polysomnography, slow-wave sleep was significantly lower in children with migraine (20.6%) than in TTH (24.6%) ($p = 0.03$), and slightly more REM time: 122.3 min in migraine vs. 101.8 min in TTH ($p = 0.03$) with no significant difference in total sleep time (461 min vs. 480 min). The children with migraine had a mean of 5 REM periods vs. 4 periods in TTH.

Conclusion The difference in sleep macrostructure with reduced slow-wave sleep in migraine and REM in TTH may influence daytime performance in children with headache. It is necessary to conduct further research on a larger group of patients with headaches in order to better correlate the prevalence of sleep disorder symptoms with the type of primary headache and daytime functioning.

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Efficacy of cinnarizine and sodium valproate in migraine prophylaxis: a clinical trial

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Background Calcium-antagonists (CA) are heterogeneous group of drugs with different efficacy in migraine prophylaxis. Several studies have firmly demonstrated flunarizine (FLU) and verapamil as the proven calcium-antagonists for migraine prophylaxis. Cinnarizine (CIN), is another CA with less complications and less antihistaminic action. There is very few studies to show the effect of this drug on migraine. The current study evaluates the efficacy and safety of cinnarizine on migraine in comparison to sodium valproate, an acceptable drug in migraine prophylaxis.

Methods The current study is a randomized double blind clinical trial on 133 participants with intractable migraine headache to evaluate the positive effect of cinnarizine in comparison to sodium valproate. The data was collected and analyzed by SPSS software.

Results The mean age of cases was 34.3 ± 10 years in Cinnarizine group and 33.4 ± 11 in Sodium Valproate users. The headache frequency decreased to about 50% and its severity to about 30% in both groups. Although the effect of Cinnarizine was started earlier than sodium valproate, there was no significant difference between two groups of cases in improvement of headache attacks. Statistically significant difference was noted in drug's complication led to discontinuation of treatment, 5.2% in Cinnarizine users in respect to 14% in valproate group.

Conclusion The patients who received Cinnarizine, similar to the patients on sodium valproate showed significant improvement in headache attacks, frequency, duration and severity. Cinnarizine such as sodium valproate is an effective drug in migraine prophylaxis even in intractable headache, but with lesser severe complication.

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Neuromodulation for facial pain and headache

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Introduction During the last 40 years there was an extension of neuromodulating treatments for many disciplines, now also for special forms of neuropathic facial pain and headache. Weiner reported in 1999 on peripheral nerve stimulation for occipital neuralgia and Popney and Alo in 2003 on the therapy of migraine.

Patients and methods In the five years past, we treated 5 patients with neuropathic facial pain, 6 patients with occipital neuralgia and 1 patient with central thalamic pain high parietal, with peripheral nerve field stimulation. For that 2 electrodes were implanted subcutaneously to each border of the pain area. After a test phase of 1-2 weeks and pain reduction of more than 50%, the electrodes were connected to a stimulator.

Results Except 1 patient with postherpetic neuralgia in V1 left, all patients achieved a pain reduction of more than 60 % during a follow-up of 5 years and improvement of their quality of life. 7 patients had a significant reduction in pain medication.

Conclusion Neuromodulation such as cervical spinal cord stimulation, deep brain stimulation and peripheral nerve field stimulation can be successfully applied with minimal risk in special forms of facial pain and headache.

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Obligatory use of the modern medicinal, complementary, integrated medicine for the effective, gentle fighting the medicine induced duration headaches

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The headaches belong to the most frequent complaints in Germany: Headaches have 66.7 per cent of the women (24 million) and 53.2 per

cent of the men (18,5 millions) within a year at least one times. Costs in the amount of 462 million euros/year arise from it. The indirect costs amount to 2.3 billion euros. Fifteen million people have migraine. The time period in which a medicine induced duration headache develops is 4.7 years for free saleable painkillers for Triptane at 1.7 years. 2% (1,64 millions) have for the German medicine induced duration headaches. With the retention of the usual Tristan and others migraine means into combination with acupuncture, therapeutical local analgesia after Trang (TLA after Trang) could medicine induced duration headaches be reduced except for 0%.

The TLA after Trang, physiotherapy, phytotherapy, TENS, Moxibustion, which are saving acupuncture analgesia with the Anaesthetic and pain poor, side effect free, bleeding after the step scheme after Trang can soothe or cure the duration headaches. If the effect of the combination therapy is not sufficient, the pain infusion still can improve the pain fighting with Procain, Novaminsulfon and aspirin between the treatment appointment of 1 week. Blockade of the spinal nerves, of the plexus cervicalis, the Ganglions stellatum, the Ganglions pterygopalatinum and become the demonstrates the PDA in the C2-C7 area with contrast medium pictures.

Patients with unbearable duration headaches can be happy which can to improve her quality of life help them that they have found therapy methods finite. The patients despite side effect rich and not sufficiently pain medicine with unbearable pains until her death without the effective therapy after Trang is more refraining to set at once from a rejection of the therapy after Trang by any institution for aid and bodily injury because must bear.

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Primary headaches in multiple sclerosis: comorbidity or symptom?

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Aim The aim of this study was to investigate the prevalence of primary headaches and neuralgic pain (according to International Headache Society criteria) in patients with Multiple Sclerosis (MS).

Study design We studied 33 patients with clinically definite MS (diagnosis was confirmed by MRI criteria), and 24 (72.7%) of them had complains on headaches. Only 6 (18.2%) of them reported that headaches developed after diagnosis of MS, the rest reported the presence of premorbid headaches.

Results The distribution of different types of headaches were like following: Tension Type headaches had 15 patients, or 62.5% out of 24, Migraine - 6, or 25% out of 24 patients, Cluster headache was found in 1 patient (4.2%) and Trigeminal neuralgia was found in 2 patients (8.3%). The association between different types of headaches and types of the MS was following: neuralgia was found in two youngsters with relapsing-remitting MS, the Tension type headaches had prevalence in secondary progressive MS (12 out of 15 patients) and migraine was associated again with relapsing-remitting MS, but in age group of late 20-ies - mid 30-ies.

Conclusion Primary headaches are common in MS patients. Despite on many investigations, further analysis must be done toward understanding of the connections between the type of MS and type of headaches and if the headache or pain syndrome is the part of the MS or is coinciding with the demyelinating disease. Another studies are needed to clarify the mechanisms underlying the association

between migraine and relapsing-remitting MS, and tension type headaches and secondary progressive MS.

This is first report in the framework of undergoing research of Pain Syndrome and clinical features of MS in Armenia.

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Brain-derived neurotrophic factor gene VAL66MET polymorphism modulates reversible cerebral vasoconstriction syndromes

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Objective Brain-derived neurotrophic factor (BDNF) could affect endothelial function and sympathetic activities, which constitute a potential pathogenesis of reversible cerebral vasoconstriction syndromes (RCVS). Here we investigated whether the functional BDNF Val66Met polymorphism was associated with RCVS disease severity.

Methods Patients with RCVS and normal controls were prospectively recruited and genotyped for the BDNF Val66Met polymorphism. Consecutive magnetic resonance angiography (MRA) and transcranial color-coded Doppler sonography were employed to evaluate patient vasoconstriction. Genotyping results, clinical parameters, vasoconstriction scores, mean flow velocities of the middle cerebral artery (V_{MCA}), and Lindegaard indices were analyzed.

Results Fifty-four patients with RCVS (M/F = 7/47; mean age: 47.3 ± 11.0 years) and 104 age- and gender-matched normal controls finished the study. Three patients (5.6%) developed posterior reversible encephalopathy syndromes (PRES) and three (5.6%) developed ischemic stroke. The genotype frequencies for the BDNF-gene Val66Met polymorphism did not differ comparing patients and control subjects. Compared to Met/Met homozygotes, Val carriers had higher mean vasoconstriction scores of M1 (1.36 ± 1.07 vs. 0.58 ± 0.67 , $p = 0.002$), A1 (1.43 ± 0.84 vs. 0.89 ± 0.78 , $p = 0.024$), and the basilar artery (0.78 ± 0.96 vs. 0.28 ± 0.67 , $p = 0.031$), and higher V_{MCA} values (110.5 ± 34.9 vs. 82.2 ± 20.8 cm/s, $p = 0.002$). None of the Met/Met homozygotes, but 34.4% of the Val carriers, had V_{MCA} values of > 120 cm/s. Clinical features and risk of PRES or ischemic stroke were not associated with the polymorphism.

Conclusions BDNF Val66Met polymorphism is unlikely to play a role in the genetic susceptibility to RCVS but may be associated with increased vasoconstriction severity.

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Voxel-wise assessment of white and gray matter damage in patients with migraine: a combined TBSS and VBM study

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Objective Seminal studies in small and selected groups of migraine patients suggested an involvement of the white matter (WM) and gray matter (GM) beyond the resolution of conventional imaging. Aim of this study was to assess the patterns of regional distribution of damage in the normal-appearing WM (NAWM) and GM in a large group of migraine patients with different clinical (aura [MWA] vs. no aura [MWOA]) and radiological (presence vs. absence of WM hyperintensities [WMHs]) characteristics, using tract-based spatial statistics (TBSS) and voxel-based morphometry (VBM).

Methods Using a 3.0 T scanner, high-resolution T1-weighted and diffusion tensor MRI scans were acquired from 82 migraine patients (40 with aura, 34 with WMHs) and 27 matched healthy controls. Lesion probability maps (LPMs) were created averaging WMHs maps. VBM analysis was performed using SPM5 and an ANCOVA model, including age, gender and intracranial volume as nuisance variables. TBSS analysis was performed using FMRIB's Diffusion Toolbox.

Results WMHs were mostly located in the WM subcortical areas with an aspecific pattern. No abnormalities of the brain WM were detected in patients with migraine (considered as a whole and subdivided in the different study groups). In MWA GM loss involved, predominantly, the posterior brain regions (parieto-temporo-occipital regions). In migraine patients, the presence of WMHs was related to a more complex and diffuse pattern of GM loss (frontal, occipital, temporal cortex). The factorial analysis showed no interaction between aura and lesions.

Conclusions and discussion The regional pattern of GM involvement differs among migraine patients according to their clinical and radiological characteristics. The absence of interaction between aura and WMHs support the notion of different pathogenetic mechanisms underlying the pleomorphic manifestations of migraineurs.

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Functional connectivity of the visual network in patients with migraine and different disease phenotypes

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Objective To explore alterations in the visual network at rest (i.e., without external stimuli) in a large group of migraine patients, outside the attack, with different clinical (aura [MWA] vs. no aura [MWOA]) and radiological (presence vs. absence of white matter hyperintensities [WMHs]) characteristics.

Materials Resting state (RS) functional MRI data were acquired from 87 migraine patients (43 with aura, 38 with WMHs) and 25 matched healthy controls (HC). FC was investigated by examining the correlation between the primary visual cortex (V1) and any other area in the brain using REST software. The cross correlation spatial maps obtained from each subject entered in a factorial analysis, corrected for age and sex, to assess the within-group differences as well as the selective effect of aura and lesions. The correlations between RS changes and clinical data were assessed using linear regression analysis.

Results Compared to HC, the whole sample of migraine patients had an increased FC between V1 and the bilateral dorsolateral prefrontal cortex (DLPFC), the bilateral intraparietal sulcus (IPS), and the bilateral inferior frontal gyrus (IFG). Compared to MWOA, MWA had an increased connectivity between V1 and the anterior cingulate cortex (ACC). FC did not differ between patients with vs. those without WMHs. The factorial analysis showed no interaction between aura and lesions. In the entire sample of patients, no correlations were found between FC changes and disease duration and frequency of attacks.

Conclusions Abnormalities of FC within the visual network do occur in patients with migraine. Such abnormalities are likely to reflect a central dysregulation of visuo-spatial attention and short-term spatial memory. MWA patients had a selective abnormal connection between the visual network and the ACC, which is involved in intentional motivation of eye movements, whereas the presence of WMHs is not likely to modulate visual network rewiring.

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Chronic paracetamol treatment increases the endothelial cell ultrastructural changes evoked by cortical spreading depression

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Background Chronic paracetamol administration increases the frequency of cortical spreading depression (CSD) and Fos expression in the somatosensory cortex suggesting increased cortical excitability and trigeminal nociception (Supornsilpchai et al., 2010). This study was conducted to determine whether chronic paracetamol exposure affects the endothelial cell ultrastructural changes evoked by CSD.

Methods Male Wistar rats were separated into acute and chronic paracetamol and control groups (8 rats each). Paracetamol (200 mg/kg body weight, intraperitoneally (i.p.) was administered 1 hour and 30 days before CSD induction in acute and chronic paracetamol group, respectively. 1,2-Propanediol (12.5% in 0.9% saline i.p.) was administered to control rats. CSD was induced by topical application of 3 mg of KCl to the frontal cortex. The endothelial cell ultrastructural changes were examined using electron microscopy.

Results Changes in the ultrastructure of cerebral microvessels were evident in the KCl-treated group. These changes were characterized by an increase in microvilli and pinocytotic vesicle formation. The number of microvilli in capillaries and arterioles were 1.27 ± 0.56 and 10.75 ± 5.28 microvilli per vessel in the chronic control group and 3.26 ± 1.33 and 23.75 ± 9.03 microvilli per vessel in the chronic paracetamol treated group, respectively. The average density of pinocytotic vesicles in capillaries and arterioles were 34 ± 9 and 44 ± 7 vesicle per μm^2 in the chronic control group and 32 ± 6 and 59 ± 11 vesicle per μm^2 in the chronic paracetamol treated group, respectively. The number of microvilli and pinocytotic vesicles in capillaries and arterioles in chronic paracetamol treated group and chronic control groups were statistically different. No significant change in endothelial cell ultrastructure was observed between the acute paracetamol treated group and the acute control group.

Conclusion Chronic paracetamol exposure may increase the frequency of headache by causing vascular changes in the cerebral cortex.

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A novel mutation in *SLC1A3* associated with pure hemiplegic migraineT. Freilinger^{1,2}, J. Koch³, M. Dichgans^{1,2}, H. Mamsa⁴, J.C. Jen⁴¹Department of Neurology, Ludwig-Maximilians-Universität München, Klinikum Großhadern, Munich, Germany;²Institute for Stroke and Dementia Research, Klinikum der Universität München, Munich, Germany;³Department of Paediatrics, Salzburger Universitätsklinikum, Salzburg, Austria;⁴Department of Neurology, UCLA School of Medicine, Los Angeles, CA, USA

Introduction Hemiplegic migraine, either familial (FHM) or sporadic (SHM), is a severe subtype of migraine with aura characterized by hemiparesis during the aura. Mutations in three genes involved in ion translocation (*CACNA1A*, *ATP1A2* and *SCN1A*) have been identified in FHM and rare individuals with SHM. Enhanced glutamate release facilitating cortical spreading depression has been observed in murine FHM models and proposed to underlie migraine with aura. Here, we describe a 16-year-old boy with SHM, in whom a novel mutation was identified in the gene *SLC1A3* encoding a glial glutamate transporter EAAT1.

Clinical and genetic findings Since age 11, the patient has suffered several episodes of right-sided hemiparesis with aphasia, followed by migrainous headache; of note, no (episodic) ataxia or epileptic seizures were observed, and family history for HM was negative. Mutation testing in the known FHM genes was negative. Based on the previous finding of a mutation in *SLC1A3* in a child with episodic ataxia, hemiplegia, migraines, and seizures, we sequenced *SLC1A3* to find a heterozygous nucleotide change c.1159A > C (NM_004172). Analysis of the parental DNA revealed presence of the variant in the father (who is affected by migraine without aura), suggesting incomplete penetrance. This variant was not detected in 100 control chromosomes. It alters a highly conserved residue (T387P) in the functional motif important in transport, as confirmed by in vitro glutamate uptake assays demonstrating a 70% decrease in the mutant protein.

Conclusions We discovered in a boy with SHM a novel nucleotide variant in *SLC1A3* which likely represents a pathogenic mutation because of evidence of strong evolutionary conservation for the wild type residue and marked deleterious impact on glutamate transport by the mutant protein. Our observation suggests that, similar to mutations in *CACNA1A* that enhance glutamate transmission, mutations in *SLC1A3* that impair glutamate reuptake can be associated with HM.

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Adolescent's primary headache: epidemiology and socio-economic factors

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Background Headaches are one of frequent complaints diagnosed in children and adolescents. The objective of this study is to evaluate the prevalence rates for headache among the Lithuanian sample of early-adolescents and the role of possible related socio-economic factors. This study is a part of the Cross-National Survey on Health Behavior

in School-aged Children - World Health Organization Collaborative Study (HBSC).

Methods In total, 5,557 students (2,904 (51.6 %) boys and 2,728 (51.6 %) girls aged 11, 13 and 15 years old from Lithuania were surveyed in the 2005–2006 school-year. The research was carried out according to the methodology of the HBSC study using the anonymous standardized questionnaire. The response rate was 90 %. The evaluation of an impact of socio-economic factors was based on 8 items:

- (1) family income,
- (2) background and parents' occupation,
- (3) family structure,
- (4) parents support,
- (5) schoolwork pressures,
- (6) spending time with friends,
- (7) being bullying at school.

Results The overall prevalence of frequent headache (at least once a week) was 30.9%. Boys are less at risk than girls ($c^2 = 163,048$; $df = 1$; $p < 0,000$) and the prevalence increases with age. Family income had a strong association with adolescent's headaches and significantly more prevalent among girls from low income families ($c^2 = 13,889$; $df = 2$; $p < 0,001$). Adolescents who lived in two-parent families and had good relationships with their parents experience less headache cases ($c^2 = 20,415$; $df = 3$; $p < 0,000$). The school environment (pressure at school, peers relationship) showed a significant association with the headache prevalence.

Conclusion The findings underline the role of family and school social support in the prevalence of adolescent's headache, which should be considered by health promoters.

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Unilateral and bilateral trigeminal autonomic symptoms in cluster headache

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Aim To investigate prevalence of unilateral and bilateral trigeminal autonomic symptoms in cluster headache (CH).

Methods Hundred and seventy patients with CH according to the ICDH-II were studied using a standard questionnaire with regard to the clinical features with special interest on accompanying trigeminal autonomic symptoms.

Results Hundred and seventeen patients had episodic, 49 patients had chronic CH and 4 patients fulfilled criteria for probable CH. The male-to-female ratio was 3.6:1, mean age 44 years. The vast majority of the trigeminal autonomic symptoms occurred on the headache side. The most frequent reported trigeminal autonomic symptom was lacrimation (92%) followed by nasal congestion (64%), rhinorrhea (70%), conjunctival injection (62%), ptosis (54%), lid edema (34%), miosis (29%) reddening of the face (25%) and sweating of the forehead (24%) or face (24%). Rarely, autonomic symptoms occurred bilaterally: rhinorrhea (6%), sweating of the forehead (6%) or of the face (4%), reddening of the face (4%) miosis (1%) and lacrimation (<1%). Interestingly, 20% of the patients reported a side shift of the cluster attacks and in this case the side of the trigeminal autonomic symptoms followed the pain. Most of the patients (78%) suffered from more than three accompanying symptoms.

Conclusions The data suggest that a thorough and systematic observation reveals bilateral trigeminal autonomic symptoms in cluster headache.

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Migraine and progenitor endothelial cells

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Purpose Endothelial dysfunction in migraine (investigated by ultrasound imaging and biological markers) has been shown in several studies. Endothelial progenitor cells (EPC) indicate endothelium regeneration ability. The purpose of this study is to quantify the number of EPC colonies in migraine patients and its relation with clinical parameters.

Methods Prospective study of 47 patients with migraine (33 migraines without aura and 14 migraines with aura, according to IHS 2004 criteria) and 23 healthy controls. We excluded subjects with known vascular risk factors and acute or chronic inflammatory/infectious conditions. The main characteristics of migraine attacks (frequency, severity and duration) and the duration of the disease were recorded. EPC counts (colonies/10⁶ cells cultured) were determined in peripheral blood during intercritical periods.

Results Migraine patients had lower EPC colony counts than controls (17.9 ± 6.0 vs 9.4 ± 5.0; *p* < 0.0001). No significantly differences were found between migraine with or without aura (9.1 ± 4.8 vs 10.2 ± 5.7; *p* 0.701). EPC colony counts ≤ 10 correlated with clinical diagnosis of migraine with a sensitivity of 91% and a specificity of 73%. Inverse correlation between counts of EPC colonies and time of evolution of migraine was observed (*p* < 0.0001). No correlations were found among EPCs and other clinical parameters of migraine (frequency, severity or duration of attacks).

Conclusion EPC counts are lower in migraine patients and correlate with the duration of the disease. These findings suggest the persistence of an altered endothelial function in patients with migraine.

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Feasibility of a brief intervention for medication-overuse headache: a pilot studyE.S. Kristoffersen^{1,2}, J. Straand¹, M.B. Russell^{3,4}, C. Lundqvist^{2,3,5}

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Background We have previously demonstrated that people with medication-overuse headache (MOH) in the general population can be identified by using a short screening instrument for behavioural dependence, the Severity of Dependence Scale (SDS). Short simple information was enough to detoxify the majority of those with MOH. We have used this background information to adapt the “brief intervention” (BI) scheme to be used for MOH in general practice.

Methods The method involves a simple approach for identifying patients with high likelihood of MOH using only one question about headache frequency and the SDS score. The structured BI involves

giving feed-back to the individual patient on his/her score and consequences this might have regarding the individual risk of medication overuse contributing to the headache. Finally, advice is given regarding measures to be taken, how the patient should proceed and the possible gains for the patient.

A course for structured intervention based on the BI principles was offered to a pilot group of six general practitioners (GPs). The screening question for headache frequency was sent by mail to all 18–50 year old patients on the GPs list. Those who reported chronic headache were then examined by GPs who performed the BI on MOH suspected cases. The pilot study was undertaken in order to focus on the logistics and methodology and did not involve a control group. Follow up with interviews of the patients was performed one month later.

Results and conclusion The GPs involved reported that the BI was feasible to implement within a busy practice and that the BI represented a new instrument for communication with these patients. Results regarding the patients are currently being analyzed and will be presented at the meeting.

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Primary chronic headache; treatment patterns and health service contacts the akershus study of chronic headacheE.S. Kristoffersen^{1,2}, R.B. Grande^{2,3}, K. Aaseth^{2,3}, C. Lundqvist^{2,4,5}, M.B. Russell^{2,3}

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Objective To investigate use of health services and pharmacological and non-pharmacological treatment for primary chronic headache from the general population.

Background Primary chronic headaches are associated with disability, frequent use of health services and various treatments. Patients in specialised headache clinics, general practices and the general population differ. Most current knowledge about primary chronic headache is from selected specialised clinics. Knowledge of pattern of medication use and use of alternative treatments is also important.

Methods An age and gender stratified cross-sectional survey included 30,000 persons aged 30–44 years from the general population. A posted questionnaire screened for chronic headache. Those with self-reported chronic headache were interviewed. The International Classification of Headache Disorders was used. Participants with primary chronic headache were asked about previous physician contacts, medication usage including the Severity of Dependence Score (SDS) and alternative treatment.

Results The questionnaire response rate was 71%, the interview participation rate 74%.

Of primary chronic headaches, 19% had never consulted a physician, 63% had consulted their GP, and 17% consulted both GP and neurologist for headache. Those with chronic tension-type headache (CTTH) and medication-overuse headache (MOH) had similar consultation pattern. Co-occurrence of migraine significantly increased consultations with GP and neurologist.

87% used acute medications for their headache and 46 % overused medication.

9 % used acute medication daily. The SDS score was significantly higher for MOH than CTTH for all levels of physician contact. Primary chronic headache subjects in contact with physicians had significantly higher SDS than those without such contact. Only 4 % of primary chronic headaches used prophylactic treatment.

63% had used alternative treatment, mostly physiotherapy, acupuncture and chiropractic. Use of alternative treatment differed between different physician contact levels.

Conclusions The use of headache medication, neurologist contact and alternative treatments for headache increases the more complex the headache is.

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Antialgic effect of low intensity laser in the treatment of cervicogenic headaches

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Background and aims Cervicogenic headache (CH) is any type of headache originating in low neck structures. It is characterized by nuchal and/or frontotemporal pain triggered by disturbances in the neck region at the C1, C2 or C3 level. Blockade of the major and minor occipital nerves is performed for therapeutic and diagnostic purposes. To determine the effect of low intensity laser (GaAlAs) applied to the region of the major and minor occipital nerves and/or of the C₂ root on the symptomatic side for the treatment of cervicogenic headaches, as an alternative procedure to conventional blockade.

Methods Twenty patients from the Headache Outpatient Clinic of the University Hospital of FMRP/USP were submitted to the procedure. Each patient was evaluated by a neurologist, who made the diagnosis of CH (SJAASTAD, 1990). The patients were submitted to laser applications (780 nm, 70mW, continuous) on the symptomatic side at 8 trigger-points located by palpation in the region of the major and minor occipital nerves, with one D = 157,5 J/cm² per point being applied once a week for 4 weeks. The patients filled out a pain diary (scores of 0 to 10) and were evaluated on four occasions: A0 (before the 1st application), A1 (immediately after the last application), A2 and A3 (30 and 60 days after the last application).

Results The weekly mean pain score was calculated (AO = 9.635; A1 = 2.638; A2 = 2.788; A3 = 2.937) and analysis of the results identified statistically significant differences (p = 0.001, paired t-test) between A0 and A3 regarding pain intensity.

Conclusion On the basis of the above data, we may suggest that low intensity laser promoted a reduction of the intensity and frequency of symptoms.

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Manipulation of vision by prismatic spectacles blunts migraine in meniere patients

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The chronic use of weak asymmetric base-in prism spectacles (WABIPS) developed by Utermöhlen in 1941¹ is a non-invasive treatment of Ménière vertigo, also reported to be effective against motion sickness². We evaluated this treatment in a cohort study of 336 unilateral Ménière patients (according to AAS) with 97% subjective satisfaction and reduction of vertigo symptomatology, and 57% significant reduction and stopped concomitant medication. We found also that before treatment 137 (40.8%) of patients with Ménière also had migraine episodes (according to IHS). After 12 months treatment 59 (17.6 %) had still migraine episodes. Migraine lifetime prevalence is 17%³. From this report, it seems reasonable to suspect that Ménière and migraine constitute a heterogeneous population⁴. Apart from this effect, data shows that migraine can be influenced by visual factors⁵, such as induced by WABIPS which may have consequences for the presenting dynamic visual images to people sensitive to migrainous phenomena. Further studies might include WABIPS for patients with migraine presenting dynamic visual images.

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Conflict of interest Vente E. In the last 5 years we have received sponsoring to attend congress from Menarini, Teva Pharma, Almirall and MSD. Part of the statistical analysis of this work has been financed with help of The Utermöhlen Stichting and Instituut voor Zintuigfysiologie, TNO, Soesterberg, The Netherlands. The registration fees has been paid for 50% by Menarini this time.

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Efficacy of intravenous magnesium sulfate in acute attacks of migraine

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Attacks of migraine are one of the common causes for emergency ward admissions. despite effective abortive treatments a completely safe, cheap and effective drugs seems to be lacking. some of these drugs have distressing side effects or contraindicated in some medical conditions. during recent years some investigators has attached a great importance to the role of magnesium in migraine.

Materials and methods In this double blind randomized placebo controlled study among patients admitted in emergency ward with attack of headache, 30 migraine patient (IHS criteria) was selected and randomized to two groups, receiving either iv 10 cc normal saline or magnesium sulfate 2gr iv slowly over 5 min. if after 30 minutes no headache relief was noted in both groups, in the second phase magnesium sulfate and normal saline was administered in a cross over manner eg: placebo group received mg (2gr) and active arm received normal saline. both groups were visited immediately after injection and at 30 min, 2 hr and 24 hr intervals to monitor probable side

effects and relief of headache and associated symptoms. Statistical analysis was performed between two groups with t-test and p-value. **Finding and results** In 14 out of 15 (93.3%) patients in active group there was significant relief of headache (13 complete relief and 1 partial relief and 1 got no relief but in **all of them** there was complete relief of nausea, vomiting, photophobia and phonophobia. **none of 15 pts (0%)** in placebo arm report headache relief but associated symptoms was relieved in 2 pts. **interestingly** in second phase after magnesium administration to placebo group in 14 pts out of 15 (93.3%) there was significant relief of both headache and associated symptoms. no significant side effect of mg except flushing was noted. our study showed a clear cut efficacy of 2gr mgso4 in acute migraine but large scale study is recommended.

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Quantitative electroencephalographic (QEEG) parameters in children with posttraumatic chronic headache (PCH)

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Objective It is known that posttraumatic chronic headache is very frequent condition in childhood population (6-12 year of age). The precise assessment of this condition by neurometric tools is extremely important. The aim of our research was to study children with PCH and assess their QEEG changes connected to different cognitive processes.

Method We have investigated 24 children with PCH (Age range 9-12 year, 18 boys, 6 girls) and 31 normal children of the same age without PCH (20 boys and 11 girls). All children with other comorbidity and with low IQ were excluded from study. QEEG was conducted on Neurotravel device (version 6.12). Spectral analysis and frequency bands were identified in all of them. Assessment of cognitive processes were done by simplest Raven's test. 2 correct answer from 7 Raven's sample was recognized as normal.

Results In children with PCH the power and amplitude of low frequency delta activity (0.5-1 Hz) known as mental activity delta was significantly lower (~ 40%) than in control ones. This opinion was confirmed from spectral analysis evidences and by frequency bands mapping. Besides, the errors when making Raven's tests were more frequent in PCH children (4 and more) than in control group.

Conclusions Cognitive processes in children with PCH is more handicapped compared with their normal teenagers. Thus, the basic management of such patients needs to be supported with cognitive aids in order to prevent different, even slightly expressed cognitive declines linked with the PCH.

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Association of obesity and migraine in children

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Objective To determine the possible relationship of obesity and migraine in Israeli children and to compare the findings to an earlier study from Turkey.

Background The possible association of migraine and obesity has been investigated in adults, but only one study, from Turkey, has been conducted so far in children.

Methods The files of all children with a diagnosis of migraine who attended the day care department of a tertiary university-affiliated pediatric medical center in Israel from 2004 to 2009 were reviewed. Data were collected on patient background (age, sex, weight, height, ethnicity, religion) and migraine symptoms, frequency, and duration. Body mass index (BMI) and BMI standard deviation score (SDS) were calculated according to the CDC criteria, and patients were divided as follows: normal weight (BMI SDS -1 to +1), overweight (BMI SDS -1 to < 2), obese (BMI SDS ≥ 2).

Results The study group included 132 patients, 56 male and 76 female, aged 3-18 years. Ninety-seven (73.5%) were normal weight, 27 (20.5%) were overweight, and 8 (6%) were obese. There were no significant differences among the weight groups in migraine symptoms, attack frequency, disease chronicity, or disease duration. By contrast to the earlier study from Turkey, no significant association was found between pediatric migraine and obesity.

Conclusions The link between migraine and obesity in children remains controversial. The difference in results between our study and those in a group of Turkish children highlights important factors that researchers should focus on in further studies of this issue, such as age, disease duration before admission, frequency of attacks per month, and degree of overweight. Importantly, ethnicity and genetic background may also play an influential role.

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Role of RBC-Mg and visual aura intensity in (FSS and complex partial seizure) epilepsy and migraine with aura patients

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Objectives RBC-Mg concentrations influence on visual aura in (FSS and complex partial) epilepsy and migraine with aura patients.

Introduction Magnesium is a potential modulator of seizure activity and development of cortical spreading depression (CSD) through enhance the sensitivity of the N-methyl-D-aspartate (NMDA) receptors to glutamate. Visual phenomena: lightnings, disturbed contours of objects, or skotoma, can be due to ophthalmological diseases, but can also occur as symptoms generated by the central nervous system ("aura") in migraine or epilepsy. Aura is a brief subjective symptom that may represent the initial manifestation of a partial epileptic seizure with objective signs or constitute the entire epileptic attack (focal sensory seizure (FSS)). The visual aura of the migraine attack has been explained by the cortical spreading depression (CSD), neuroelectric event beginning in the occipital cortex and propagating into contiguous brain region.

Materials Twenty patients with migraine with aura (MA) (12 females and 8 males, mean age: 30) and ten patients with FSS and Complex Partial epilepsy (5 females and 5 males, mean age: 30.9) were diagnosed according to the classification of IHS and ILAE. FSSs were

subdivided according to the type of sensation in somatosensory, simple visual or ocular sensory, viscerosensory, and experiential sensations, who have definitive epileptogenic EEG activity in the temporal-parietal-occipital area. 10 ml of venous blood sample was collected and measured red blood cells magnesium concentrations by atomic absorption spectrometry (850 nm, Perkin-Elmer 3030).

Results Low RBC-Mg concentrations were found in 42% patients of MA and 55% in FSS and complex partial epilepsy patients during aura seizures.

Patients with lower RBC-Mg concentrations ($<1.80 \pm 0.24$) had in 93% aggravation of visual aura intensity during attacks.

Conclusions Low RBC-Mg could be a peripheral expression of the reduced brain magnesium concentration observed in MA and (FSS and complex partial) epilepsy patients. Magnesium supplements could be benefits in reduction the intensity of visual aura in both groups.

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Adverse events related to the NTI splint: report from the headache hope study

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Background Migraine is a prevalent and disabling condition, for which treatment options remain limited. Many patients do not wish to take oral preventive medications. The NTI splint is FDA approved for the treatment of migraine. However, the use of this option amongst headache experts is limited in part due to fear of potential dental, rather than systemic, adverse events.

Objectives This study used a web based questionnaire to collect data from dental providers on the methods of use and observed adverse events of the NTI splint in their practices.

Methods A web-based questionnaire was e mailed to dental providers in the United States.

Respondents were identified from dental laboratory and distributor records of documented NTI splint providers.

Questions on the methods of use of the NTI splint and outcomes were asked.

Analysis of the data is expressed as a percentage of total respondents.

Results Of 6,312 panelists contacted, 567(9%) responded.

Respondents were largely male (506/567: 89%) and had on average prescribed 160 NTI splints each.

The total number of NTI splints provided by this group of dental professionals was 90,720.

512/567 responded to the question regarding changes in occlusion secondary to NTI splint use.

The number of patients reported to develop a clinical observation of abnormality of occlusion with an anterior open bite as a result of NTI splint use was reported at: 1.6% of 78,711 cases.

Only 0.3% of patients reported aspirating the device; however 0% reported documented aspirations on X ray.

The dental providers rated the NTI splint as an effective treatment for headache in the majority (over 90%) of the patients they treated.

Conclusions Headache can be effectively and safely treated with the NTI splint in dental practices.

Sponsor: National Dentex Corporation.

Conflict of interest Dr. Blumenfeld has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

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Headache in 25 consecutive patients with atrial septal defects before and after percutaneous closure: a prospective case series

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The effect of atrial septal defect (ASD) closure on headache and migraine remains a matter of controversy. The objectives of the study were (i) to determine headache prevalence in consecutive patients with ASD scheduled for percutaneous closure using the classification of the International Headache Society and (ii) to compare headache characteristics before and after closure of ASD. Twenty-five patients were prospectively included over 27 months. Mean duration of follow-up was 12 ± 4 months. Prevalence of active headache was increased compared to general population: Any headaches 88%, migraine without aura 28%, migraine with aura 16%. After ASD closure, we observed a trend towards a lower headache frequency (median frequency 1.0; IQR 2.6 vs. 0.3; IQR 1.5 headaches per month; $p = 0.067$). In patients with ongoing headaches, a decrease in headache intensity (median VAS 7; IQR 3 vs. 5; IQR 3.8; $p = 0.036$) was reported. Three patients with migraine with aura before the intervention reported no migraine with aura attacks at follow-up, two of them reported ongoing tension-type headache, one migraine without aura. In summary, this prospective observational study confirms the high prevalence of headache, particularly migraine, in ASD patients and suggests a possible small beneficial effect of ASD closure.

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Headache and BOTOX®: a case report of hemicrania continua responsive to botulinum toxin type-A

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Introduction Hemicrania continua (HC) is a rare headache disorder characterized by a continuous unilateral headache that varies in intensity, without disappearing completely. HC is typically responsive to Indomethacin, although patients resistant to this drug have been described. We present a case of HC who has shown remarkable response to Botulinum Toxin type A (BT-A).

Case presentation A 12-year old boy presented with a 2-year history of pain over the right side of his head, worst behind his right ear. The pain was constant, dull aching in nature with periods of exacerbation. The exacerbations were mostly nocturnal with bursts of fireworks like pain, occurring in clusters many times over a period of 3-4 days.

During these clusters, he cries, grabbing his right ear and develops red marks in front of this ear with ipsilateral facial pallor. The longest pain free period was not more than 2 weeks. Clinical examination including ENT and Maxillofacial assessments were normal. Investigations including a MRI brain were unremarkable.

The symptoms failed to respond to treatment with various medications including analgesics, Carbamazepine, Gabapentin, Amitriptyline or Pizotifen. Indomethacin test, trial treatment with Indomethacin and Occipital nerve block with Lidocaine were also unsuccessful. Behavioural therapy was also tried with no benefit.

Subsequent treatment with BT-A into the Occipitalis muscle has shown a remarkable and sustained response for 3 months but required further injection after 3 months for recurrence which has maintained his symptom relief, allowing the child back to full time school after a 2-year period.

Conclusions BT-A injections have been shown to be beneficial in adults with chronic migraines. However literature reports of its use in Paediatric cases are limited with none found on HC. Our case supports further trials of BT-A in children with HC poorly responsive to medications.

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Menstrual headache: subtypes, clinical features and treatment

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Introduction Menstrual migraine has been included in the second edition of IHS. Menstrual tension-type headache has not been recognised yet. Our aim is to evaluate the prevalence of different subtypes of menstrual headache, to analyze their clinical features and the treatment prescribed.

Material and methods We prospectively included women attending several neurology outpatient clinics (January–November 2008). Women included should be of child-bearing age, their reason for seeking neurologic care was headache and their headache appeared during the menstrual period. Their headache was classified: pure menstrual migraine (PMM), menstrual-related migraine (MRM), pure menstrual tension-type headache (PMTH) and menstrual-related tension-type headache (MRTH). Clinical features of each type and medication prescribed before/after neurological evaluation were analyzed.

Results 133 patients were included (mean age 34.8 ± 8.9 years). 29.3% suffered from PMM, 58.7% MRM, 4.5% PMTH and 7.5% MRTH. Clinical features: 75% slow onset; 56.4%PMM, 57.7%MRM hemicranial location; 84%PMTH, 50% MRTH holocranial/posterior; 87.2% PMM, 71%MRM pulsatile quality, 100% tensional type oppressive quality; 71.8% PMM, 60.3% MRM

severe intensity, 50%PMTH, 60%MRTH moderate intensity. Before neurological evaluation 50% were not receiving prophylactic treatment (PMM 69%, MRM 37.9%, PMTH 80%, MRTH 60%). Amitriptyline in MRTH (33.4%), betablockers/amitriptyline in MRM (20.8%/13.8% respectively). 100% of tension-type headache were treated with NSAIDs. Migraine patients: NSAIDs alone (58%), associated with triptans (10.2%), with triptans alone (31.8%). After neurological evaluation prophylactic treatment was prescribed in 83.5% MRM (42.3% topiramate), 58.4% PMM (16.7% topiramate, 8.9% betablockers). Amitriptyline in tension-type headache (33.4% PMTH, 40% MRTH). Symptomatic treatment prescribed: NSAIDs in tension-type headache (83.3% PMTH, 70% MRTH), triptans with NSAIDs (48.7%) or alone (33%) in migraine patients.

Conclusion Our data suggest that menstrually related tension-type headaches exists with a prevalence about 12%. Evaluation by a neurologist allows to easily recognise and classify these types of headaches. This parameter has a great influence in therapeutic final decision.

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Immunoreactivity of calcitonin gene-related peptide (CGRP) and its receptor components in human and rat spinal trigeminal nucleus

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Calcitonin gene-related peptide (CGRP) has a key role in the migraine pathophysiology and is associated with activation of the trigemino-vascular system. The trigeminal ganglion, storing CGRP and its receptor components project peripheral to the intracranial vasculature and central to different regions in the brain stem with A δ - and C-fibers; this constitutes an essential part of the pain pathways activated in migraine attacks. Therefore it is of importance to identify the regions within the brainstem that processes nociceptive information from the trigeminovascular system, such as the spinal trigeminal nucleus (STN).

Immunofluorescence method was used to study the distribution of CGRP and its receptor components, calcitonin like receptor (CLR) and receptor amplifying peptide 1 (RAMP1), in human STN (Sp5C), and compare that of rat, using a set of newly characterized antibodies (Eftekhari et al. 2010).

We observed immunoreactivity for CGRP and its receptor components in the STN. The highest density of CGRP immunoreactive fibers were found in a network around fiber bundles in the superficial laminae. Except immunoreactive fibers, CGRP positive neurons were found in the rat brainstem (on the level of the inferior olive and the hypoglossal nucleus). However, no positive neurons were found in the human brainstem. The CLR and RAMP1 expression were predominantly found on fibers in the spinal trigeminal tract (Sp5), with some fibers spanning into the superficial laminae. Co-localization between CGRP and its receptor components were rarely noted. Interestingly, RAMP1 and CLR positive fibers were also detected close to the central canal of the brainstem of both human and rat.

This study demonstrates the expression of CGRP and its receptor components in the STN, and for the first time indicating the possibility of CGRP signaling in the human STN. Our results suggest STN as a possible site of action for the recently developed CGRP receptor antagonists.

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Migraine in patients with colonic sensorimotor activity and irritable bowel syndrome

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Background and aims We have recently shown that in patients with migraine and functional dyspepsia an alteration of postprandial gastric sensorimotor function is evident. 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 yrs, range 28-60, 11 female, 5 constipated), 18 patients with IBS (42 ± 13 yrs, range 29-72, 14 female, 7 constipated) and 10 healthy volunteers (28 ± 6 yrs, 9 female) underwent the recto-sigmoid barostat test as previously described. IBS diagnosis was made according to Rome III criteria. 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 In IBS patients discomfort threshold was significantly lower than in HV, but no difference was found between patients with and without migraine.

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.

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Benign intracranial hypertension associated to progesterone utrogestan: about one case

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Objective Reporting a case of benign intracranial hypertension which occur with an hormonal therapy by progesterone utrogestan®.

Patients and methods A 27 years old woman pregnant in her 16th week of amenorrhea received for two months 200 mg/day of progesterone utrogestan® indicated for first trimester bleeding presented headache, vomiting, and a bilateral papilloedema grad III at the eyeground. An exhaustive biologic and morphologic assessment allows to eliminate infectious, vascular, and tumoral causes of this ICHT and to suspect the role of progesterone therapy. After utrogetan® discontinuation the evolution was spectacularly favorable with disappearance of all neurologic symptoms without any corrector treatment. The case was reported to the pharmaco-vigilance unit where it was analyzed, discussed and recorded.

Results Using the WHO's method of drug side effects imputability to analyze this Adverse event, we found I3 score for the intrinsic imputability and B2 score for extrinsic imputability.

Conclusion Benign Intracranial Hypertension BICH or pseudotumor cerebri is defined as an elevation of the cerebrospinal liquid pressure in the absence of an expansive intracranial processus, a cerebral venous sinus thrombosis or a hydrocephaly. It might be drug induced as in the case reported here, where the progesterone therapy was incriminated. A severe evolution is possible with vision loss by an optic atrophy. The treatment consists of drug discontinuation with an eventual excess weight reduction and high dose corticotherapy. The evolution is characterized by a rapid recovery; surgical treatment is reserved to the rare rebellious cases.

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Optimal medication use in headache: a new conceptualization of acute headache medication adherence

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Background Research has extensively examined adherence with medications taken on a daily basis; however, this literature provides little relevant information regarding adherence with acute medications that are essential to the management of migraine as well as other disorders, such as asthma. Self-efficacy, or confidence in one's ability use medication optimally, is key to fostering medication adherence, but is behavior-specific. We argue that the behaviors necessary to optimally use acute medications differ from the behaviors necessary to optimally use daily medications. A new model that accounts for key variables associated with optimal use of acute medications is needed.

Methodology Literature review revealed information regarding daily medication use. Phenomenological interviews with headache sufferers ($n = 10$) and health care providers who work with headache sufferers ($n = 14$) described medication-taking behaviors required to optimally manage headache disorders.

Conceptualization *Patient behaviors*

Acute medication use requires moment-to-moment evaluation of multiple changing variables that influences behaviors such as timing, dosage, type of medication, available treatment options, and circumstances of medication use. Daily medication use requires taking a set dose of medication at predetermined times. *Physician tasks*.

For acute medication, instructions from physicians are insufficient to describe all aspects of medication use. Therefore, physicians must provide education about the disorder and the effect of each type of medication used, enabling patients to make effective in-the-moment

decisions regarding taking medication. For daily medication, instructions from physicians should explicitly describe and ensure the understanding of optimal timing, dosage, and circumstances of medication use.

Implications Current models of medication adherence may be of limited utility for acute headache medications. Conceptualizing acute headache medication adherence as a set of optimal medication-taking behaviors acknowledges the inherent complexity involved in taking acute (as opposed to daily) medication, and can inform targeted interventions for suboptimal medication-taking behaviors.

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Rizatriptan treatment of acute migraine in patients taking Topiramate for migraine prophylaxis

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Objective To assess efficacy and tolerability of rizatriptan ODT for treatment of acute migraine in patients utilizing topiramate for migraine prophylaxis.

Background There are limited data from prospective controlled trials demonstrating benefit of triptans in patients who continue to experience migraine attacks while utilizing prophylactic medication.

Methods This was a worldwide, randomized, placebo-controlled, double-blind, multiple-attack study in adults with > 1-year history of ICHD-2 migraine, taking a stable dose of topiramate for migraine prophylaxis yet experiencing at least 2 moderate/severe migraine attacks per month. Patients treated 3 moderate/severe attacks in crossover fashion (2 with rizatriptan 10-mg ODT, 1 with placebo) and were randomly assigned to one of three treatment sequences (1:1:1 ratio). The primary endpoint was pain relief at 2 hours.

Results Of 108 patients randomized to treatment, 100 (93%) treated a study migraine. The response rate for 2-hour pain relief was significantly greater with rizatriptan compared with placebo (55.0% vs. 17.4%, $p < 0.001$). Response rates also favored rizatriptan on all secondary endpoints: sustained pain relief from 2-24 hours (32.6% vs. 11.1%, $p < 0.001$), 2-hour pain freedom (36.0% vs. 6.5%, $p < 0.001$), normal functional ability at 2 hours (42.2% vs. 12.7%, $p < 0.001$), and overall treatment satisfaction at 24 hours (60.8% vs. 33.6%, $p < 0.001$). Treatment was generally well tolerated, and few adverse events (AEs) were reported. Overall, 16 (15.8%) patients reported at least one AE following treatment with rizatriptan, and 3 (3.2%) patients reported at least one AE following placebo (note: treatment strategy was 2:1, rizatriptan to placebo, across attacks). Most AEs were of mild severity, and no serious AEs were reported during the study.

Conclusion Rizatriptan 10-mg ODT was superior to placebo at all endpoints examined in the treatment of acute migraine in patients utilizing topiramate for migraine prophylaxis. Rizatriptan was generally well tolerated in this population.

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Efficacy of rizatriptan for the treatment of acute migraine in sumatriptan non-responders

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Objective To assess the efficacy and tolerability of rizatriptan ODT in the treatment of acute migraine in patients who are non-responders to sumatriptan.

Background Thirty to forty per cent of migraineurs report dissatisfaction with sumatriptan treatment. It is unclear whether those who fail to respond to sumatriptan 100 mg will respond to other triptans.

Methods This was a randomized, placebo-controlled, double-blind, multiple-attack study in adults with a >1-year history of ICHD-2 migraine who reported that they generally do not respond to sumatriptan treatment ($\geq 50\%$ unsatisfactory response). In the baseline phase, participants treated a single moderate/severe migraine attack with open-label generic sumatriptan 100 mg. Those who continued to experience moderate/severe pain at 2 hours post-dose were eligible to enter the double-blind treatment phase. In this phase, participants treated three moderate/severe attacks in crossover fashion (2 with rizatriptan 10-mg ODT, 1 with placebo) after being randomly assigned to one of three treatment sequences (1:1:1 ratio). The primary endpoint was pain relief at 2 hours.

Results Of 109 patients randomized to treatment, 102 (94%) treated a study migraine. The response rate for pain relief at 2 hours was significantly greater with rizatriptan as compared with placebo (51% vs. 20%, $p < 0.001$). Response rates also favored rizatriptan on the secondary endpoint of 2-hour pain freedom (22% vs. 12%, $p = 0.013$), as well as on sustained pain relief (38% vs. 14%, $p < 0.001$) and sustained pain freedom (20% vs. 11%, $p = 0.036$) 2-24 hours postdose. Treatment was generally well tolerated. Most AEs were of mild severity, and no serious AEs were reported during the study.

Conclusion Rizatriptan 10-mg ODT was superior to placebo at providing 2-hour pain relief and 2-hour pain freedom in the treatment of acute migraine in patients who do not generally respond to sumatriptan 100 mg. Rizatriptan was well tolerated in this population.

Conflict of interest Taylor F. Merck Honoraria for Migraine Specialist Advisory Board, Speaker's Bureau and Scientific Advisory Committee for this study. Merck Research funded studies with payments to the Park Nicollet Institute for Research and Education and none to me directly. No others potentially pertinent to this information in past 12 months.

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Headache in a neuro psychiatric clinic

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Aim and objective Present study is being carried out to find acceptability of headache clinic in a psychiatric hospital & to study

socio demographic, clinical profile of patients presenting with primary complaint of headache and to study the psychiatric co-morbidity and primary diagnosis.

Place The study was conducted in psychiatry OPD of Tekchand Sidana Memorial Psychiatric Hospital And Deaddiction Centre, Sri Ganganagar, Rajasthan, India.

Material and methods 100 consecutive patients presenting with chief complaint of headache were included in the study. The patients were initially worked up by clinical psychologist using a semi structured performa for detailed sociodemographic variable psychiatric history & mental state examination. These patients were seen by the psychiatrist where history study was reassessed and a detailed physical and neurological examination was done to reach a provisional diagnosis. The patients were then advised laboratory investigations, EEG, CT scan and MRI as & when required. The help of other consultants such as ENT, physician, ophthalmologists and neurologists were taken in some cases.

Results The study is in progress, so far it is apparent that large number of patients suffer from primary headache, Migraine (30 %) and tension induced (40 %) & mixed headache. But more than 50 % of patients had co-morbid psychiatric diagnosis like major depressive disorder, generalized anxiety disorder, substance abuse. About 10 % of patients were diagnosed as secondary headache with various neurological conditions. The detailed analysis will be presented & discussed in the light of other similar studies.

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Transcatheter PFO closure among patients with episodic and chronic migraine

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Objective To compare the benefit of PFO closure in subjects with episodic (EM) versus chronic migraine (CM).

Methods 3,300 subjects who underwent transcatheter PFO closure at least 6 months ago were contacted by mail and directed to an internet based survey. The survey questioned subjects regarding procedural indications, device related complications, and migraine frequency prior to and after PFO closure. Subjects select ed 1 of 5 migraine frequency categories before PFO closure and recently: 0-1 migraine days per month (MD/Mo); 2-5 MD/Mo; 6-15 MD/Mo; 16-25 MD/Mo; or > 25 MD/Mo.

Results 1,075 patients responded to the survey. 257 patients provided baseline and recent migraine frequency data and were used for this analysis. 68% noted migraine as a primary indication for closure. 42.3% reported one or more adverse events including palpitations 31%, chest pain 19%, atrial fibrillation 3.3%, device related stroke 0.4%, and transfusion 0.4%. The distribution of migraine frequency prior to PFO closure was: 0-1 MD/Mo 5.9%; 2-5 MD/Mo 30.5%; 6-15 MD/Mo 33.2%; 16-25 MD/Mo 23.8%; and > 25 MD/Mo 6.6%. 75% of subjects with EM reported improvement of at least 1 frequency category while 4 patients (4.8%) reported an increased frequency of migraine yielding a mean reduction of 1.1 frequency categories for the group. 94.8% of the CM group reported improvement of at least 1 frequency category with a mean reduction of 2.2 frequency categories. Subjects with CM were more likely to respond (drop of ≥ 1 frequency category) to PFO closure than those with EM ($p = 0.0006$).

Conclusion These preliminary results suggest that while both groups respond, patients with CM are more likely to experience a reduction in migraine frequency compared to those with EM. A

controlled study is warranted to evaluate the benefit of PFO closure in patients suffering with CM, a group with a large unmet treatment need.

Conflict of interest Dr. Dodick has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

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Psychometric properties of the Lithuanian version of the migraine disability assessment questionnaire

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Background Migraine is a common neurological disorder with high levels of pain and disability. There is no valid migraine disability assessment tool in Lithuania. Development of one more new instrument for small country is unnecessary. Original Migraine Disability Assessment (MIDAS) questionnaire is reliable and valid instrument to determine the degree of migraine-related disability, to improve patient-physician communication, and to identify patients with high treatment needs.

Objective To perform cross-cultural adaptation of MIDAS and to evaluate psychometric properties of the Lithuanian version (MIDAS-LT).

Materials and methods Cross-cultural adaptation of questionnaire for Lithuanian speaking population was performed following International Society for Pharmacoeconomics and Outcomes Research recommendations. Psychometric properties were tested on Vilnius university hospital Santariskiu clinics out-patients with active migraine. Internal consistency, test-retest reliability and construct validity were assessed. Test-retest examination was done in two weeks after initial evaluation of disability. Nine hypothesis according 90-day headache diaries' and Lithuanian Short Form-36 version 2 (SF-36v2) data were constructed for the evaluation of construct validity.

Results 145 patients (mean age 36.04 ± 10.02 ; 80.7% females and 19.3% males; 82 patients had migraine without aura and 63 with aura) participated in the study. MIDAS-LT demonstrated acceptable internal consistency (Cronbach alpha 0.81 [95% CI; 0.76 - 0.85], item total correlations 0.36 - 0.83), and test-retest reliability (interclass correlation coefficient 0.90 [95% CI; 0.82 - 0.94]). Correlations for all constructed hypothesis according headache diary data and SF-36v2 assessment were significant ($p < 0.001$).

Conclusions MIDAS-LT can be used as migraine disability self-assessment instrument in Lithuanian speaking population.

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Prevalence and impact of headache in children with medically unexplained neurological symptoms (MUNS) presenting to a tertiary paediatric neurology centre

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Background Pain syndrome, particularly headaches are common in children presenting with medically unexplained neurological syndrome (MUNS).

Aim To study the frequency and provide disability data on headache syndrome among our cohort of MUNS and the factors influencing their condition.

Methods Of the 652 admissions to tertiary paediatric neurology service over 3 year period (2007–2009), 82 episodes of admissions (12.6%) in 55 children, documented to have MUNS were identified. 52 were studied retrospectively for data on predominant neurological manifestations, pre-existing clinical diagnosis of headache syndrome, and their impact on mobility and school attendance.

Results 18/52 (35%) - six males and twelve; median age of 13y 6 m and range of 6 to 16y within MUNS cohort had diagnosis of a headache syndrome. In 5/18 headache was the predominant presenting feature. In 10/18, the headache was contributory to the presenting feature. In the rest it was not symptomatic at the time of MUNS presentation. The headache diagnoses according to IHS classification was: Migrane without aura (7), Migrane with aura (1), secondary headache (5), tension type headache (1), sporadic hemiplegic migrane (1), unspecified (3). School attendances were poor (10) /variable (3); mobility was poor (crutches/wheelchair) (5) and fluctuating (4) in those presenting with headache within MUNS cohort. 5 each were either on migraine prophylaxis or other treatments for headache. The co-morbidity included: weight problems (5), nutritional deficiency (2), psychiatric issues (5), others (7). Ongoing mental health(10) and social services (4) input were recommended at discharge.

Conclusion Headache was presenting feature in 28% (15/52) within MUNS cohort. The diagnosis of pre existing headache syndrome does not seem to influence the presenting MUNS symptomatology. However, the educational, medical and psychosocial co-morbidity is high in this group. Early integrated multi-disciplinary approach addressing the environmental/personal influences may help in improving outcome.

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3-year follow-up of secondary chronic headache: the akershus study of chronic headache

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Objective To investigate the 3-year course of a population based sample of secondary chronic headaches.

Methods This is a cross-sectional epidemiological study with follow-up. An age and gender stratified random sample of 30,000 persons aged 30-44 years from the general population received a mailed questionnaire. Those with a self-reported chronic headache were interviewed by neurological residents. The questionnaire response rate was 71%. The participation rate of the initial interview was 74% and it was 87% at the 3 years follow-up. The International Classification of Headache Disorders was used.

Results Of those followed-up, 36% had chronic headache attributed to head and/or neck trauma (chronic post-traumatic headache), 20% had cervicogenic headache (CEH) and 44% had headache attributed to chronic rhinosinusitis (HACRS). The headache index (frequency x intensity x duration) was significantly reduced in chronic post-

traumatic headache and HACRS, 26% and 45% respectively, while it was unchanged in CEH.

Conclusions Secondary chronic headaches have various courses dependent on the diagnosis. Recognizing the different types of secondary chronic headaches is of importance and might have management implications.

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Personality traits and psychological distress in persons with chronic tension-type headache: the akershus study of chronic headache

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Objectives To investigate personality traits and level of psychological distress in persons with chronic tension-type headache (CTTH) from the general population.

Methods An age and gender stratified random sample of 30,000 persons aged 30-44 years from the general population received a mailed questionnaire. Those with a self-reported chronic headache were interviewed by neurological residents. The questionnaire response rate was 71% and the participation rate of the interview was 74%. The International Classification of Headache Disorders was used. To assess personality traits and level of psychological distress, the Eysenck's Personality Questionnaire (EPQ) and the Hopkins Symptom Checklist-25 (HSCL-25) was used.

Results Persons with CTTH had a significantly higher neuroticism score and had a significantly higher level of psychological distress than healthy controls from the general population. Headache- or medication days per month had no significant influence on the neuroticism- and lie scores or the HSCL-25 score.

Conclusions Persons with CTTH revealed higher level of neuroticism and psychological distress than healthy persons. Whether this is due to pre-morbid psyche and/or secondary to the chronic pain is a question that future studies should address.

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A preliminary analysis of GRIK4 genotype and outcomes of topiramate treatment in high frequency episodic migraine

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Background There are striking individual differences in treatment response to topiramate as a preventive treatment for migraine. Glutamatergic neurotransmission is known to be associated with migraine.

Objective To evaluate whether polymorphisms in GRIK4, a gene coding for a glutamate receptor, are associated with outcome in the preventive treatment of migraine with topiramate.

Methods We analyzed data from a randomized, double-blind, placebo-controlled study of adult subjects with high frequency episodic migraine. Subjects were randomized in a 1:1 ratio to treatment with either topiramate 100 mg daily or matching placebo for a 20 week double blind treatment phase. Responders were defined as subjects who had a reduction of 50% or more in the number of migraine days relative to baseline for weeks 17–20. We assessed association of selected 61 tag-SNPs of the GRIK4 for genotyping, covering nearly the whole gene.

Results A total of 385 subjects were randomized to study treatment. We had genotypes on 304 subjects, and, of these, 262 were in the efficacy evaluable population (128 in the topiramate group and 134 in the placebo group). The topiramate and placebo treatment groups were comparable in baseline headache characteristics. After 20 weeks of treatment, the responder rate for the topiramate group (78/128, 60.94%) was higher than for the placebo group (60/134, 44.78%). Genotype-wise analysis revealed an association of rs6589833 ($p = 0.012$), rs2155258 ($p = 0.047$) and rs1939630 ($p = 0.008$) with topiramate response. In the additive model-wise analysis, rs6589833 ($p = 0.005$), rs951370 ($p = 0.025$), rs948029 ($p = 0.026$), rs6589845 ($p = 0.047$) and rs493656 ($p = 0.047$) showed association with topiramate response. In addition, rs6589833 ($p = 0.007$) and rs49356556 ($p = 0.047$) showed association in the dominant model analysis and rs1939670 ($p = 0.032$) showed association in the recessive model analysis.

Conclusions These preliminary results suggest that sequence variations in GRIK4 may be associated with topiramate treatment response in the preventive treatment of subjects with high frequency episodic migraine.

Conflict of interest Dr. Lipton receives research support from the NIH [PO1 AG03949 (Program Director), PO1AG027734 (Project Leader), RO1AG025119 (Investigator), K23AG030857 (Mentor), K23NS05140901A1 (Mentor), and K23NS47256 (Mentor)], the National Headache Foundation, and the Migraine Research Fund; serves on the editorial boards of Neurology and Cephalalgia and as senior advisor to Headache, has reviewed for the NIA and NINDS, holds stock options in Neuralie Inc. and Minster Inc; serves as consultant or has received honoraria from: Allergan, Autonomic Technologies, Boston Scientific, Bristol Myers Squibb, Eli Lilly, Endo, GlaxoSmithKline, Minster, Merck, Nautilus Neuroscience, Neuralie, Novartis, and Pfizer.

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Adipoq polymorphisms and clinical outcome in topiramate migraine preventive treatment

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Background Obesity is known to be an exacerbating factor of migraine. ADIPOQ codes for adiponectin, a protein involved in both obesity and migraine.

Objective To determine if ADIPOQ polymorphisms predict migraine response and body weight (Bwt) change in the preventive treatment of migraine with topiramate.

Methods We analyzed data from a randomized, double-blind (DB), placebo-controlled study of adult subjects with high frequency episodic migraine. Subjects were randomized in a 1:1 ratio to treatment with either topiramate 100 mg daily or matching placebo for a 20-week DB treatment phase. We assessed association of six candidate SNPs of the ADIPOQ gene and change of the 28-day rate of migraine days using a linear regression model. In addition, we evaluated the association between Bwt change and ADIPOQ polymorphisms.

Results A total of 385 subjects were randomized to study treatment. Genotypes were analyzed for 304 subjects and, of these, 262 were in the efficacy evaluable population (128 in the topiramate group and 134 in the placebo group). The topiramate and placebo groups were comparable in baseline Bwt and headache characteristics. After 20 weeks of treatment, the topiramate group showed significant reductions in both the number of migraine days from baseline to the DB treatment phase (-6.6 ± 3.8 vs. -5.3 ± 3.6 ; $p = 0.000$) and Bwt change ($-3.0 \pm 6.6\%$ vs. $0.48 \pm 3.7\%$; $p = 0.001$) comparing to placebo group. Three SNPs [rs822396 ($p = 0.029$), rs1501299 ($p = 0.008$) and rs37674261 ($p = 0.009$)] showed association with change in the 28-day rate of migraine days. No evidence showed the association between Bwt change and the change in the 28-day rate of migraine days or association between Bwt change and the 6 SNPs of ADIPOQ gene.

Conclusions These results suggest that sequence variations in ADIPOQ may be associated with topiramate response in the preventive treatment of subjects with high frequency episodic migraine, regardless of body weight change during treatment.

Conflict of interest Dr. Lipton receives research support from the NIH [PO1 AG03949 (Program Director), PO1AG027734 (Project Leader), RO1AG025119 (Investigator), K23AG030857 (Mentor), K23NS05140901A1 (Mentor), and K23NS47256 (Mentor)], the National Headache Foundation, and the Migraine Research Fund; serves on the editorial boards of Neurology and Cephalalgia and as senior advisor to Headache, has reviewed for the NIA and NINDS, holds stock options in Neuralie Inc. and Minster Inc; serves as consultant or has received honoraria from: Allergan, Autonomic Technologies, Boston Scientific, Bristol Myers Squibb, Eli Lilly, Endo, GlaxoSmithKline, Minster, Merck, Nautilus Neuroscience, Neuralie, Novartis, and Pfizer.

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Cerebral microbleeds in elderly migraineurs

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Background We and others identified migraine to be a risk factor for subclinical cerebellar infarction, deep white matter lesions (WMLs) and brainstem lesions (1–3). Microbleeds are considered another type of small vessel damage, which have not been studied in migraine yet.

Methods We diagnosed 63 participants of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER; 4) to have a lifetime history of migraine (25 with aura [MA], 35 without aura [MO], 3 aura status unknown). There were 359 headache-free controls (age range 73–85 years). Microbleeds were scored on T2*-weighted MRI images using established criteria (5), blinded for clinical history. We a priori stratified for supra- and infratentorial microbleed location, based on suggested increased vulnerability of cerebellum and brainstem in migraine. Infarcts were scored and WML volumes were calculated automatically. Logistic regression models were run controlled for age, gender, cardiovascular risk factors, aspirin and pravastatin use.

Results Overall prevalence of microbleeds was not different across groups: MA 24%, MO 31%, controls 24%. Stratified by location however, infratentorial microbleeds were more frequent in MO vs. controls (14% vs. 3.9%; OR 3.7; 95% CI 1.1–12), especially in men (25% vs. 3.5%; OR 16 [2.2–114]). Among migraineurs, those with vs. those without microbleeds had far more often any infarct (65% vs. 20%; OR 5.8 [1.5–23]), especially lacunar infarcts (41% vs. 8.9%; OR 5.8 [1.3–26]) and infratentorial infarcts (35% vs. 6.7%; OR 5.5 [1.0–30]). Moreover, migraineurs with microbleeds tended to have higher WML-loads than those without microbleeds.

Conclusion A history of migraine without aura is an independent risk factor for infratentorial microbleeds in lifetime migraineurs. Microbleeds in migraineurs are strongly correlated with lacunar and infratentorial infarcts, and WMLs (trend). Small vessel vulnerability or vasculopathy is suggested to explain the increased risk for brain lesions in migraine.

1. Kruit (2004)
2. Kruit (2006)
3. Scher (2009)
4. Shepherd (1999)
5. Greenberg (2009)

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Pilot trial: computerized mobilization of the cervical spine for the treatment of chronic neck pain and associated headache

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Background Physical therapy has been successfully used for the treatment of chronic neck pain. However, manual treatment interventions share a common disadvantage, they are imprecise and inconsistent.

Objective Investigate the safety and efficacy of computerized mobilization of the cervical spine for the treatment of chronic neck pain.

Methods Pilot, open, trial utilizing a device capable of precise three dimensional mobilization of the neck. We recruited patients with chronic neck pain over a period of 6 months. We excluded patients with myelopathy, radiculopathy, and discopathy. Treatment sessions lasted 20 minutes, twice a week, for 6 weeks. Parameters of treatment: continuous mobilization in the sagittal plane with a range of zero to 40°. The angular velocity allowed 0.5 to 2°/sec. We evaluated patients with weekly visual analogue score (VAS), neck disability index (NDI), muscle algometry, neck range of motion, surface EMG of the Trapezius muscles and SF-36 quality of life questionnaire.

Results We recruited 10 patients, 8 women and two men, with a mean age of 50.5 ± 13.5 years. Nine patients reported significant headache

with neck pain. Seven patients with Tension type headache and two patients with cervicogenic headache. Treatment was not associated with any significant adverse effects. Pain scores dropped by 2 ± 0.5 VAS points at the end of the study. Composite Neck range of motion (in the sagittal, horizontal, and coronal planes) showed a significant improvement at the end of the study (p = 0.034). NDI showed marked improvement by the fourth week with a p < 0.05, this improvement remained significant at the end of the study and two weeks after the completion of the study. The headache NDI subscale showed marked reduction of headache intensity.

Conclusions Preliminary results show that computerized mobilization is safe. The data suggests that this method is effective for both the neck pain and associated headache.

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The nucleus raphe magnus contributes to the production of morphine antinociception in the acute pain

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Aim of Investigation Our studies was examined whether pretreatment of naloxone, opioid receptor antagonists into the PAG would alter antinociception elicited by electrical stimulation of the NRM.

Methods The experiments were carried out on white male rats by the models of tail-flick (TF) and hot plate (HP) tests using standard electrophysiological techniques. Latency increase of these reflexes indicated the degree of antinociception. Steel Electrodes was stereotaxically implanted into *Nucleus Raphe Magnus* (NRM) according to Paxinos and Watson atlas coordinates. An agonist (morphine, 0.5–3 mg/kg) and antagonist (naloxone, 0.3–2.5 mg/kg) of opioid receptors were used for neuropharmacological analysis. Same volume of saline was injected for control animals. Experiments was performed in accordance with the standards of the International Pain Society.

Results Stimulation of the NRM elicited a potent antinociceptive response on the tail-flick and hot-plate tests. Pretreatment with the naloxone, at doses between naloxone (0.3–2.5 mg/kg) produced dose-dependent inhibition of antinociception elicited from the NRM on the tail-flick and hot-plate tests. Subthreshold stimulation of the NRM against a background of subanalgesic dose morphine 0.5 – 0.8 mg/kg induced potentiation of morphine effect.

Conclusions Our data indicate functional interactions between opioid and nonopioid antinociceptive systems and modulation of the pain is mediated by a set of neural circuits.

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Late onset visual aura associated with an internal carotid artery stenosis reversible after endarterectomy

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Visual aura is the most common type of aura. However, a late onset of aura is usually symptomatic. We report the case of a 72 year old woman who developed migraine with aura in her seventies which completely resolved after carotid endarterectomy.

This patient had a past medical history of arterial hypertension, coronary angioplasty and migraine without aura since adolescence. In May 2006 she presented with frequent migraine attacks and, for the first time in her life, visual aura. The visual auras were always left homonymous hemianopsia followed by severe migrainous headache, with frequent migraines without aura in between. She was already regularly followed for asymptomatic right internal carotid artery stenosis, estimated at 60%.

She was started on maintenance dose of 250 mg Aspirin daily with increase to 1 g during the attacks. Although this regime decreased the frequency of attacks, she still had one migraine with aura every month and two severe attacks without aura every week. In October 2007 she experienced a regressive ischemic stroke in right carotid artery territory. Ultrasounds and MR angiography showed a nearly occluded carotid artery. She underwent a right carotid endarterectomy. Since then, with a follow-up more than 2 years, she has no more any visual aura.

The aura is linked to the phenomenon of cortical spreading depression (CSD). Recently it has been suggested in a mouse model that microemboli may trigger CSD, often without causing microinfarction. We hypothesize that this patient experienced late onset of visual aura, initially without ischemic stroke, due to the severe carotid artery stenosis.

Conflict of interest C. Lucas has perceived personal fees for activities (consulting, clinical research) with Allergan, Almirall SAS, Astra Zeneca Pharmaceuticals, Boehringer Ingelheim, Bouchara Recordati, Glaxo-Smith Kline Inc, Menarini, Merck, Pfizer Inc, Sanofi-Aventis, Servier.

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Cadasil: migraine with aura as first symptom in three notch 3 positive sblings

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Purpose Cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL) is hereditary arteriopathy caused by mutation NOTCH3 gene on chromosome 19. Its cardinal clinical features included headache, strokes in the young age and vascular dementia in persons with positive family history. In CADASIL patient is headache usually referred as migraine mostly migraine with atypical or prolonged aura. Migraine, as the first symptom, can precede the stroke and neuropsychiatric disorders by a mean of 10 years. The Head magnetic resonance imaging (MRI) with diffuse leukoencephalopathy prominent in temporal lobes is pathognomic.

Case report We present a clinical, neuroradiological features, skin biopsy and pedigree in three NOTCH3 positive sblings (2 sisters - 45 and 43 years old and brother 33 years old). Their clinical picture includes migraine with prolonged aura. Magnetic resonance imaging (MRI) revealed diffuse leukoencephalopathy with involvement of bilateral anterior temporal lobes. Skin biopsy demonstrated granular osmiophilic material deposits in dermal arterioles, diagnostic for CADASIL. Both

sisters additionally manifest Raynauds syndrome with paroxysmal white-blue-red discoloration of the fingers and toes induced by cold or stress.

Conclusion In CADASIL person with migraine as initial symptom can be helpful the head MRI. The leukoencephalopathy presentation is pathognomic to distinguish headache attributed to genetic disorders, CADASIL especially.

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Randomized controlled trial of telcagepant combined with ibuprofen or acetaminophen in the acute treatment of migraine

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Objective To evaluate the efficacy and tolerability of the CGRP receptor antagonist telcagepant when co-administered with ibuprofen or acetaminophen for the acute treatment of migraine.

Background Combining telcagepant with analgesics that have a different mechanism of action could produce greater efficacy.

Methods Pilot randomized, double-blind, placebo-controlled trial. Patients were randomized to treat a moderate/severe migraine with either telcagepant 280 mg + ibuprofen 400 mg (N = 171), telcagepant 280 mg + acetaminophen 1000 mg (N = 171), telcagepant 280 mg (N = 170), or placebo (N = 171). The primary efficacy endpoint was 2-hour pain freedom. The study had 80% power to detect an additive effect of ≥ 15 percentage points (telcagepant combination versus telcagepant alone) and 48% power to detect an additive effect of ≥ 10 percentage points.

Results The percentages of patients with 2-hour pain freedom were greater in each active treatment group compared to placebo ($p < 0.001$): telcagepant + ibuprofen = 35.2%, telcagepant + acetaminophen = 38.3%, telcagepant = 31.2%, placebo = 10.9%. No significant differences were seen for the combinations versus telcagepant, but both combinations were numerically better than telcagepant alone. All active treatments were generally well-tolerated. The percentage of patients reporting any adverse event within 48-hours was higher in the active treatment groups than placebo: telcagepant + ibuprofen = 30.3%, telcagepant + acetaminophen = 31.6%, telcagepant = 24.8%, placebo = 18.2%. Adverse events reported by ≥ 4 patients in ≥ 1 of the groups that included telcagepant were fatigue, nausea, dizziness, somnolence, dry mouth, and tremor. One patient in the telcagepant group, who had also been taking their own non-study acetaminophen, had ALT and AST elevations ≥ 3 times the upper limit of normal.

Conclusions The combination of telcagepant 280 mg with either ibuprofen 400 mg or acetaminophen 1000 mg showed numerically greater treatment effects than telcagepant 280 mg alone, but the differences were not significant in this pilot study. The active treatments were generally well tolerated although the combination treatments were associated with a higher percentage of adverse events. Telcagepant combination treatments may merit further evaluation in studies powered to detect smaller additive benefits.

Conflict of interest Dr. Lipton receives research support from the NIH [PO1 AG03949 (Program Director), PO1AG027734 (Project Leader), RO1AG025119 (Investigator), K23AG030857 (Mentor), K23NS05140901A1 (Mentor), and K23NS47256 (Mentor)], the National Headache Foundation, and the Migraine Research Fund;

serves on the editorial boards of *Neurology* and *Cephalalgia* and as senior advisor to *Headache*, has reviewed for the NIA and NINDS, holds stock options in Neuralieve Inc. and Minster Inc; serves as consultant or has received honoraria from: Allergan, Autonomic Technologies, Boston Scientific, Bristol Myers Squibb, Eli Lilly, Endo, GlaxoSmithKline, Minster, Merck, Nautilus Neuroscience, Neuralieve, Novartis, and Pfizer.

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Telcagepant does not reduce exercise tolerance in patients with exercise induced myocardial ischemia

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Objective To determine if telcagepant adversely affects exercise parameters of myocardial ischemia.

Background CGRP is a potent vasodilator. Telcagepant is a CGRP receptor antagonist being evaluated for treatment of acute migraine. It is unknown whether a CGRP receptor antagonist reduces compensatory vasodilatory capacity during myocardial ischemia.

Methods Double-blind, placebo-controlled, 2-period, single-dose crossover in 61 patients with reproducible exercise induced angina and treadmill exercise time. In each period, patients received a single oral dose of telcagepant (N = 14, 900 mg or N = 46, 600 mg) or placebo. Patients were randomized to treatment and in each period performed a Bruce treadmill exercise test at T_{max} post telcagepant. The primary endpoint was designed to test the lower bound of the 2-sided 90% confidence interval (equivalent to a 1-sided lower 95% confidence interval) for a total exercise duration treatment difference (telcagepant - placebo) > -60 seconds.

Results Data were analyzed for all subjects and stratified by dose. Mean total exercise duration for telcagepant was 405.38 seconds (95% CI: 375.91, 434.85) and for placebo was 412.28 seconds (95% CI: 382.72, 441.85); mean treatment difference (telcagepant - placebo) was -6.90 seconds (90% CI: -17.66, 3.86). The mean treatment difference in total exercise duration (600 mg telcagepant - placebo) was -10.61 seconds (90% CI: -22.94, 1.72). The mean treatment difference in total exercise duration (900 mg telcagepant - placebo) was 4.75 seconds (90% CI: -16.69, 26.20). There were no significant between-treatment differences in exercise time, maximum exercise heart rate, maximum ST segment depression (STD) or time to 1 mm STD among pooled data or upon stratification for dose.

Conclusions The findings suggest that antagonism of the CGRP receptor has no statistically significant effect on compensatory vasodilatory capacity during myocardial ischemia as assessed by

exercise duration, chest pain, or STD in patients with chronic angina and limiting exercise-induced cardiac ischemia.

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Personality traits and psychological distress in secondary chronic headaches: the akershus study of chronic headache

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Objective To investigate personality traits and level of psychological distress in a population based sample of secondary chronic headaches.

Methods An age and gender stratified random sample of 30,000 persons aged 30-44 years from the general population received a mailed questionnaire. Those with a self-reported chronic headache were interviewed by neurological residents. The questionnaire response rate was 71% and the participation rate of the interview was 74%. The International Classification of Headache Disorders was used. To assess personality traits and level of psychological distress, the Eysenck's Personality Questionnaire (EPQ) and the Hopkins Symptom Checklist-25 (HSCL-25) was used.

Results The data are currently being analyzed, and will be presented at the congress.

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Childhood migraine: a sign of social discomfort

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Introduction In recent years the occurrence of migraine in growing up age has reached high peaks. Several cause have been mentioned, such as, family environment problems and greater difficulties for young people to cope with the events of life.

Materials and methods In order to evaluate the truthfulness of these statements the reports of headache suffering boys and girls who had witnessed in the last 5 years (2006-2010) the occurrence of headache in the months of greater suffering (January, February, March) were re-evaluated.

The parameters taken into consideration were the loss of a family figure (separations, divorces, death of a parent or a brother or sister), problems in the relationships with the rest of the family, school problems and in the group of peers.

The characteristics of migraine (intensityxduration (Pain Index), days of headache/month) were compared among subjects showing the preceding characteristics and those who did not.

The first group was made up of 286p.(MwoutA251, MwA34; 178 f.108 m. average age 10,8 +/-3 range 6-18 years), the second of 246p.(MwoutA231, MwA15;149 f.97 m. average age10,9 +/-3,3 range 6-17 years).

The presence of psychiatric disturbances evaluated by means of the CDI and FABC anxiety scale was also evaluated.

Results In the first group greater values were found for migraine (P.I.6 +/-2,1vs.5,2 +/-1,9 $p < .05$, g/month 5,7 +/-6,7vs.5,24 +/-4,3 $p < .05$).

Also the concurrent existence of other pathologies were different (CDI 16,9 +/-6,2vs13,3 +/-3,4 $p < .05$; anxiety FABC 6,4 +/-1,8 vs.4.9 +/-1.3 $p < .05$).

Conclusions The presence of the loss of a family figure is very high (from 15% 2006–to 44% 2010), followed by school problems (17%–24%), family problems (7%–22%), problems with the peers (10%–19%). The close relationship between migraine and social discomfort must stimulate us to paying greater attention to such problems, as well as taking over the entire family nucleus, albeit supporting through behavioral courses in therapy the migraine suffering child.

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The inhibition of monoacylglycerol lipase by URB602 shows anti-nociceptive effects: study in animal models of hyperalgesia

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Endocannabinoids, such as anandamide (AEA) and 2-arachidonoyl glycerol (2-AG), are promising pain modulators. It has been clearly demonstrated that endocannabinoids are hydrolysed by specific enzymes: fatty-acid amide hydrolase (FAAH) is an intracellular hydrolase that catalyzes the cleavage of bioactive of several endogenous fatty acid amides, such as anandamide (AEA), while the hydrolysis of 2-arachidonoylglycerol (2-AG), another important endocannabinoid, is mainly catalysed by the monoacylglycerol lipase (MAGL). The development of MAGL inhibitors could offer an opportunity to study the anti-inflammatory and anti-nociceptive role of 2-AG, which have not yet been elucidated. In this study we evaluated whether systemic inhibition of MAGL, may alter nociceptive responses in a well-known animal model of migraine based on the hyperalgesia induced by nitroglycerin administration at the tail flick test and formalin test (4 hours after its administration). The analgesic effect of URB602 (a MAGL inhibitor, 2 mg/Kg, i.p.) was evaluated in male Sprague-Dawley rats. The animals underwent tail-flick and formalin tests, both performed in baseline conditions and after nitroglycerin-induced hyperalgesia. Rats were pre-treated with nitroglycerin (10 mg/kg, i.p.) and treated with URB602, 60 minutes before the tail flick test and formalin test. URB602 did not shown any analgesic effect per se at tail flick test, but it inhibited nitroglycerin-induced hyperalgesia. In the formalin test, URB602 inhibited the behaviour nociceptive only in the phase I in baseline conditions and in the phase II in nitroglycerin-induced hyperalgesia. The present data suggest that inhibition of MAGL activity, with the theoretical consequent increase in spinal content of 2-AG, may modulate pain perception in a specific animal model of migraine.

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Effect of cortical spreading depression on basal and evoked traffic in the trigeminovascular sensory system

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We monitored the spontaneous and evoked activity of second-order trigeminovascular sensory neurons in rats to test whether afferent traffic increased following a potential migraine trigger and by what mechanism any such change was mediated. Neurons responded to both electrical and mechanical stimulation of the dura mater and facial skin with a-delta latencies. The neurons (N = 9) were spontaneously active with a basal discharge rate of 10.7 ± 2.3 discharges per second. Injection of 5 mL of 2 mg ml⁻¹ xylocaine (total amount 10 mg) into the trigeminal ganglion produced a fully reversible reduction of the spontaneous discharge rate of neurons to $40\% \pm 7\%$ of control. Spontaneous activity had returned to normal ($106\% \pm 21\%$) by 90 minutes post-xylocaine injection. Xylocaine reduced the evoked responses of neurons to dural stimulation to $37\% \pm 17\%$ and to facial skin stimulation to $53\% \pm 15\%$ of control. Induction of cortical spreading depression (CSD, a possible migraine trigger) by local cortical injection of 50 nL of potassium chloride increased the spontaneous discharge rate of responsive neurons from 2.1 ± 0.7 , (N = 10) to 6.5 ± 1.2 discharges per second at 20 minutes post-CSD initiation. Injection of 10ug of xylocaine into the trigeminal ganglion at this time failed to reverse or arrest this increase in discharge rate; discharge rates continued to rise to 8.7 ± 1.9 discharges per second at their peak. These results suggest that there is a continuous resting traffic in trigeminovascular sensory fibres and that CSD probably does not act to increase this traffic- rather it must produce its effect on trigeminovascular sensation by a mechanism intrinsic to the CNS. The results therefore suggest that the pain of migraine in humans may not be the result of peripheral sensory stimulation, but may arise by a central mechanism.

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A role for both the PAG and the NRM in craniovascular sensation

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In experiments on rats, we demonstrated that chemical and electrical activation of the periaqueductal grey matter (PAG) or the nucleus raphe magnus (NRM) selectively inhibits the responses of second-order craniovascular neurons to electrical or mechanical stimulation of the dura mater, compared with stimulation of the facial skin. Injections of local anaesthetic (xylocaine) into the NRM selectively potentiated the responses of craniovascular neurons to electrical or mechanical stimulation of the dura mater ($178 \pm 28\%$), compared with stimulation of the facial skin ($119 \pm 7\%$). There was no significant effect of the injection of xylocaine into the PAG on responses to trigeminal stimulation. Injections of sodium glutamate into either the NRM or PAG selectively inhibited the responses of trigeminovascular neurons to

electrical or mechanical stimulation of the dura mater (NRM to $72 \pm 10\%$; PAG to $60 \pm 8\%$), compared with stimulation of the facial skin (NRM to $93 \pm 7\%$; PAG to $97 \pm 12\%$). Additionally, injections into either the NRM or the PAG of glutamate reversed the increase in discharge rate neurons produced by the potential migraine trigger cortical spreading depression (NRM 100% à $289 \pm 92\%$, à $109 \pm 13\%$; PAG: 100% à $488 \pm 77\%$, à $159 \pm 25\%$). Such injections also reversed or reduced the increase in discharge rate produced by another potential migraine trigger, bright flashing light (NRM 100% à $236 \pm 27\%$, à $92 \pm 7\%$; PAG: 100% à $376 \pm 97\%$, à $220 \pm 50\%$). These results suggest that trigeminovascular sensation is under tight control by brainstem nuclei, whereas other trigeminal sensation is not. Modification of the activity of neurons in these two brainstem nuclei can modulate the effect of potential migraine triggers on trigeminal sensation. These nuclei could be relay points in an hypothesised cortico-brainstem-trigeminal pathway responsible for triggering migraine.

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Prospective analysis of factors related to migraine aura - the pamina study

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Objectives To examine factors increasing and decreasing the risk of occurrence of migraine with aura prospectively by means of a daily diary.

Patients and methods Out of 327 patients with migraine completing a comprehensive 90 days diary, we selected all patients who recorded at least one episode of migraine aura. To find risk indicators for migraine aura we calculated univariate and multivariate generalized linear mixed models (random factor patient) using bias-corrected sandwich estimators for the covariance matrix. In the univariate analyses, a total of 56 variables were included. Factors which showed a p-value <0.05 were included in the multivariate analysis.

Results We included 54 patients (50 female) aged 40 ± 12 years and analysed a total of 4485 patient days. Migraine aura was recorded on 354 days. Visual aura was present on 317 days and additional or other aura symptoms on 127 days. In the univariate analysis, the risk of migraine aura was increased statistically significantly on days 1-3 of menstruation (odds ratio (OR) 2.41) and by following factors recorded on the day before aura: smoking (OR 2.45), glaring lights (OR 2.37), disturbing smells (OR 2.29), disturbing noise (OR 1.99), physical exhaustion (OR 1.96), tiredness (OR 1.88), hunger (OR 1.78), psychic exhaustion (OR 1.74) and psychic tension (OR 1.69). In contrast, the risk of aura was decreased by progesterone-only contraceptives (OR 0.40), holidays and days off (OR 0.40) and relaxation after stress (OR 0.48). In the multivariate analysis, smoking (OR 2.29), menstruation (OR 2.23), hunger (OR 1.66) and holidays and days off (OR 0.42) remained statistically significant.

Conclusion Smoking and menstruation are the most prominent factors increasing the risk of occurrence of migraine aura, whereas holidays and days off decrease the risk. This is the first prospective study suggesting that smoking is a risk factor for migraine aura.

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Successful treatment of cluster headache with the antihistamine terfenadine

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Episodic cluster headache is a well documented and debilitating condition. There is no absolute treatment for cluster headache, only symptomatic medication. The pathophysiology of cluster headache is still unclear though a number of hypotheses, including histamine involvement, have been proposed in an effort to explain the aetiology of this condition. Research into the association of histamine is minimal.

This case study reports a 59 year old man who suffered with episodic cluster headaches for 16 years, from the age of 25 to 41. The attacks lasted for 3 hours, occurring up to 6 times a day, with an average of 2–3 bouts a year, each lasting 2 to 3 months. Standard cluster treatment including oxygen, triptans, oral and rectal ergotamine, intranasal lidocaine, lithium and corticosteroids proved to be of minimal use. Prophylaxis with the antihistamine Terfenadine 60 mg proved very effective. The first dose was taken at the onset of a cluster attack and aborted the attack; the patient continued taking Terfenadine 60 mg twice daily for 3 days and had no further attacks during this period. He had no further cluster attacks until 4 weeks later when again he took Terfenadine 60 mg at the onset of a cluster attack, again with complete resolution of his symptoms. Only 3 doses of Terfenadine were required on this occasion to abort the bout and no further attacks have been suffered since then.

It is proposed that antihistamine prophylaxis for cluster headache should be considered as a recognised treatment for patients unresponsive to standard treatment. A wider breath of evidence through prospective and randomised control trials should be sought.

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Migraine burden in an Albanian patients cohort

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Purpose To find the correlation between migraine and work ability by using the MIDAS questionnaire.

Methods We studied the data of 106 migraine patients randomly presented at the Specialist's Polyclinic Nr 2 of Tirana. The diagnosis is made according ICHD IIR1 criteria (2005). The MIDAS questionnaire, Albanian variant, evaluated in a previous study (2000, MK, JK) is used. The age of patients, age of headache, gender, education and the drug treatment are used as variables of the study. The neurological examination and possibly the laboratory exams are required. The SPSS 17.0 program is applied to get the statistical data.

Results The mean age of patients was 34.57 years old (SD 11.22). There were 83 (78.3%) female and 23 (21.7%) male. 71.7% of patients were suffering of migraine without aura. 58 patients (54.7%) had finished the high school and 23 (21.7%) the undergraduate studies. There were 38 patients (35.8%) under correct treatment and 68 (64.2%) using wrong treatment regimen. There is a statistically significant correlation between the age of disease and the treatment

and between the treatment and MIDAS degree. No significant correlation between migraine form and age of patients and migraine form and gender or education is found.

Conclusion The correct treatment of migraine is an important factor in diminishing the burden of migraine especially in the newly diagnosed patients.

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The neural basis of decision-making under risk in medication overuse headache patients: an FMRI study

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Introduction Medication overuse headache (MOH) represents one of the common disorders associated with chronic substance use and it can be speculated that MOH shares some pathogenetic mechanism with other kinds of drug addiction (Calabresi et al., 2005). A PET study supports the link between MOH and addiction showing, in MOH patients, a persistent orbitofrontal hypofunction, known to occur in drug dependence (Fumal et al., 2006). The abnormal activation within the neural basis of decision-making under risk seems to underlie the maladaptive behaviour of substance abuse, including impaired decision making (Tom et al., 2007).

Subjects and methods To test the hypothesis of a dysfunction of the neural circuit of decision-making under risk in MOH patients, we investigated with functional Magnetic Resonance Imaging (fMRI) 8 female MOH patients (MOH group) (mean age: 32 ± 9 ys) and 8 female control subjects (C group) (mean age: 36 ± 6 ys), during the execution of a decision utility paradigm, while subjects decided whether to accept or reject gambles that offered a 50/50 chance of either gaining one amount of money or losing another amount. We used the paradigm by Tom et al. (2007) that successfully identified a diminished neural sensitivity to losses among individuals who were less loss averse and thus more risk seeking, a feature of substance abusers.

Results We observed activations in the targets of the mesolimbic and mesocortical dopamine systems in both groups. Moreover MOH patients showed, in comparison to C group, an hypoactivation in the ventral tegmental area (VTA) and in substantia nigra (SN) and an hyperactivation in ($p < 0.001$ uncorrected) in superior medial frontal gyrus.

Conclusion Our results seem to support the hypothesis of a dysfunction in the neural basis of decision-making under risk in MOH patients.

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Cardiac cephalalgia: heartache to headache

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Cardiac cephalalgia is recognized by the ICHD-II, with cardiac disease manifesting as headache.

Patient 1 A 70-year-old woman with migraine, coronary artery disease (CAD), hyperlipidemia, hypertension, and stroke presented with a 2-year history of positional headache. It occurred daily, developed with standing and intensified after walking or Valsalva. The headache would immediately improve with activity cessation, and disappear completely if she lay down. She denied migrainous/autonomic features or systemic symptoms. General medical and neurological examinations, cerebral MRA/MRV, orthostatics, labs, tilt table, and radionuclide cisternogram were unremarkable. Brain MRI revealed a chronic left caudate lacunar infarction. Stress echocardiogram was mildly positive for myocardial ischemia; she experienced the same headache during exercise, but no chest pain. Her headache resolved with isosorbide dinitrate. Cardiology continued medical management of her CAD, as she had mild echocardiogram abnormalities and good functional aerobic capacity.

Patient 2 A 79-year-old woman with CAD, hypertension, hyperlipidemia, and migraine presented with thunderclap headache. She had slowed speech, but no aphasia or other neurological symptoms, no complaints of dyspnea, chest pressure/pain. Cardiac, neurologic, and general medical exams were normal, with no signs of heart failure. Head CT was negative. CTA revealed 40% stenosis in left-ICA, 75% stenosis in right-ICA, and no vertebral or intracranial stenosis. EKG showed nonspecific ST-segment abnormalities. Initial troponin-T was < 0.01; 8 hours later, it was 0.11 and CK-MB was 6.9. Coronary angiography showed high-grade stenosis of mid-RCA distal to previously placed bare-metal stent. A drug-eluting stent was placed, with no residual stenosis and excellent distal flow. The headache resolved with oxycodone/acetaminophen.

Myocardial ischemia can present solely with headache. Cardiac cephalalgia should be considered in patients with a new/different headache and cardiac risk factors. In these patients, investigations to exclude myocardial ischemia should be pursued. Failure to recognize/treat cardiac cephalalgia can have serious consequences.

Conflict of interest Dr. Dodick has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

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Frequencies of genetic polymorphisms related to triptans metabolism in chronic migraine

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Migraine is a common type of headache, and the most aggressive form is usually treated with triptans, whose efficacy is extremely variable. A genetic basis for migraine is evident and many susceptibility genes have been described, as well as gene polymorphisms possibly implied in therapy response. During a study aimed to find relations between genotype and response to triptans administration, we characterized a migraineurs population for polymorphisms in the genes coding for monoamine oxidase A, g-protein beta 3 and the cytochromes CYP3A4 and CYP1A2. Alleles and genotypes distributions were compared with known frequencies of healthy Caucasian populations. A significant association with chronic migraine was found for the long allele of monoamine oxidase A 30 bp VNTR and CYP1A2*1F variant.

Thus, the study of functional interaction between CYP and MAO A SNPs might be of striking impact for tailored drug selection in

chronic migraine in order to skip the misuse/overuse of triptans leading to a superimposed medication overuse headache.

Reference

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Genetic polymorphisms related to triptans efficacy and overuse in chronic migraine

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Migraine is widespread form of headache, and triptans are usually the best therapeutic acute option, although efficacy is extremely variable. Several SNPs in genes involved in metabolism and target mechanisms of triptans have been described. In order to define an association between genetic profile and triptans response, we classified a migraineurs population on the basis of triptans response and characterized it for polymorphisms in the genes coding for monoamine oxidase A, G-protein beta 3 and the cytochrome CYP1A2. Analysis of association between genotypic and allelic frequencies of the analyzed SNPs and the grade of response to triptans administration showed a significant correlation for the MAOA uVNTR polymorphism. The further stratification of patients in abuser and non-abuser groups revealed a significant association with triptans overuse and, within the abusers, with drug response for CYP1A2*1F variant.

These data contribute to determine the triptans treatment outcome, which frequently prompts to triptans overuse risk and then to Medication Overuse Headache (MOH).

Reproducibility and validation of genetic association studies in the research area of CM ± MOH management strongly need of standardized and more accurate methods for unambiguous classification of therapy efficacy, till now based on patient self-reports.

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Psychiatric comorbidity and suicide risk in patients with chronic migraine

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The aim of this study was to explore the impact of mental illness among patients with migraine. We performed MedLine and

PsycINFO searches from 1980 to 2008. Research has systematically documented a strong bidirectional association between migraine and psychiatric disorders.

The relationship between migraine and psychopathology has often been clinically discussed rather than systematically studied. Future research should include sound methodologically-based studies focusing on the interplay of factors behind the relationship between migraine, suicide risk, and mental illness.

Reference

Pompili M, Serafini M, Di Cosimo D, Dominici G, Innamorati M, Lester D, Forte D, Girardi N, De Filippis S, Tatarelli R, Martelletti P (2010) Psychiatric comorbidity and suicide risk in patients with chronic migraine. *Neuropsychiatric Disease and Treatment* 6:81-91

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Patient outcome in migraine prophylaxis: the role of psychopharmacological agents

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Migraine is a serious illness that needs correct treatment for acute attacks and, in addition, a treatment prophylaxis, since patients with migraine suffer during acute attacks and also between attacks.

A systematic review of the most relevant clinical trials of migraine headache and its epidemiology, pathophysiology, comorbidity, and prophylactic treatment (medical and non-medical) was carried out using “Medline” and “Psych-info” from 1973 to 2009.

Approximately 110 trials met our inclusion criteria and were included in the current retrospective study.

The most effective pharmacological treatment for migraine prophylaxis is propranolol and anticonvulsants such as topiramate, valproic acid, and amitriptyline. Non-medical treatments such as acupuncture, biofeedback, and melatonin have also been proposed. Peripheral neurostimulation has been suggested for the treatment of chronic daily headache that does not respond to prophylaxis and for the treatment of drug-resistant primary headache. The majority of the pharmacological agents available today have limited efficacy and may cause adverse effects incompatible with long-term use.

This study was limited by the highly variable and often insufficient reporting of the complex outcome data and by the fact that migraine prophylaxis trials typically use headache diaries to monitor the course of the disease. The results of the different studies were also presented in different ways, making comparison of the results difficult.

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Rehabilitating chronic migraine complicated by medication overuse headaches: how can we prevent migraine relapse?

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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 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 as well as effective medications, therefore, representing a treatment choice. Regarding drug abusers, the initial relief step always consists of drug interruption. 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 old and new drugs by avoiding abuse due to non-responsivity of the abused drug.

Reference Farinelli I, Dionisi I, Martelletti P (2010) Rehabilitating chronic migraine complicated by medication overuse headaches: how can we prevent migraine relapse? *Intern Emerg Med* DOI 10.1007/s11739-010-0410-9

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Efficacy of stellate ganglion block on new daily persistent headache

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Aim New daily persistent headache (NDPH) is a primary headache that is characterized by sudden onset in a person with no past history of headache and is followed by a shift to a persistent headache within several days. NDPH has been considered as one of the most refractory headaches. In this study, we performed stellate ganglion block (SGB) on NDPH patients to assess its possible efficacy.

Method Four NDPH patients were investigated. They were diagnosed based on the NDPH diagnostic criteria set forth in the ICHD-II. SGB was performed three times per month to everyday depending on the symptoms.

Results

Case 1 A 37-year-old woman had a non-pulsating headache that developed in the whole head since last year. The degree of the headache was moderate. Triptans, NSAIDs, antiepileptic drugs, and muscle relaxants provided ineffective relief. Tricyclic antidepressants were slightly effective whereas SGB was effective.

Case 2 A 17-year-old woman had a right side non-pulsating headache that developed 6 months ago. The degree of the headache was moderate to severe. NSAIDs, tricyclic antidepressants, anxiolytics, and triptans provided ineffective relief whereas the headache was relieved following SGB.

Case 3 A 68-year-old man had a throbbing headache that developed in the whole head from the age of 64 years. The degree of the headache was moderate. Various oral administrations and SGB provided ineffective relief.

Case 4 A 35-year-old man experienced a sudden onset of a non-pulsating headache in the whole head 4 months ago. The headache continued to persist. The degree of the headache was moderate. Triptans, NSAIDs, anxiolytics, muscle relaxants, and tricyclic antidepressants were ineffective, but SGB was effective.

In 3 of the 4 cases, SGB administration provided effective relief of the headache in NDPH patients.

Conclusions The present study suggests that SGB may be useful for the treatment of drug-resistant NDPH.

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Hemicrania continua-like syndrome after ipsilateral lateral medulla infarction with significant painrelief on occipital nerve stimulation

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In a 50-year-old female, smoker, match to clinical, MRI, SSEP, blinkreflex and quantitative sensory testing (QST) data a right-sided lateral medulla infarction (LMI) on the level of the pars interpolaris trigeminal nucleus.

Remarkable features: initiating intolerable exploding headache combined contralateral absent and impaired pain/temperature and touch/vibration sense respectively (because of lesioned sensory fibres within spinothalamic tract?) with an intact medial lemniscus (normal SSEP). The lesioned 2nd trigeminal branch (QST) is more compatible with pars interpolaris than caudalis V nucleus involvement.

After one week a persistent ipsilateral hemicranial pain with nasal congestion, mild lacrimation and partial ptosis during exacerbations (VAS 6 to 8–9) occurs. A negative response on indometacin 150mg/day exists. Subsequently a diagnosis of a close temporally event-related and side concordant hemicrania continua (CH) phenotype is made. Migraine features does not exist. No effect exists on betablockers, dopaminergics, morfinomimetics, oxcarbamazepin, lamotrigin and nortriptylin. Occipital steroids injection causes painfreedom during 1½ day.

Twenty months later (november, 2007) the patient is added to a pilot study with occipital nerve stimulation on 3 patients with treatment resistant chronic cluster headache in our centre resulting in a persistent significant painrelief to VAS 2 to 6–7 with disappearance of autonomic signs until now. On non-stimulation all features recur. Definite anatomic and pathophysiological conclusions can not be made. A variable affected trigeminal and extracranial touch/pain sensation exist in LMI.

Inconsistent indomethacin response is reported in secondary HC. Validation of the indotest has been proposed.

In LMI autonomic features doesn't occur besides sympathetic Horner's syndrome and headpain is mostly mild/absent. The superior salivatory nucleus with many regulative parasympathic connections may be involved.

Literature

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Clinical and electroencephalographic profile of posttraumatic headache in children and adolescents

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Purpose To present the clinical characteristic and electroencephalographic profile of posttraumatic headache in children and adolescents.

Method In a prospective hospital - based study, 100 children (29 girls and 71 boys), aged 3-14 years old, 90 after brain concussion and 10 after contusion were studied. The children were examined within one

week after trauma, and then after 3, 6 and 12 months. EEG was performed in all patients and repeated in children with persistent headache. The evolution of EEG recordings in children with chronic headache was presented.

Result 83% of children complained of headache after brain concussion and contusion. The majority had acute posttraumatic headache, but 27% had chronic headache, mainly tension type. EEG was normal in 48 (48%) patients. The pathological EEGs showed general slowing, focal findings with localized slowing, spike - wave complexes.

Conclusion The important risk factor for the occurrence of post-traumatic headache were the age of child at the moment of injury and the period of unconsciousness. The routine performance of an EEG in children with posttraumatic headache is not indicated because in most of the cases it is unrevealing. Children should be closely monitored for possible clinical complication and neurological deterioration.

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The pharmacological effect of BGC20-1531, a novel prostanoid EP₄ receptor antagonist, in prostaglandin E₂ human model of headache

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Background and objective Using a human Prostaglandin E₂ (PGE₂) model of headache we examined whether a novel selective and potent and selective EP₄ receptor antagonist, BGC20-1531, may prevent headache and dilatation of the middle cerebral (MCA) and superficial temporal (STA) artery.

Methods Eight healthy volunteers were randomly allocated to receive 200 and 400 mg BGC20-1531 and placebo, followed by a 25-min infusion of PGE₂ (0.40 µg/kg/min). We recorded headache intensity a 10-point verbal rating scale, and measured blood flow velocity in the MCA (V_{MCA}) and the diameter of the STA by ultrasonography.

Results A large variation in the severity of the PGE₂-induced headache between the subjects on placebo day had been observed. Five out of eight subjects did not reach the therapeutic plasma concentration of BGC20-1531. We found no difference in headache responses between both pretreatment days and placebo day ($P > 0.05$). Both doses of BGC20-1531 did not prevent dilation of the MCA and the STA ($P > 0.05$).

Conclusion The EP₄ receptor antagonist, BGC20-1531 did *not* prevent PGE₂-induced headache and dilatation of cranial arteries. However, insufficient exposure to BGC20-1531 and variability in headache response has confounded the outcome of the study and further investigations are needed.

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Dizziness as a discriminating feature in children with primary headaches

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Purpose Even though there are separate and clear criteria for the diagnosis of migraine and tension type headaches established by the International Headache Society, the diagnosis of aforementioned may be troublesome especially in pediatric population. The purpose of the study was to find out the discriminating features between migraine and tension-type headaches focusing mainly on dizziness (the frequency of dizziness in paediatric migraineurs and in children suffering from tension-type headaches (TTH), evaluation if dizziness was a part of migraine aura, migraine headache or a separate symptom e.g in benign paroxysmal vertigo of childhood.

Material and methods Study group consisted of 60 children aged from 6 to 18 years old (30 migraineurs and 30 TTH patients) hospitalised in Developmental Neurology Department, Medical University of Gdansk between 2004–2009 due to migraine with or without aura or TTH. The type of aura was visual (10 children) and sensory (4 children). Children suffering simultaneously from migraine and TTH were excluded from the survey. In all children paediatric, otorhinolaryngological, ophthalmological, psychological examinations, electroencephalogram and neuroimaging were performed.

Results Dizziness was diagnosed in 52 % children with migraine and 31 % with TTH. Benign paroxysmal vertigo was diagnosed in 12% of migraineurs. In 10 % dizziness was the symptom of migraine attacks, more often it was a sign of an aura (25%). We did not find statistically significant difference in frequency of dizziness between patients with visual and sensory aura. Dizziness in children with TTH was much milder than in children with migraine.

Conclusions Occurrence of dizziness coexisting with a headache is supportive for the recognition of migraine in pediatric population, but does not exclude the recognition of TTH.

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Primary idiopathic stabbing headache with a possible seasonal pattern

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Introduction Primary Stabbing Headache is recognized as an intense pain with preferential localization in the cutaneous area of the first division of the trigeminal nerve, with no autonomic symptomatology and lasting a fraction of seconds. Its cause is not completely understood but some features possibly reveal a common physiopathology with TACs. There are no robust descriptions of a seasonal variation and those anecdotal case reports relate to recurrences of pain occurring only during winter and in patients with previous respiratory tract infections.

Clinical report A 70 year old woman recurred to our Neurology Department due to a 30 year old history of headache, described as “stabbing”, with preferential parietal localization, occasionally with auricular irradiation, occurring several times a day, lasting a few seconds and returning every 7 months, exclusively “in Spring and Autumn”. Actually it interferes with sleep. She has no accompanying symptoms, namely disautonomic ones. She had already been observed by several doctors, with subsequent several different diagnoses, but without successful treatments. In our department the neurological observation and the cranial MRI were unremarkable. The diagnostic hypothesis of Primary Stabbing Headache was made and we started indomethacin (25 mg *tid*) with a good response.

Conclusion Primary Stabbing Headache is an infrequent entity and its correct diagnosis has obvious therapeutic implications. In this case, the reappearance of the episodes with a seasonal pattern and its occurrence by night suggest a possible common physiopathology with

TACs. This might be the reason why there are descriptions of favorable responses to melatonin in patients with Primary Stabbing Headache. To our knowledge there are no such cases with a well established chronic seasonal pattern.

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A dependency scale predicts prognosis of medication overuse headache the akershus study of chronic headache

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Medication overuse headache (MOH) is common in the general population. It has several characteristics similar to drug dependency. The objective of this study was to test the hypothesis that the severity of dependence scale (SDS) can predict MOH prognosis regarding medication overuse and headache frequency.

A cohort of 151 people with chronic headache and medication overuse from the general population were followed-up after 2–3 years. SDS scores, information on headache frequency and medication use were collected at baseline and follow-up. Main outcomes were SDS scores, no of days of headache and number of days with medication overuse at baseline and follow-up. Pearsons χ^2 tests and paired Student's t-tests were used.

Of those with primary or secondary chronic headaches with medication overuse, 72% and 48% respectively had stopped medication overuse. Chronic headache was significantly more frequent among those who continued to have medication overuse (81% v. 49%, $p = 0.002$ for primary, 96% v. 60%, $p = 0.005$ for secondary headaches). For participants with primary headaches and medication overuse, the baseline SDS score was a significant predictor of both presence of medication overuse and presence of chronic headache at follow-up. The SDS could not predict similar improvement among those with secondary headaches. The SDS score was reduced slightly but significantly in primary headache subjects who had detoxified but not for secondary headaches. The SDS remained elevated as compared to levels for subjects who had not had medication overuse at baseline.

Our conclusion is that the SDS score predicts medication overuse among chronic headache patients and also predicts the probability of headache and medication improvement over time.

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Migraine and lateral ventricular asymmetry: a clinical and neuroimaging study

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Objective The purpose of this study was to evaluate the association of lateral ventricles asymmetry (LVA) with chronic migraine and to assess its clinical importance.

Materials and methods We have included 95 consecutive chronic migraine (CM) patients who presented LVA on 1,5T MRI examination. The measurements of the LVA were made electronically at the frontal horn level and the degree of ventricular asymmetry was classified as being minimal (control group), mild, moderate or severe according to the ratio of the larger frontal horn diameter to the smaller one (Grosman H.). Patients were evaluated with a detailed structured questionnaire based on criteria of the International Classification of Headache Disorders (ICHD), 2nd edition, and collected data were analyzed.

Results We compared the clinical features of migraine in minimal and severe LVA patients. The mean age was similar in both patients groups (41.5 ± 15.7 vs. 38.5 ± 14.92). There was no significant statistical difference in disease duration (mean duration 19.58, SD 13.26) and migraine attacks frequency (26.2 ± 5.2 headache days per month). The prevalence of LVA all-out (mild, moderate and severe) in the study population was 51%. We ascertained a younger age at the migraine onset in severe LVA patients (14.11 SD 8.11 vs. 21.88 SD 10.28 , $p < 0.05$), as well as longer attack duration in the same group (63.3 SD 47.49 vs. 20.5 SD 19.4 , $p < 0.01$).

Conclusions Asymmetry of the lateral ventricles of the brain is a relatively common MRI finding in CM patients that has important clinical correlates and deserves more attention. According to the results of this study, lateral ventricles asymmetry could be considered as a factor that may influence migraine severity.

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Chronic migraine: clinical and epidemiological study and chronification factors

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Objective About 14% of episodic migraine (EM) patients progress to chronic (CM) migraine during one year of followup [Katzarava Z. et al, 2004].

The purpose of this study was to evaluate specific social and demographic features as well as the comparative clinical picture of CM and EM in order to define potential factors of chronification.

Materials and methods We performed a randomized epidemiological study of primary headaches in Republic of Moldova on 2665 responders, using a detailed structured questionnaire based on criteria of the International Classification of Headache Disorders (ICHD), 2nd edition, 2004.

Results Of the total sample, 93 patients (3.5%) suffered from CM and 441 (16.5%) from EM. Mean age of migraine sufferers was 38.5 ± 1.47 vs. 37.8 ± 0.67 years and disease duration - 10.3 ± 0.83 vs. 8.5 ± 0.42 years ($p < 0.05$).

We ascertained some specific features of CM patients: the majority were women (84.9%), from rural area (67.7%), with low level of education (74.3%), physical workers or not employed (64.5%), and with poor financial status (72%).

Head or neck trauma has been reported in 33.8% CM vs. 25.1% EM patients ($p < 0.05$), mood disorders - in 54.5% CM vs. 44.3% EM, and drug abuse in 29.9% CM patients.

Conclusions The results of the current study emphasize that some factors (sex, low educational and financial level, drug abuse, head or

neck trauma, and associated mood disorders) may influence migraine chronification.

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New online tools to monitor migraine headache

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A headache diary - based on the IHS classification criteria - is mandatory in clinical practice and research, given the consistent discrepancy between retrospective questionnaires or inquiry and daily state reporting. Uniformity between centers and countries, as well as clarity and user-friendliness, are highly desirable. In addition, electronic diaries are more reliable than paper-and pencil forms and when accessed safely through the internet have numerous advantages.

We will present two tools to monitor migraine according to the IHS through the internet.

- (1) An online headache diary with migraine monitor - the direct graphical representation over time of headaches, migraine attacks and medication use per day, as well as the menstruation in women.
- (2) A real-time diary, employed through smartphone by prompting the user in daily life, which captures migraine headache, prodromal features of migraine, and current health behavior.

This application also allows for tailored coaching of health behavior in response to the diary entry, which the user receives directly through the smartphone.

The technical feasibility, acceptance and utility of both tools were successfully tested. The online diary with migraine monitor was recently employed in a Dutch headache center by 28 migraine patients who kept it for 80 days at average, as well as by the neurologist, who used it before, within and between consultations. The real-time diary was tested in 47 migraine patients. In five of them this was done recently as part of an advanced software application with an extended 'back office' for data management.

Both tools can be easily used in clinical practice and in research. We want to share these developments also with the aim to contribute to the issue of usability and best practice in migraine monitoring, and to the convergence in headache diary use.

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Epidemiology, etiology and study of clinical findings of headache

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Background and methods In a cross-sectional epidemiological study of headache disorders in neurology clinic (August 22-November 20, 2009), information on types of headaches, quality, severity, location, duration, frequency, precipitating factors, age of onset, influence of menstruation and pregnancy, positive familial history, use of oral contraceptive pills and other epidemiological

factors including socioeconomic and age/sex composition was collected. Any types of headaches was ascertained by a clinical interview and examination using the operational diagnostic criteria of the International Headaches Society. The prevalence of migraine and tension type headache was also analyzed in relation to variables of life style (physical activity and sleep pattern) and associated signs and symptoms (nausea, vomiting, photophobia and phonophobia).

Results In this study migraine and tension headache were also compared in variable aspects with each other.

- (1) Headache was more prevalent in women than men (F/M = 3/1).
- (2) The most common types of headache included: tension type headache T.T.H (41.4%), migraine (31.2%) and unclassified headaches (17.2%).
- (3) Migraine and T.T.H were more prevalent in early adult life and middle ages.
- (4) In both migraine and tension type headache the time profiles (duration, frequency, age of onset), quality and location were like that noted in textbook and previous studies.
- (5) In both migraine and tension type headache the most conspicuous precipitating factor was stress and mental tension and frequent headaches were accompanied with psychiatric problems (e.g. depression and or anxiety).
- (6) Nausea, vomiting, phonophobia and photophobia were the most common associated symptoms in both of them.
- (7) Positive familial history and aggravation of headache in premenstrual period were more commonly seen in patients with migraine than tension type headache.

In conclusion using the operational diagnostic criteria of International Headache Society in clinical practice, treating, teaching, clinical and epidemiological research is very useful and must also be applied for patients.

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Epidemiologic and clinical characteristics of migraine and tension-type headaches among hospitals staffs

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Background Headache is a common symptom that constitutes a major health problem to all countries in the world. This study was conducted to estimate the prevalence of migraine and tension -type headaches (TTH), its associated occupational risk factors among hospitals staffs, and to report on clinical characteristics of migraine and TTH with using the International Headache Society (IHS) diagnosis criteria.

Method A random sample of 1,023 staffs constituting a 20% sample of the hospitals staff population was selected. Sampling method was categorical random sampling. Within each group sampling was carried out systematically. Data were collected by screening questionnaire followed by clinical interviews, general physical and neurological examination, and diagnostic criteria of IHS. Prevalence of migraine, TTH and coexisting migraine and TTH were estimated as 11.2% (115 cases), 19.5% (199 subjects) and 3.2% (33 subjects) respectively. In this study, clinical characteristics of headache including type, site, number, intensity, concomitant symptom of headaches had been surveyed.

Result TTH and migraine headaches were significantly associated with self reported abnormal sleep pattern and female gender ($P < 0.001$). Also TTH was negatively associated with total 24hr duration of sleep and history of involvement in second job

significantly ($P < 0.026$). The average of prevalence of migraine and TTH were lower than their counter parts in western countries but higher than previous studies conducted in other Asian countries.

Conclusion Clinical characteristics were almost parallel with IHS criteria, headache-related missed work rates were higher for subjects with migraine headache, and also TTH and migraine were separate disorders and were not as a part of a continuum of headache disorders. Headache disorders deserve more attention, especially concerning strategies leading to adequate primary prevention, diagnosis and treatment.

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Effect of migraine on economic status and quality of life of patients

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Background Migraine as one of the most common types of headaches with high intensity and prevalence, affects life significantly. This study was devised to determine the effects of migraine on economic status and life quality of sufferers.

Methods "Pain database questionnaire", prepared by the International Association for the Study of Pain (IASP) in the year 1995, was translated to Arabic. Then we modified it regarding cultural, geographical and social characteristics of Syria. 65 patients (55 women and 10 men) were recruited from neurology clinic consultants. Those patients who met the International Headache Society (IHS) criteria for migraine were interviewed using IASP questionnaire. Pain effects on sleep, marital life, social, recreational and sexual activities, quality and quantity of drug consumption as well as using paraclinical procedures were considered.

Results Significant decrease in sleep duration was seen during pain (7.4 ± 1.9 h) compared to pain-free conditions (6 ± 3.7 h) ($P < 0.001$). The effects of pain on marital life, social, recreational and sexual activities during pain were compared with pain-free conditions based on a zero to ten ranking schedule. Wilcoxon test showed statistically significant ($P < 0.02$) differences.

Conclusion We concluded that the economic effect of migraine and its impact on patients' quality of life are significant and should be considered in health planning and disease management.

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Headaches and ischemic stroke in spontaneous dissection of the intracranial vertebral artery

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Background and purpose Recent progress in magnetic resonance imaging (MRI) technique enables us to diagnose intracranial vertebral artery dissection (IVAD) noninvasively. IVAD has been rarely reported but it may be under diagnosed. We sought to determine the clinical features of IVAD.

Methods Japanese guideline was used for the diagnosis of IVAD based on the MR imaging. We retrospectively determined clinical features of headache, neurological deficits, and MRI findings in 20 patients with ischemic stroke caused by IVAD admitted from April 2007 to December 2009 (mean age, 54 ± 19 years old; 16 males, 80%).

Results In 8 patients (40%), no episode of headache or neck pain coincided with ischemic stroke was found. There was no traumatic episode except one patient with minor trauma in the neck. Headache was observed in 12 patients (60%), headaches in the unilateral occipital; 3, in the bilateral occipital; 3, in the bilateral temporal; 2, and in the whole skull; 4. Pulsatile headache was observed in 4 patients (33%) and the intensity of headache was ranged from slight or trivial in 9 (88%) to moderate in 4 (12%). The neurological deficits were so slight in 12 patients (NIHSS score ranged from 0 to 3) that significant delay of the onset to admission was observed (ranged from 6 hour to 24 hour).

Conclusion Majority of patients with IVAD may not have headache and neck pain. Such a slight symptom may result a delay of hospital visit.

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Impact of hormonal contraception on the risk of migraine: cross-sectional study including 1613 French women

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Migraine is a common neurologic disorder which concerns more often women than men. Its occurrence may be influenced by the events of endogenous or exogenous hormonal life. Risk assessment of hormonal contraceptives on migraine is important because of higher risk of ischemic stroke among migrainous women using combined estrogen-progestin contraceptives. While many studies have assessed the impact of combined estrogen-progestin contraceptives on migraine, studies on progestin only contraceptives remain scarce. In particular, there is no published data on the risk of migraine among women using progestin with antigonadotropic effect. The aim of this cross-sectional study including 1613 childbearing women is to assess the impact of hormonal contraceptives on the risk of migraine, targeting especially the impact of progestin-only contraceptives. In our study, the risk of migraine was significantly associated with family history of migraine (OR = 4.38, CI: 3.38-5.68). In addition, the earlier age of first contraception is associated with higher risk of migraine (p trend = 0.03). Our results suggest that the risk of migraine is increased among current users of 3rd generation estrogen-progestin contraception or pills that have a high estrogen potency (OR = 2.66, CI: 1.11-6.37), compared to never users of hormonal contraception. In contrast, no significant association was found between migraine and current use of antigonadotropic doses of progestin (OR = 1.84, CI: 0.80-4.26) or use of progestin only pills (OR = 2.11, CI: 0.95-4.70). These results obtained with cross-sectional study need to be confirmed by prospective or randomized studies.

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Skull base metastasis presenting as positional headache

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This 78 year old man was admitted with a short history of continuous headache. Neurological examination, MRI brain without contrast and lumbar puncture were normal. Further investigations of deranged LFTs revealed metastatic renal carcinoma and he was transferred to the palliative care hospital for symptom management. He continued to have severe headache and a neurology opinion was sought.

He was most comfortable on his right side, and was unable to sit or stand for more than a few minutes because of severe global headache. This improved to a bearable level on lying on his right side again. Neurological examination was normal. Intracranial hypotension was considered. A repeat MRI brain with contrast was considered to be normal. CSF was again normal (opening pressure marginally reduced; 8 cm CSF). Because he was unable to sit or stand a blind lumbar blood patch was performed. This was unhelpful and a second blood patch was considered.

While waiting for this he was assessed by the palliative care physiotherapist. On elongation and retraction of the cervical spine into postural alignment whilst in the sitting position he became transiently headache free. An MRI of his cervical spine showed an abnormality of his skull base, which in retrospect was evident on both previous MRI's. Metastatic tumour tissue was noted to involve the right lower clivus and foramen magnum. This involved the articulation of C1 with the skull base and the hypoglossal canal. Repeat neurological examination revealed a right 12th nerve palsy with associated tongue atrophy. He is now receiving palliative radiotherapy.

Presumably his positional headache is due to instability of the skull base on C1 or pressure on pain sensitive structures in the skull base. Not all orthostatic headache is due to low CSF pressure and this case highlights the importance of considering alternative causes.

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Machine learning techniques in migraine without aura

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Background and goals Epidemiological studies have provided evidence for a genetic component in migraine without aura (MO). However, no variants convincingly associated with MO have been reported, and its genetic basis remains largely unclear. In the context of a genome-wide association study (GWAS) in MO (performed in the setting of the International Migraine Genetics Consortium; IMGC), we aimed at implementing different 'machine learning' techniques, namely Support Vector Machines (SVMs), Bayesian Network Learning (BNL) and a technique to retrieve aggregate effects from GWAS data.

Methods and preliminary results For SVMs, we used a set of 628 SNPs derived from our MO GWAS ($p < 1 \times 10^{-3}$). When optimizing the procedure, we found that a polynomial kernel performed best to separate affected / unaffected status. 10-fold cross-validation on the set of 628 SNPs resulted in an AUC of 0.914. We are now planning to apply this model to other migraine datasets available through the IMGC (including a large population-based Australian MO sample). Further, BNL can be used to derive correlation between a given SNP and the phenotype as well as between different SNPs. Both the structure of the network (parent and child nodes of the phenotype,

direction of arcs in the network) and the probability distribution behind the network can be learned efficiently from existing data. We will present first promising results from BNL.

As a final approach, we aimed to transform variation across loci which were nominally associated in our MO GWAS dataset, into quantitative scores and relate these scores to disease status. Using large sets of scored alleles, we could derive aggregate risk scores from larger sets of SNPs. Our preliminary analysis revealed significant aggregate scores, although single variants had only smaller effects.

Conclusion Our pilot study emphasizes that 'machine learning' can make a useful contribution to unravel the genetics of migraine.

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A care pathway proforma improves the documentation of the initial assessment of non-traumatic headaches in the emergency department

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Aim To evaluate the use of a care pathway in the documentation of the initial assessment of patients who presented to the emergency department with a non-traumatic headache.

Methods We retrospectively reviewed the medical records of 92 consecutive adult patients who presented to the emergency department of a large teaching hospital with a non-traumatic headache over a three-month period.

Results The current headache care pathway proforma was used in only nine of the cases; 83 were clerked 'freehand'. The documentation of the history and physical examination findings were allocated a score, out of a maximum of 21, based on the documentation criteria in the care pathway. Where the care pathway had been used, the scores were consistently much higher (mean score 16.22, $p = 0.09$) than that of the freehand clerking (mean score 8.14 $p < 0.0001$). A large proportion of patients in both groups underwent computed tomography scanning of the head. Many were subsequently discharged from hospital without a definitive diagnosis or arrangements for neurological follow-up.

Conclusion Patients with non-traumatic headache could benefit from the use of a simple care pathway in the emergency department, however they are under-utilized at present. By emphasizing the crucial elements of history and examination, care pathways improve the documentation of the clinically and medico-legally significant elements of the history, encourage thorough examination, and are a useful tool to guide the decision-making of clinicians in the emergency department. Care pathways facilitate the rapid and accurate diagnosis of potentially life-threatening secondary headaches, and expedite the safe discharge of patients with benign headaches, thus improving the care of this important group of patients.

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Does migraine improve through ketogenic diet?

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Introduction Ketogenic diet (low-carbohydrate, high-protein and lipids diet, inducing ketone bodies hepatic mitochondrial production) improves drug-resistant epilepsy, maybe by ketonic modulation of neuronal excitability.

From seventies, low-calorie ketogenic diet, poor in carbohydrate (<1 g per kg) but rich in proteins (1.2–1.6 g per Kg), is adopted to achieve rapid adiposity loss in obese persons, producing ketone bodies by lipid catabolism. This diet, according to WHO suggested protein intake upper limits (2.5 g per Kg), is usually adopted for short-time periods (2–4 weeks).

We report two 45 y.o. migraineurs sisters, monozygotic twins, that have had a headache improvement with a low-calorie ketogenic diet.

Case report Twins were examined for a high frequency migraine without-aura. Previously they were followed by another Headache-Clinic, abandoned more than one year before because of absence of improvement and weight gain (around +20 Kg in less than 2 years). Fortunately, they continued to fill-in the headache diary.

Both diary analysis evidenced meanly five attacks/month (10–15 days/month). However, they have had for 3 times, both in the same periods, a 1-month headache free phase every 3 months, exactly clashing with 21-days cycles of low-calorie ketogenic diet that carried them to their ideal weight.

Discussion Ketogenesis was already suggested as useful to improve several neurologic disorders, but migraine. However, ketogenesis reduces cortical spreading depression propagation. This mechanism is maybe involved in our patients headache improvement.

Conclusions We auspicate studies about ketogenic diet influence on migraine, since it could be useful to reduce both headache burden and the weight-gain that usually complicates several prophylactic treatments.

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Cephalgia in multiple sclerosis

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According to literature data, 25–40% of the population suffer from cephalgia. It prevails among people of employable age and is associated with life quality deterioration. In multiple sclerosis (MS), cephalgia occurs in the cases of brain stem involvement, location of plaques around the ventricular system. The presence of cephalgia considerably impedes early diagnosis of MS having no pathognomic clinical signs. The only reliable modality for MS verification is MRI with high intensity of magnetic field (1.5T and higher), (F.Barhof's criteria).

Objective of the study Evaluating the role of venous disorders in cephalgia pathogenesis in MS.

Materials and methods The results of the study of 28 MS patients were summarized.

Results MS duration ranger from 1 to 5 years and more. The course of the disease was of progressive nature with persistent cephalgesic syndrome, meteosensitivity, events of neurologic symptom fluctuation which were regarded by outpatient clinic neurologists as recurrent MS exacerbation.

The findings of initial MRI with low intensity of magnetic field in the 28 patients suggested multifocal affection of the white substance of the brain. Given persistent cephalgia in the 11 patients, MRI was repeated using a vascular program on a unit with magnetic field intensity of 1.5T. the analysis of MRI scans demonstrated that blood filling of cerebral vessels of the carotid and vertebrobasilar system was intact in all examined patients. At the same time, the net of

venous vessels was affected, mainly on cephalgia side: dilated, twisted veins with dominant transverse sinus in the right (7 patients) or in the left (4). The administered venotonic and dehydrating therapy with correctors made it possible not only to control cephalgia but also to rule out MS exacerbation, as well as to avoid groundless prescription of expensive immunomodulating therapy.

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DNA sequencing of mitochondrial complex i predicts riboflavin efficacy in migraine

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Introduction Daily high-dose riboflavin supplementation is a useful treatment in mitochondrial disorders and migraine. This effectiveness is higher in carriers of mutations in Complex I of mitochondrial respiratory chain, an enzymatic complex involved in oxidative phosphorylation, synthesized by mitochondrial DNA (mtDNA). However, although some mtDNA mutations were occasionally described in migraineurs, Complex I mutations were never detected in migraine. Aim of this study is to look for Complex I mtDNA mutations in a group of migraineurs treated with high-dose riboflavin and compare mutations of responders with non-responders.

Materials Complex I genome and mtDNA control region (as control) was sequenced in 67 migraineurs treated with riboflavin, blind for treatment efficacy.

Results Complex I mutations were found in 4 patients, all responders to riboflavin. Control region mutations were found in 5 patients, only 1 resulted to be responders to riboflavin. At two-tailed Fisher exact test, groups resulted to be statistically different ($p = 0.048$).

Discussion In our patients, Complex I mutations could account for an enzymatic dysfunction, improved by riboflavin.

Conclusions Our findings support hypothesis that it will exist a relationship between migraine and mitochondria.

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The major metabolite of dihydroergotamine (dhe) after oral inhalation and iv administration does not significantly contribute to the pharmacologic activity

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DHE has been used to treat migraine for over 60 years. Early pharmacokinetic (PK) studies were performed using relatively non-specific assays following oral administration. It has been suggested that part of the reason for the long duration of action of DHE is its potent and long-lasting metabolite, 8'-hydroxy-DHE (8'-OH-DHE). A sensitive (20 pg/ml) LC-MS-MS method for analyzing 8'-OH-DHE was developed, and results from two PK studies where DHE was administered by IV or oral inhalation are reported here. Receptor binding studies were also performed on some serotonin subtype receptors using the maximum 8'-OH-DHE concentrations found in the first study.

In the two studies, 30 healthy subjects (17 males, 13 females) received 1.0 mg IV or orally inhaled DHE and had measurable concentrations of 8'-OH-DHE at 12 hours following IV administration that allowed for calculation of the 8'-OH-DHE half-life. In most subjects, there were insufficient samples above the limit of quantitation from orally inhaled DHE to allow accurate calculation of the 8'-OH-DHE half-life.

Results Mean C_{max} concentrations after IV administration for DHE and 8'-OH-DHE were 45,289 pg/ml and 424 pg/ml respectively for the first study ($n = 16$) and 42,201 pg/ml and 335 pg/ml respectively for the second study ($n = 14$). After IV administration, the average elimination half-life from both studies of 9.4 hours for 8'-OH-DHE was not significantly different from that calculated for DHE (10.2 hours). Receptor binding studies showed that there was little or no receptor occupancy/activation at serotonin subtype receptors when the C_{max} concentration of the 8'-OH-DHE from the first study was tested.

Conclusions The results of these two studies suggest that the 8'-OH-DHE metabolite does not have a longer half-life than the parent compound and its contribution to the pharmacologic activity when given via IV or oral inhalation is minimal.

Conflict of interest Dr. Silberstein has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

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LevadexTM, a novel orally inhaled treatment for acute migraine: efficacy and tolerability results of a phase 3 study

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Background Triptans are known to have inconsistency of response, high recurrence rates, slow onset of action and potential for medication overuse headaches (MOH). IV DHE provides rapid relief, low recurrence rates and no reported MOH. However, IV DHE is difficult to administer and has poor tolerability. LEVADEX is a self administered, novel inhaled formulation of DHE in development.

Methods Randomized, double-blind, placebo-controlled, two-arm, multicenter study. The co-primary efficacy endpoints were pain relief, photophobia, phonophobia, and nausea free at 2 hrs post dosing. Secondary endpoints also were evaluated. Safety evaluations: clinical assessments, laboratory evaluations, pulmonary function, and cardiac evaluations.

Results 903 subjects randomized, 792 (mITT population) included in the primary analysis. 59% of LEVADEX treated subjects had pain relief at 2 hours compared to 35% for placebo ($p < 0.0001$). Subjects who were nausea free, photophobia free and phonophobia free at 2 hours 67%, 47%, 53% respectively for the treatment group and 59%, 27%, and 34% for the placebo group (p values of 0.02, 0.0001 and 0.0001, respectively). The pain relief rate at 10 minutes was 9% for active group compared to 6% for placebo ($p = 0.15$). Sustained pain relief, 2–24 and 2–48 hours for the active arm 44% and 36% and 20% and 17% for the placebo ($p < 0.0001$ and 0.0001 respectively). The drug was well tolerated. No drug related SAEs. Most common adverse event was drug aftertaste (6% vs 2%).

Conclusions In this trial, LEVADEX demonstrated rapid and sustained efficacy in treating acute migraine. LEVADEX was well tolerated with an AE profile similar to that of placebo.

Conflict of interest Dr. Silberstein has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

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Efficacy evaluation of LevadexTM in treating a broad spectrum of acute migraine attacks

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Objectives To evaluate efficacy and safety of LEVADEX, a novel orally inhaled formulation of dihydroergotamine (DHE) in development, in treatment of a broad spectrum of acute migraine attacks.

Background Migraine patient treatment needs often are unmet due in part the inability of existing therapies to relieve symptoms consistently across a broad spectrum of acute migraine attacks.

Methods This is a post hoc analysis of a randomized, double-blind, placebo-controlled, two-arm, multicenter study. Efficacy rates at 2 hrs were compared between patients with moderate vs severe migraine, with aura and without, and with nausea and vomiting and without. Comparison was also made between patients using triptans at the time of entry and not using them.

Results 903 patients randomized; 792 patients in MITT were included in primary analysis. PR and PF for migraine with moderate intensity and severe intensity were 70% and 32% compared to 45% and 24%. PR and PF for migraine with nausea were 54% and 26% compared to 69% and 32% for those without. PR and PF for those with vomiting were 42% and 28% compared to 60% and 29% for those without. Migraine with aura had a PR and PF of 55% and 27% compared to 62% and 29% for those without. 43% of patients reported using triptans and 57% not using triptans. 58% and 26% of patients using triptans had pain relief and were pain free at 2 hrs (PR,PF), respectively, compared to 59% and 30% of patients not using triptans.

Conclusions In this Phase 3 trial, LEVADEX was effective in treating acute migraine with moderate and severe intensity, migraine with nausea and vomiting and those without, migraine with aura and those without, and migraine in patients currently using triptans and patients not using triptans. LEVADEX has the potential to treat a broad range of migraine.

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Efficacy evaluation of levadexTM in treating resistant migraine including migraine with allodynia, morning migraine, disabling migraine and migraine treated late

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Background Triptans are not likely to relieve migraine associated with cutaneous allodynia, morning migraines and migraine attacks late in their course. Injectable DHE has been used to treat nonresponsive migraines for decades, however it is inconvenient to administer and is often associated with nausea. LEVADEX is a self-administered, novel inhaled form of DHE in development, 1.0 mg nominal (~ 0.5 mg systemic) dose, with T_{max} and AUC similar to IV infusion, but with markedly lower C_{max}.

Methods This is a post-hoc analysis of a large randomized, double-blind, placebo-controlled, two-arm, multicenter study. The presence of allodynia at the time of drug administration was determined by a standard questionnaire. Time to treatment was determined using an electronic diary. Morning migraine was defined as headache occurring prior to 7 AM.

Results 903 patients randomized; 792 patients treating at least one qualifying headache were included in primary analysis. At baseline, 53% of patients reported allodynia. 57% with allodynia at baseline reported pain relief at 2 hrs (34% placebo (PL), $p < 0.0001$) compared to 60% of those that were non-allodynic (35% PL, $p < 0.0001$). 30% were pain free at 2 hrs (8% PL, $p < 0.0001$) compared to 27% non-allodynic (12% PL, $p = 0.0002$). The pain free rate at 2 hrs for morning migraines was 21% (4% PL, $p = 0.004$) compared to 30% for rest of the day migraines (12% PL, $p < 0.0001$). There was no correlation between time to treatment of migraine and pain relief or pain free rates at 2 hrs. LEVADEX was equally effective in severely disabled and less disabled migraine patients.

Conclusions In this trial, LEVADEX was statistically similar in each case in treating migraine with and without allodynia, morning migraine, disabling migraine and migraine treated late in its cycle. LEVADEX has the potential to treat migraines that often are resistant to other acute migraine therapies.

Conflict of interest Dr. Silberstein has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

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Evaluation of safety and efficacy of levadexTM (MAP0004) in treating acute menstrual migraine

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Objective To evaluate the efficacy and safety of LEVADEXTM (MAP0004), a novel orally inhaled formulation of dihydroergotamine (DHE) in development, in the treatment of an acute menstrual migraine.

Background Menstrual migraines are reported to be more disabling, longer lasting, and less responsive to traditional treatments than nonmenstrual migraines. MAP0004, 1.0 mg nominal dose (approximately 0.5 mg systemic equivalent dose), has t_{max} and AUC similar to IV infusion, but with lower C_{max}. Results from a large Phase 3 study were analyzed to evaluate MAP0004 in the treatment of menstrual migraine.

Methods This is a post hoc analysis of a randomized, double-blind, placebo-controlled, two-arm, multicenter study. Menstrual migraine was defined as a migraine occurring within the period 2 days prior to 3 days after the onset of menstrual flow. Pain relief and sustained pain relief (SPR) at 2–24 hours and 2–48 hours were compared between MAP0004 and placebo in menstrual migraines.

Results 903 patients were randomized; 792 patients treating at least one qualifying headache were included in efficacy analysis. Information about last menstrual period was available in 318 patients. 97 (31%) of them had menstrual migraine. For the 97 patients with menstrual migraine, the 2 hour pain relief rate was 62% for MAP0004 and 34% for placebo. 2–24 and 2–48 hour SPR were 51% and 39% for MAP0004 and 20% and 17% for placebo, respectively. In all the measures, the response to MAP0004 was statistically superior to placebo ($p < 0.05$). MAP0004 was well tolerated.

Conclusions In this Phase 3 trial, MAP0004 was effective in treating acute menstrual migraine.

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Evaluation of efficacy and safety of levadexTM (MAP0004) in reversing central sensitization and treating migraine in established allodynic patients

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Objective To evaluate the efficacy and safety of LEVADEX (MAP0004), a novel orally inhaled formulation of dihydroergotamine (DHE), in treating acute migraine in allodynic patients.

Background Current migraine treatments may not relieve symptoms in patients who have established central sensitization (CS), clinically manifested by cutaneous allodynia. Intravenous DHE has been shown, in animal studies, to reverse established CS. This analysis of a large Phase 3 study was undertaken to evaluate the efficacy of MAP0004 in reversing CS and treating acute migraine attack in patients with cutaneous allodynia.

Methods This is a post-hoc analysis of a large randomized, double-blind, placebo-controlled, two-arm, multicenter study. The presence or absence of allodynia at the time of drug administration and at 2 hours post administration was determined by a standard questionnaire. Pain measures were compared between allodynic and non-allodynic patients.

Results 903 patients were randomized; 792 patients treated at least one qualifying headache were included in efficacy analysis. At time of treatment, 57% of patients reported allodynia. 53% of these had resolution of allodynia at 2 hours with MAP0004 compared to 41% in the placebo group ($p = 0.02$). 57% of MAP0004 patients with allodynia at time of treatment reported pain relief at 2 hours compared to

34% of placebo patients with allodynia ($p < 0.0001$). The SPR rate at 2–24 hours was 45% for the allodynic MAP0004 population compared to 20% for the placebo allodynic population ($p < 0.001$). There was no statistically significant difference in MAP0004 response between the allodynic and non-allodynic groups.

Conclusions In this Phase 3 trial, MAP0004 was equally effective in treating migraines with and without allodynia and was effective in reversing established allodynia.

Conflict of interest Dr. Silberstein has acted as a consultant, speaker or received research support from Allergan Pharmaceuticals.

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The efficacy and tolerability of levadex™ (orally inhaled DHE) for the treatment of migraine in subjects with concomitant asthma

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Objective To evaluate the efficacy and tolerability of LEVADEX™ for the treatment of migraine in subjects with asthma.

Background Asthma can be a common concomitant disorder for patients with migraine. Since individuals with asthma can sometimes have problems with tolerability of inhaled medications and absorption may be different, we evaluated the efficacy and tolerability of LEVADEX in a subgroup of patients from a large Phase 3 migraine trial (previously reported Silberstein et al 2009) who reported to have concomitant asthma.

Methods Of 792 subjects who treated a migraine headache with Placebo (P) or LEVADEX (L), 80 reported having a diagnosis of asthma (L = 44, P = 36). In this subgroup, we analyzed the key efficacy parameters (2 hr pain relief, photophobia-free, phonophobia-free, and nausea-free), as well as the occurrence of adverse events (AEs), and pre-study and post-study spirometry. P-values were calculated without adjustment for multiple comparisons.

Results For efficacy parameters at 2 hours, the following results were observed in subjects with asthma for L or P. Pain relief: L66% P39% $p = 0.02$, Photophobia free: L48% P25% $p = 0.04$, Phonophobia free: L57% P39% $p = 0.11$, Nausea free: L71% P50% $p = 0.11$. Mean change from baseline in FEV₁ was +60 ml for L and –20 ml for P. 34% of subjects reported AEs: L32% P36%. The most common AEs in the body system were infections and infestations (L16%, P19%). No serious adverse events were reported.

Conclusion In this subgroup analysis, LEVADEX was effective and well-tolerated in subjects with migraine and concomitant asthma. A long term study evaluating safety of LEVADEX in subjects with migraine and concomitant asthma is ongoing.

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Carissa congesta wight: a magical ethnomedicinal plant for migraine

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During survey for ethnomedicinal flora of Bhinga forest range representing north central Tarai forest of UP on May 01, 2010 we met Mr. Tilak Ram Varma, the forest watchman in *Gulra Beet* (Mohakama Rihar) on the bank of Cane River. He told us that 15 years ago when he was nursery gardener and suffering from migraine for last five years. Once he was sitting in the forest and saw number of young lateral branches of the *Carissa congesta* Wight (syn. *C. carandes* Auct.: *C. carandes* L.) plant and spontaneously he reached there and took out four young twigs and chewed. After half an hour he felt some irritation in his nose and immediately sneezed for three or four times. Later on he felt that there is something thread like in his nose. He wanted to remove it. He found about five meters of fine thread coming out of his nose in one stretch. He felt lightness in his head and immediately no pain. Till date he never felt any pain. He told that he has prescribed several people to get rid off from headache and always successful. This thread like substance deposited in head may be the causal reason for pain. He told that the plant is now a magical ethnomedicine for the locality. Further intensive research on biochemical and pharmaceutical study for the same is warranted.

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Migraine recurrence rates: case for standardization of the definition

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Background Many physicians prefer to refer to recurrence rates to assess extended migraine relief. However, recurrence rate endpoints differ widely in definition. Several different definitions are presented below to illustrate variability in these assessments.

Methods Post-hoc analysis of a Phase 3 study comparing LEVADEX™ (orally inhaled DHE) to placebo. Four different previously published recurrence rate definitions were used:

- Numerator: subjects with 2 h pain relief and moderate or severe pain during 2–24 or 2–48 hours. Denominator: subjects with 2 h pain relief.
- Numerator: includes in addition to (a), subjects with pain relief who used rescue medication during 2–24 or 2–48 hours. Denominator: same as (a)
- Numerator: same as (a). Denominator: number of subjects in MITT population
- Numerator: same as (b) Denominator: same as (c).

These same endpoints can be calculated for pain free criteria.

Results Of 903 subjects randomized; 792 subjects treating ≥ 1 attack are included in the efficacy analysis. The recurrence rates for the LEVADEX treatment group during 2–24 h were 6.5%, 22.4%, 3.8%, and 13.2% for definitions a,b,c, and d, respectively. Corresponding rates for the placebo group were 15.3%, 39.4%, 5.3%, and 13.6%, respectively. During 2–48 h, the recurrence rates in the LEVADEX treatment group were 10.3%, 30.2%, 6.1%, and 17.7% and in the placebo group were 18.2%, 41.6%, 6.3%, and 14.4% for definitions a,b,c, and d, respectively.

Conclusion Recurrence rate, often used to assess sustained effects of acute migraine therapies, can vary widely in definition and can be

misleading, depending on the specific one applied. A standardized definition should be developed to make such comparisons easy and more meaningful. In a Phase 3 study, LEVADEX demonstrated low recurrence rates regardless of the definition used.

Conflict of interest Dr. Lipton receives research support from the NIH [PO1 AG03949 (Program Director), PO1AG027734 (Project Leader), RO1AG025119 (Investigator), K23AG030857 (Mentor), K23NS05140901A1 (Mentor), and K23NS47256 (Mentor)], the National Headache Foundation, and the Migraine Research Fund; serves on the editorial boards of *Neurology* and *Cephalalgia* and as senior advisor to Headache, has reviewed for the NIA and NINDS, holds stock options in Neuralie Inc. and Minster Inc; serves as consultant or has received honoraria from: Allergan, Autonomic Technologies, Boston Scientific, Bristol Myers Squibb, Eli Lilly, Endo, GlaxoSmithKline, Minster, Merck, Nautilus Neuroscience, Neuralie, Novartis, and Pfizer.

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Analysis of plasma levels of metalloproteinases in patients with migraine

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Objective The metalloproteinases (MMPs) are involved in neuroinflammation and neurodegenerative disorders. MMP-9 levels are increased in migraine during cortical spreading depression. We analyzed the plasma levels of the most important families of MMPs in patients with migraine.

Material and methods A sample of blood using EDTA tubes was centrifuged at 3500 rpm (4°C) to obtain plasma and it was frozen at -80°C. The quantitative determination of plasma levels of MMPs was performed using Searchlight™ technology (Aushon, Pierce) with the kit Array Matrix Metalloproteinase 9-PLEX (MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, MMP-10, MMP-13, TIMP-1 and TIMP-2). We analyzed the plasma of 80 migraineurs (40 chronic and 40 episodic, with and without aura) interictally and 40 healthy volunteers. Most of the patients with chronic migraine were taking prophylactic drugs, in contrast with episodic migraineurs.

Results Higher plasma levels for MMP-2: 439.3 (264.9-1287.2) vs. 253.72 (223.1-317.8) ng/ml, $p < 0.001$; MMP-3: 6.1 (2.5-9.5) vs. 2.5 (1.8-5.3) ng/ml, $p < 0.05$; MMP-10: 0.6 (0.3-1.2) vs. 0.28 (0.1-0.7) ng/ml, $p < 0.05$; MMP-13: 0.88 (0.43-3.0) vs. 0.43 (0.4-1.6) ng/ml, $p < 0.05$; TIMP-1: 95.85 (57.3-136.7) vs. 59.17 (45.7-66.2) ng/ml, $p < 0.001$; and TIMP-2: 89.14 (64.1-111.6) vs. 59.41 (53.4-71.8) ng/ml, $p < 0.001$ were found in migraineurs versus healthy controls. In these cases, the presence of aura was associated with even higher levels of MMP-3, MMP-10 and TIMP-2 in a statistically significant way. There were no differences between episodic and chronic patients or amongst those taking or not preventative treatment.

Conclusions Levels of gelatinases (MMP-2), stromelysin (MMP-3 and MMP-10) and collagenase (MMP-13) and its inhibitors (TIMP-1 and TIMP-2) were higher in migraineurs, suggesting a dysfunction of the cerebrovascular system that predisposes to the development of neuroinflammation.

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The treatment of parietal headache and atypical facial pain with peripheral nerve field stimulation (PNFS): a clinical case report

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Introduction We report the case of a patient with parietal headache associated to atypical facial neuralgia successfully treated with PNFS.

Clinical case A caucasian 55-year old man affected by serious atypical right facial neuralgia unsuccessfully treated both with drugs and with retrogasserian neurolysis came to our hospital for debilitating facial pain extended to right auricular and parietal area.

Pain did not improve even with high dosage of carbamazepine (1,200 mg/die). The pain was continuous and it expanded from the trigger facial point to the auricular and parietal area with frequent peaks, causing strong crisis that forced the patient to bed.

A Medtronic (Minneapolis, USA) octopolar lead was inserted through a 2 cm-long incision in front of the tragus, directed caudally and medially towards the right labial incisure and placed subcutaneously. During the 45-day period of test stimulation, the patient reported no painful peaks of pain, persistency of continuous but completely tolerable pain (NRS improved from 10 before PNfS to 4 after PNfS) and a reduction in the assumption of carbamazepine (from 1200 mg/die before PNfS to 400 mg/die after PNfS). The patient was then implanted with a Medtronic neurostimulator mod. Synergy Versitrel, placed in the right abdominal subcutaneous pocket.

Conclusion As reported in literature, this case report confirms that PNfS is an effective approach to treat frontal, parietal, cervicogenic and cluster headaches, even when associated to atypical or trigeminal neuralgia refractory to optimal medical therapy.

Keywords Frontal and parietal headache, atypical facial neuralgia, cervicogenic headache, trigeminal neuralgia.

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A case of sporadic hemiplegic migraine with prolonged neurological deficit

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Background Migraine in older age groups has been neglected. In 2-3% of all cases of migraine, the first attack occur at ≥ 50 years of age. The focal deficit in sporadic hemiplegic migraine usually lasts for less than 24hours.

Case report 52 year's female presented with frontal headache which increased in intensity overnight and the next morning, she developed slurring of speech and left sided weakness.

She was diagnosed to have two strokes in last 2 years. She has spinal stimulator device for nerve damage secondary to avulsion.

She has no personal or family history of migraines.

On examination, she had expressive dysphasia and left hemiparesis. CT brain and carotid Doppler were normal. MRI could not be performed due to spinal stimulator device. Echocardiography ruled out cardiac pathology and EEG showed no dysrhythmia. ESR, Serum B12, Folate, TSH, autoimmune and thrombophilia screen was normal. A diagnosis of hemiplegic migraine was made and she was started on topiramate. She made complete recovery in 12 days.

Two weeks after the discharge she presented with stereo typed symptoms. Repeat CT scan was normal. She improved over the next couple of days and was mobile at discharge.

On her follow up visit six weeks later, she described three episodes of severe headache, left sided weakness and expressive dysphasia, each time resolving spontaneously within few hours. She was very clear that each episode was preceded by loud noise. The dose of topiramate was increased.

She is asymptomatic on following visits.

Conclusion The focal deficit in sporadic hemiplegic migraine can last for several days. Good history is, of course, most important in establishing the correct diagnosis, coupled with repeated normal neuroimaging.

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Is there an increased cardiovascular risk in pediatric migraineurs?

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Several studies suggested that the migraine disease in adults increases the risk of cardiovascular events. The aim of our study was to investigate different cardiovascular cytokine levels and lymphocyte populations in the peripheral blood of pediatric migraineurs and healthy controls.

We have investigated 94 migraine patients (M) (age (median, range) 15 [13 - 19] years), 15 hemiplegic migraineurs (HM) (15 [15 - 18] years), 29 migraine with aura (MA) (17 [14 - 18] years) and 50 migraine without aura (MO) 13 [11 - 16] years) patients and 51 controls (C) (16 [10 - 24] years). The prevalence of lymphocyte subsets (CD4, CD8, Th1 (CXCR3), Th2 (CCR4)), regulatory T cells (CD4, CD25, CD127), iNKT, NKT and NK cells (CD3, CD161, 6B11) and the plasma levels of sCD40L, t-PA, MCP-1, IL-8, sP-selectin, sVCAM-1 were measured by flow cytometry method in the peripheral blood of the migraineurs during the interictal phase.

The prevalence of the CD8 cells were decreased in all migraine subtypes compared with controls. The plasma level of the cardiovascular risk cytokine sCD40L showed an increase in the M and HM groups compared with controls and in the HM subtype vs MO. The plasma level of the t-PA was higher in the M, MO and HM groups than in the controls. The sVCAM-1 concentration was elevated in all migraine subtypes compared with controls and showed higher level in the HM group than in the MO patients.

Recent studies proved that the migration of CD8 cells plays an important role in the atherogenesis. The decreased prevalence of the CD8 cells in the peripheral blood might be connected to the development of atherosclerotic lesions. The elevated plasma concentrations of the cardiovascular cytokine sCD40L, t-PA and sVCAM might indicate an increased cardiovascular risk in pediatric migraineurs.

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Diagnostic delay and misdiagnosis of cluster headache

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Objectives Cluster headache (CH) diagnostic criteria are clearly defined, as well as therapeutic guidelines, specially those referred to symptomatic treatment. We intend to evaluate the translation of this consensus to the clinical practice.

Methods We retrospectively reviewed the clinical histories' of all patients diagnosed of CH (IHS-II criteria) who had attended in the specialized Headache Unit in "Hospital Central de Asturias" and "Centro Médico de Asturias" in the last ten years. We analyzed several parameters, especially those related to diagnostic and therapeutic aspects.

Results The total number of patients was 106 (94 men and 12 women) with a mean age of 43 (22-74). First-degree familial history of CH was found in 13% of patients. CH was chronic in 16% of patients, while the rest had an episodic form. The mean age of onset was 32 years old (15-63). There was a diagnostic delay between the first symptoms and a well-established diagnosis of 5,3 years. Up to 35% of patients had been initially diagnosed of migraine. Before the consult in our Headache Unit, only 18% of patients had been treated with subcutaneous sumatriptan or intra-nasal triptans during the attacks.

Conclusions It is highly surprising that CH in which clinical features are so eloquent, support such a significant diagnostic delay. It is also striking that many patients who had been correctly diagnosed were receiving completely nonspecific medication while ineffective. It seems necessary to implement the knowledge of this primary headache in those health care levels involved (primary and emergency care, mainly).

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Secondary headache in periodontitis

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Background Headache is a very common disease, symptom with high lifetime prevalence. Often it is difficult to differentiate primary and secondary headaches, especially when main disease's clinical symptoms of is not significant.

Aim It was our aim to describe and classify headaches associated with inflammatory disease of oral cavity, especially with periodontitis. We have notice, that sometimes inflammatory and dystrophic diseases of oral cavity have poor clinical symptoms and they are not diagnosed. In spite of types of headaches such as migraine, cluster etc, headache associated with periodontitis is secondary headache.

Objective/methods 83 patients were observed (39 M/44F, age range 14-45 years) to have several types of headaches associated with periodontitis. Periodontitis was diagnosed primarily by detailed clinical observations. Mild form of periodontitis was diagnosed in 13 cases, moderate in 21 and severe form in 51 cases. Moreover, 55 patients had other neurological syndromes like hypothalamic(37) and brain stem syndrome (18). Periodontitis in those patients was diagnosed several years earlier. 13 patient had acute form of periodontitis, 21 patients had chronic form and 49 patients - chronic form with aggravation. Patients had different types of headaches: 24 patients had trigeminal neuralgia, tension headache - 39, migraine 9, paroxysmal hemicranias 5, cluster headache 16. In some cases patients had several types of headache. 35 patients had been treated as patients with primary headache, until periodontitis was diagnosed. There was statistically significant correlation between effective treatment of parodontitis and improvement of headache.

Conclusions

1. Periodontitis might be associated with several types of headaches.
2. Patients with headache also need dentist consultation.
3. Oral cavity sanitation is necessary to prevent some aggravations

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Migraine in adolescent females

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Background Migraine occurs in 3 to 10% of children and adolescents and causes a considerable impact on quality of life. There is little difference between gender before puberty. After age of 11 there is predominance in females. There are epidemiological studies confirming the correlation between migraine and menarche. Severe headaches associated with menstruation are often not recognized as migraine. Sometimes menstrual migraine is correlated with dysmenorrhea. At the same prolactin is a main factor which defines normal function of ovary.

Aim

- (1) to distinguish correlation between migraine and a level of prolactin in adolescent girls;
- (2) to provide some recommendations for relevant treatment.

Methods We observed 65 outpatient females (aged from 10 to 16 years) with menstrual migraine. 45% of them had their first headache during menarche. 55% of patients had dysmenorrhea. Patients productivity was reduced by half or more from 1 to 6 days in a month due to headache. Only 7 patients had severe headaches with visual disturbances. Others had migraine without aura.

Results We determined level of prolactin in all cases. Level of prolactin was normal in 13 patients, while in others it was increased. 35% of patients had genetic risk factors - mothers or/and grandmothers had migraines also. Lifestyle modification and prevention of trigger factors was sufficient in 26 % of patients. 45 patients with high level of prolactin received: I group- dopamine agonists in addition to migraine therapy, II group only migraine therapy and III group - only dopamine agonist. There was statistically significant correlation between decrease in prolactin level and improvement of headache.

Conclusion Management of migraine in adolescent females requires to determine prolactin level. Lifestyle modification and pathogenic treatment is recommended.

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Improvement of migraine headache after transcatheter closure of patent foramen ovale in cryptogenic stroke patients

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Background Patent foramen ovale (PFO) is considered a cause of migraine headache (MHA) in young patients (pts). The prevalence of MHA is higher in cryptogenic stroke patients with PFO than in the general population. The reason of such a dependence is still unclear. The goal of this study was to analyze the effect of percutaneous closure of PFO on MHA in patients with neurological events.

Methods 149 pts at a mean age of 38 +/- 12 years underwent catheter closure of their PFO for prevention of recurrent cryptogenic stroke or TIA. 50 pts had ischemic stroke, 81 pts had TIA and 18 pts had ≥1 neurological events. A one year analysis of migraine symptoms before and after PFO closure were performed at 62 patients (46 pts with MHA with aura). Migraine severity was assessed before PFO closure and next 6 and 12 month after PFO closure -number, intensity, duration of episodes, The Migraine Disability Assessment Test (MIDAS), migraine severity scale.

Results MHA was completely abolished in 14 pts (22,5%) after 6 months and in 24 pts (38,7%) after 12 months. At the end of follow up period a significant reduction of duration, number and intensity of MHA and decrease points in the MIDAS and migraine severity scale was observed (p<0,001).

Conclusions Transcatheter closure of PFO can result in complete resolution or marked reduction in number, intensity and duration of MHA.

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Association between migraine and sleep apnea in the general population

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Objective To investigate the relationship between migraine and obstructive sleep apnea in the general population.

Method A cross-sectional population based study. A random age and gender stratified sample of 40,000 persons aged 20-80 years residing in Akershus, Hedmark or Oppland County, Norway were drawn by the National Population Register. A postal questionnaire containing the Berlin Questionnaire was used to classify respondents to be of either high or low risk of obstructive sleep apnea. 376 persons with high risk and 157 persons with low risk of sleep apnea aged 30-65 years were included for further investigations. They underwent an extensive clinical interview, a physical and a neurological examination by physicians, and in-hospital polysomnography. Those with apnea hypopnoea index (AHI) ≥ 5 were classified with obstructive sleep apnea. Migraine without aura (MO) and migraine with aura (MA) was diagnosed according to the International Classification of Headache Disorders.

Results MO and MA occurred in 12.5% and 6.8% of the participants with obstructive sleep apnea. The logistic regression analyses showed no relationship between the two types of migraine and obstructive sleep apnea, with adjusted odds ratios for MO 1.15 (0.65-2.06) and MA 1.15 (0.95-2.39). Further, estimates using cutoff

of moderate ($AHI \geq 15$) and severe ($AHI \geq 30$) obstructive sleep apnea, did not reveal any significant relationship between migraine and the AHI.

Conclusions Migraine and obstructive sleep apnea are unrelated in the general population.

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Development and validation of a cognitive impairment scale for migraine attacks - the MIG-COG

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Background The burden of migraine, both to the individual and to society, is determined by the ability to function during attacks. Impairment during attacks is caused not only by pain, but also by associated migraine symptoms, such as cognitive dysfunction.

Objective To develop a self-administered questionnaire for measuring cognitive impairment during migraine attacks.

Methods Item generation was patient-centered and optimized by a panel of experts. The initial questionnaire, based on 43 candidate items, was administered to consecutive migraine patients. Item reduction used exclusion of items with high non-responder rates and factor analysis. Convergent and construct validity was assessed by correlation with the number of spontaneous cognitive complaints and with the scores of the 43-item and Cognitive Failures Questionnaires.

Results Ninety-three patients were included (86 females), with mean age of 39 years, mean disease duration of 18 years. The reduced 9-item questionnaire identified two domains - executive functions and language, taking 1 minute to complete. Cronbach's α was 0,83. Its scoring correlated with the number of spontaneous cognitive complaints ($p < 0,001$), with the 43-item ($p < 0,001$) and the Cognitive Failures Questionnaires ($p < 0,01$). Its scoring is not influenced by gender, age, disease duration, aura, attack frequency, duration and intensity, nor current migraine prophylaxis. Test-retest Cohen's kappa was 0.55.

Conclusions MigCog questionnaire is a valid, reliable, consistent and fast self-application tool than can be used in clinical practice and in research settings. It profiles and quantifies cognitive difficulties during attacks, providing a measure of another dimension of the migraine burden and eventually, of the efficacy of acute treatment on cognitive dysfunction during attacks. It also offers patients a quantifiable way to illustrate ill-characterized, but disabling symptoms to their attending physicians.

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Comorbidity of migraine with symptoms of anxiety and depression in adolescents: a review of the literature

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Purpose of this paper is to review the prevalence and magnitude of anxiety and depression among adolescents with migraine.

Publications in the area of adolescent migraine related to anxiety and depression were identified by Medline (1966–2009), PubMed (1991–2009) and PsychInfo (1967–2009). 19 studies were identified. Mean levels of anxiety and depression symptoms as reported by the adolescent or their parent/ caregiver were modestly elevated relative to established norms or healthy controls (12 of 19 studies), but below established cutoffs for diagnosis of a DSM-IV mood or anxiety disorder. These modest elevations in symptom reports were reported in both clinical samples and in random samples from school populations. Such elevations in symptom reports are consistent with either (or both):

- affective distress in healthy adolescents that results from living with migraine, or
- an elevated prevalence of DSM-IV mood and/or anxiety disorders in adolescents with migraine.

However, inadequate diagnostic information was available from studies of school samples to know if this finding generalized beyond the clinic. In clinical samples, some evidence suggests that hypothesis (b) is an important factor, with some studies reporting 25% or more of their headache participants receiving a mood or anxiety disorder diagnosis based on clinical interview or established cut off scores on standardized tests (5 studies).

The existing literature allows only tentative conclusions about the association of anxiety or mood disorders with adolescent migraine. Conclusions are limited by small samples, the practice of reporting data only for combined samples of adolescents and young children, and for migraine and other headache types, use of diagnostic procedures of uncertain validity for identifying migraine and for diagnosing mood and anxiety disorders, and the lack of true population data. Additional research that employs population sampling, reliable diagnostics and targets exclusively adolescents with migraine is needed.

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Impact of migraine characteristics and psychological variables on health related quality of life among adolescents with migraine

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The following study aims to estimate how migraine characteristics (frequency and severity of migraines and associated symptoms of migraines) and psychological variables (symptoms of anxiety and depression and catastrophizing) affect health related quality of life of adolescents.

A sample of 62 adolescents aged 12 to 17 years (44 female; mean age = 14.3), averaging 1 to 14 (mean = 4) migraines (ICHD-2 criteria) and 1 to 22 migraine days (mean = 5.6) per 30 days was obtained from two outpatient headache clinics in Columbus, OH. Migraine frequency and severity and the severity of the associated symptoms of migraine were obtained through 4-week electronic headache diary. Symptoms of anxiety and depression were measured by the Internalizing scale on the Youth Self Report. Catastrophizing was measured through the Pain Catastrophizing scale. Quality of Life was measured through the Migraine Specific Quality of Life-Adolescent Form (MSQL-A). Poorer quality of life was associated with a greater number of migraine episodes per 30 days ($r = .34$, $p < .01$), greater migraine severity ($r = .28$, $p < .03$) and associated symptom

severity ($r = .34$, $p < .01$). Poorer quality of life was also associated with greater catastrophizing in response to pain ($r = .3$; $P < .02$). Migraine severity and associated symptoms were highly correlated ($r = .82$, $P < .01$). Regression analysis revealed that either migraine severity alone or migraine associated symptoms alone accounted for the observed migraine-related impairments quality of life. Although the independent variance in quality of life accounted for by catastrophizing was not statistically significant this may reflect the relatively small sample size. Both migraine characteristics and psychological variables were associated with impairments in quality of life in adolescents with migraine. However, we could not demonstrate that psychological variables were associated with significant variance in quality of life that was independent of variance accounted for by migraine severity or severity of migraine associated symptoms.

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Neonatal capsaicin treatment inhibits inflammatory soup induced release of calcitonin gene-related peptidex

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Calcitonin gene-related peptide (CGRP) is released during the activation of the trigeminal nerve system and centrally modulates neuronal activity in the trigeminal nucleus caudalis (TNC). Clinical studies indicate that CGRP is released during a spontaneous migraine attack. CGRP receptor antagonists are effective for the acute treatment of migraine.

Sensitization, the pathophysiological correlate of cutaneous allodynia, probably influences the efficacy of triptans. In experimental migraine models trigeminal sensitization can be induced with inflammatory soup (IS). We recently demonstrated a possible link between trigeminal sensitization and CGRP. We hypothesize that CGRP release by IS administration originates in the peripheral and central parts of the trigeminal system.

In Sprague-Dawley rats flexible catheters were placed in the cisterna magna and the jugular vein for blood sample collection. IS was injected into the cisterna magna and blood samples or CSF were collected for analysis of CGRP concentration. To demonstrate the trigeminal origin of the IS-induced CGRP release a second group of animals received neonatal subcutaneous capsaicin treatment to destroy trigeminal c-fibers. To further investigate the origin of the CGRP release RT-PCR for CGRP-mRNA of the trigeminal ganglion and the TNC was performed in both groups.

Our results show, that neonatal capsaicin treatment leads to a striking inhibition of IS-induced CGRP release in plasma and in CSF indicating that CGRP release originates from the trigeminal nerve system. The selective reduction of CGRP mRNA in the trigeminal ganglion but not in the trigeminocervical complex and data from the functional study indicate that peripheral trigeminal neurons significantly contribute to CGRP release. The contribution of central trigeminal neurons to CGRP release is likely as capsaicin treated animals still exhibit higher amount of CGRP release due to IS administration as compared to vehicle studies.

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Electronic headache diary for monitoring headaches: better than the paper one?

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Patients suffering from headache usually are asked to fill in regularly monitoring charts for their disease. These diaries become crucial in the diagnosis and management of headache disorders because provide further information concerning the frequency and the temporal pattern of attacks, the drug intake, the trigger factor, and the response to the treatment.

Objective To compare an electronic version of the headache paper diary used in our Clinic in a group of headache in-patients with medication overuse headache (MOH).

Methods 85 hospitalized MOH patients received an user-friendly electronic headache diary (Palm devise) developed according the ICHD-II criteria. Our electronic diary was structured as a calendar in which the dates were already printed. For each headache day, the patient was required to note sleep time (hours), presence of aura symptoms, time of pain onset and its features (intensity, side, type, presence of associated symptoms). An further section of the diary investigated intake of painkillers (the type of drug, the time of intake and the total number of doses taken during the 24 hours). When discharged, patients were asked to compare the two versions of the diary, through a numerical Rating Scale.

Results Our patients responded very well to the electronic headache diary (easy to understand, easy to fill in) and the patients’s level of compliance was good. Most of the patients considered the Palm device handier than the traditional paper version.

Conclusions These preliminary data show that the electronic version could be a really practical and helpful instrument for clinical headache monitoring. Paper diaries are easy to employ, but electronic diaries, programmed into a pocket computer, could be preferable and should be employed if possible. A forthcoming step in the improvement of headache management will be to set up and release an ad hoc software for palm device, smartphone and PC.

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Do travels and holidays worsen migraine?

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Background and aims Some patients complain about worsening of their migraine in trips and holidays. **Aims** To characterize the patients

and factors related to the appearance of migraine in trips and vacations.

Methods Eighty nine consecutive patients diagnosed of migraine with and without aura were studied. We analyzed demographic variables, frequency and intensity of attacks, history of anxiety, depression and stress. A structured questionnaire was supplied to evaluate if during holidays, weekends and trips there were changes in frequency or intensity of the migraine attacks, recognized triggers and motion sickness.

Results Migraine impairs with travels in 34 (38.6%) patients ($p < 0,01$) - in 29.5% increases frequency and 21.6% intensity - while 37.5% of migraineurs worsens on weekends ($p < 0,01$) and only 26.1% on holidays ($p = \text{NS}$). Patients related their attacks with travelling by car (41.6%), and plane (24.7%), and with the hot (25.9%) and windy (19.1%) destinations. Stress (59.1%), sleep changes (42%), sun exposure (31.8%) and bad positions during travel (28.4%) were considered triggers of travel headaches. 37 migraineurs (41.6%) suffer motion sickness and 34.1% have been unable to treat some attacks during trips. Travel migraine was related to older age ($p = 0,023$) and travel stress ($p = 0,024$) that increases the frequency of headaches ($p < 0,001$).

Conclusions An important proportion of migraineurs worsens their migraine during trips or suffers motion sickness. The travel induced stress is important for the impairment of migraine in trips.

Conflict of interest In reference to abstract No.493, the work was supported by a Merck research grant.

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Sinonasal computed tomographic findings in migraine: clinicopathological correlation

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Introduction Migraine is often misdiagnosed as sinus headache either by the patient or primary care physician. Computed tomography is the most widely used modality for diagnosis of sinus headache. However, several studies have emphasized the prevalence of incidental radiological abnormalities in asymptomatic individuals. The aim of this study is to analyze the computed tomographic sinonasal abnormalities in patients with migraine who were previously misdiagnosed as sinus headache with special emphasis to the clinicopathological correlation between such abnormalities and migraine.

Material and methods A retrospective review of the medical records of patients who met the IHS criteria of migraine and who were previously misdiagnosed as sinus headache was undertaken. Only patients who underwent computed tomographic imaging were included in the study. CT scans were assessed for sinus abnormalities using the Lund-Mackay score. Other evaluated findings included septal abnormalities and pneumatization of the middle or superior turbinate.

Results Two hundred and four patients were included in the study. Sinonasal radiological abnormalities were detected in 116 patients (57%). Septal abnormalities included septal deviation (31 patients) and septal impaction (23 patients). Concha bullosa of the middle or superior turbinate was reported in 29 patients. Lund-Mackay score was ≤ 5 in 49 patients and ≥ 5 in 22 patients. The correlation between the sidedness of headache and intranasal pathology was only statistically significant in patients with septal impaction and in those with concha bullosa with proven contact with the nasal septum. The effect of medical or surgical treatment of intranasal pathological conditions on the severity and frequency of migraine was analyzed.

Conclusions Sinonasal abnormalities are common in patients with migraine. However, precise correlation between the clinical presentation and radiological findings is important to select those patients with possible intranasal triggering factors for migraine that might be corrected by medical or surgical treatment.

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Differential effects of selective PDE5 inhibitors in rat cerebral arteries in vitro and in vivo

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Sildenafil and tadalafil inhibit the cGMP degrading enzyme phosphodiesterase type 5 (PDE5) and are implicated in migraine pathophysiology as well as stroke recovery. In humans, PDE5 inhibitors do not dilate cerebral arteries or change cerebrovascular reactivity. Such findings may, however, relate to technical difficulties of measuring artery changes in human. We investigated the vascular response to selective PDE5 inhibitors in rat middle cerebral arteries in vitro and meningeal arteries in vivo.

Rat middle cerebral arteries were investigated using pressurised arteriography, applying UK 114-542, sildenafil and tadalafil either intraluminally or extraluminally. Effects of sildenafil and tadalafil on dural arteries were investigated in a closed cranial window model. Abluminal sildenafil induced dilatation at concentrations above 0.1 μM (pEC_{50} , 6.62 ± 0.09 and Emax 40.32 ± 7.65) ($n = 5$). UK 114542 was slightly more potent ($n = 6$). Abluminal tadalafil ($n = 5$) showed no dilatatory effect. When applied luminally all PDE5 inhibitors elicited a minor contraction of 4-10 % at high concentrations ($n = 5$). In vivo sildenafil dilated dural arteries concomitant to a significant reduction of blood pressure in a dose dependent manner (0.5 to 3 mg/kg), with 1 mg/kg inducing 60 ± 14 % dilatation ($n = 6$). Tadalafil failed to elicit significant dilatations in vivo.

In conclusion, only when applied abuminally in concentrations where unspecific effects may prevail, did sildenafil, but not tadalafil, induce dilatation. Further, in meningeal arteries sildenafil induced dilatation above normal therapeutic range. Thus, the current results do not support a vasodilatory origin of the PDE5 inhibitor induced headache; although a relation to cerebral artery sensory signalling cannot be ruled out.

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Tolosa hunt syndrome - clinical case

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Tolosa Hunt syndrome consists of retro or unilateral periorbital pain associated with ophthalmoparesis of the III, IV or VI cranial nerves with pain relief after corticotherapy.

It is a diagnosis of exclusion.

The authors present the following clinical case: a 56 year old woman with hypertension, depressive syndrome, right facial nerve paralysis three years ago and left facial nerve paralysis two years ago. The patient was observed in the emergency room due to right periorbital and supraciliary pain associated with ipsilateral diplopia and ptosis with four days of evolution. The neurological exam showed incomplete paralysis of the III right cranial nerve: ptosis, medial rectus palsy, left looking diplopia with pupil constriction and dilation preserved. Magnetic resonance imaging identified asymmetric cavernous sinus, with right cavernous sinus signal enhancement after contrast, traducing an inflammatory process.

The blood and CSF tests were normal.

Treatment with 1 mg/Kg/day of prednisolone was initiated with pain remission after 48 hours.

After six months the magnetic resonance imaging showed resolution of the inflammatory process.

After analytical and imagiological studies, the excellent response to the beginning of corticotherapy and exclusion of other differential diagnosis, Tolosa Hunt syndrome diagnosis was established.

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Thunderclap headache secondary to acute sphenoid sinusitis

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We describe a 25 year old pregnant female with a thunderclap headache. She had no previous headache history. She did not have, nor develop, any focal neurological signs. Computerised Tomography of her Head identified an air-fluid level in the Sphenoid Sinus, in keeping with Acute Sphenoid Sinusitis. A light-protected sample of her Cerebrospinal Fluid did not show any blood breakdown products, nor any evidence of infection. Her sinusitis was successfully treated with intravenous antibiotics and intra-nasal decongestants. Acute Sphenoid Sinusitis is not recognised to present with abrupt onset severe headache in the absence of localising neurologic signs. Acute Sphenoid Sinusitis should now be considered in the differential diagnosis of thunderclap headache. Clinicians should be aware of the need to review images of the paranasal sinuses in presentations of thunderclap headache.

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Comoestas project: preliminary data on the usefulness of an informatic tool in the management of medication overuse headache

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COMOESTAS is an e-health project funded by the European Commission and conceived with the aim of offering an innovative approach for the management of Medication Overuse Headache (MOH), a chronic and disabling disease.

The core of the project is an informatic tool, called Interactive Electronic Patient’s Record (IEPR). IEPR is an “all-in-one” system that integrates people involved in the network through an electronic patient’s data record (for defining the diagnosis, the process of detoxification and the subsequent therapy), an electronic headache diary (filled in by the patient, that allows constant monitoring of clinical condition) and an advanced Alerting and Decision Support System (that supports physician in managing the therapy and in controlling relevant events impacting on patient safety). The clinical study is divided in two sections: the traditional approach, based on the classic management of MOH, and the approach of the COMOESTAS system (i.e. IEPR approach).

Patient’s enrolment in the traditional arm has been completed in all centers involved (Copenhagen, Essen, Valencia, Buenos Aires e Santiago del Chile), for a total of 389 patients included, and 57.3% of them completed the study, after 6 months from the detoxification.

An interim analysis of the classic arm data shows an initial high level of compliance that decreased during the follow-up period (especially in Latin America countries), but also a good percentage of patient’s satisfaction with the headache pattern after the detoxification and with the management of the disease (62.7% and 79.6%, respectively).

Presently 149 patients were included in the IEPR arm and they are completing the study. A very preliminary analysis shows that the constant monitoring based on the electronic diary and the alert-system of the COMOESTAS strategy permits a further improvement of the management of these patients, through a better interaction between patient and physician.

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Use of cannabis among cluster headache sufferers: frequency and effect on attacks

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Objectives To describe the frequency of cannabis use in a group of cluster headache (CH) sufferers and to determine the effect observed by users of this drug on the CH attacks.

Background Cluster headache attacks are severe and may not respond to sumatriptan or oxygenotherapy. Cannabis contains delta-

tetrahydrocannabinol, an agonist of cannabinoid receptors, which have antinociceptive properties and effects on the cerebral arteries. CH patients are heavy smokers, and there is no data about cannabis use in this population.

Methods We obtained questionnaires from CH patients in two specialized headache centers to document the frequency of cannabis use and observed effect on CH attacks according to users.

Results Among 139 patients (116 men and 23 women), 103 (74%) were active tobacco smokers, 63 (46%) had a history of cannabis use, and 27 patients (19% of the total cohort) had tried cannabis for CH attacks. The male to female sex-ratio was 5 in the cohort, and 15 in cannabis users. Among cannabis users, 25,9% had found some efficacy of cannabis, 51,8% claimed that the effect was variable or uncertain, and 22,3% saw a negative effect. During an active period, 43% of users tended to avoid cannabis, and 27% found that cannabis could trigger attacks.

Conclusions Cannabis use in CH patients is frequent, especially in men, and has legal implications, lifestyle repercussions, and potential cerebro-vascular risks. The therapeutic potential of cannabis for CH is to be considered on a scientific basis, but mixed results observed by patients suggest that structured trials with synthetic, selective cannabinoids should be the way to investigate this topic further.

Conflict of interest Dr. Donnet has perceived personal compensation for activities (consulting, clinical research) with Almirall SAS, Merck, Pfizer Inc.

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Twenty years of mid-face cluster headache diagnosed as “TMJ”

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Headache is one of the more common medical complaints and a frequent reason to consult general practitioners as well as headache specialists. Facial pain to the mid-face most commonly would be referred to otolaryngology while mid-face and lower third of face pain may be more frequently dealt with dentists. Complex facial pain may require multiple specialists for best care practices and to eliminate diagnostic entities according to area of expertise.

A 52 year-old male presents to a university-based facial pain clinic with a twenty-plus year history of “TMJ” disorder. He describes a severe and lancinating pain to the left mid-face clearly outlining the temporomandibular joint. History is noted for multiple medication trials of anti-inflammatories. He understood after consulting multiple providers including general physician, otolaryngology, neurology and multiple dental specialists including maxillofacial surgery and oral medicine that his temporomandibular joint pain required splint or oral appliance therapy. On more in depth history and interview he notes unilateral jaw pain with jaw function as well as at random. He endorses unilateral tearing of the eye combined with sensitivity to sounds when severe left-sided jaw pain is present.

Complicating factors include a bilateral disc displacement with reduction along the temporomandibular joints which is in fact not associated with pain. The history was challenged by language barrier between patient and multiple health care providers. He was able to outline specifically the temporomandibular joint as the region of pain however the site was not the source of pain.

This gentleman’s severe, unilateral pain associated with tearing of the eye and phonophobia, associated with benign jaw joint clicking sounds, jaw pain with function and labelled as a TMJ disorder with poor outcomes for twenty years ultimately found benefit from well established treatment algorithms for cluster headache.

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Acid-sensing ion channel 1- A potential site of action of amiloride in migraine with aura

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Amiloride, a common diuretic, blocks all epithelial sodium channels (ENaC) and has been shown to be effective in attenuating trigemino-vascular activation in animal models of migraine including blockade of cortical spreading depression (CSD), the experimental correlate of aura. Open label clinical experience suggests amiloride may be useful in migraine with prolonged aura. We aimed to study the potential actions of amiloride on a subtype of ENaC, the acid-sensing ion channel 1 (ASIC1), blockade of which reduces the occurrence of CSD in animal models. Eight male ASIC1 knockout mice raised on a C57BL/6 J background and 10 wild type age-matched controls were anesthetized with sodium pentobarbitone (80 mgkg⁻¹). Mice were cannulated for administration of test compounds and cortical steady state DC potentials were recorded to identify waves of spreading depolarization. Further anesthesia was maintained with isoflurane inhalation (1.5-2.5%) in oxygen-enriched air. Following a mechanically induced CSD at baseline conditions, amiloride was then administered (20 mgkg⁻¹ iv), followed by CSD initiation at 15 minutes and every twenty minutes onwards. Amiloride blocked CSD in 6 of 10 wild type mice. At the same dose amiloride failed to block CSD in 7 of 8 ASIC1 knockout mice. The study demonstrates that part of amiloride’s pharmacology includes interactions with the ASIC1 channel, which may contribute to the induction of CSD. Targeting ASIC1 channels might prove essential in treating migraine aura.

Conflict of interest Oliver Summ received a fellowship by the European Federation of Neurological Societies and fellowship by MSD.

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Prevalence and clinical characteristics of primary headaches among school children in South Korea: a nation-wide survey

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Purpose To determine the 1 year prevalence of headache and clinical characteristics of primary headaches among school children in South Korea.

Methods We conducted a cross-sectional school-based study of a randomized and proportional sample of 5,360 male and female students. The questionnaire collect demographic data, in addition to specific questions about headache according to International Classification of Headache Disorder II (ICHD-II) criteria. Valid questionnaires were returned by 94.1% of the sample. Modified criteria changed the item 'duration' in migraine (>1 hour instead of 4 hours).

Results The total sample size was 5,039 children aged 7-18 years. The overall 1 year prevalence of recurrent headache was 29.1% (boys 24.4%, girls 33.3%). Mean age for children complaining of headache (14.02 ± 3.03 yrs) was significantly higher than that of those without headache (12.73 ± 3.36 yrs). Migraine was 8.7% (boys 7.0%, girls 10.3%), 13.7% in tension type headache (TTH) (boys 10.7%, girls 16.3%), and 6.7% in non specific headache. Chronic daily headache was 3.1%. The prevalence of headache according to the age was 20.8% in 6-12 years, 32.0% in 13-15 years, and 38.2% in 16-18 years.

Conclusions Recurrent primary headache is quite prevalent among school-aged children and adolescents in South Korea, and the prevalence rates are similar to those reported elsewhere. TTH was more common than migraine. The prevalence of migraine headache increased with age. Students with headache in city and suburban were significantly higher than in rural.

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Genetic and phenotypic analysis of migraine

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Although common migraine is highly prevalent in our society, its aetiology remains relatively obscure and there are no laboratory based diagnostic tests that identify those who suffer from the disorder. Twin studies indicate that migraine has a significant genetic component, with heritability estimates of 33-65%. Therefore, in an effort to identify the molecular mechanisms underlying the disorder, we have performed a genome-wide association (GWA) study of migraine in a large homogenous sample of Australian twin families.

Analysis of the Australian Twin Migraine (ATM) GWA cohort encompassing 1851 unrelated cases and 4008 unrelated controls revealed one genome-wide significant association [odds ratio (OR) = 1.28; $P = 1.9 \times 10^{-8}$]. A sibling-TDT ('S-TDT') analysis utilising 739 (of the 1851) cases whom had a non-migraine sibling, confirmed association to this locus, with an OR of 1.44 ($P = 0.023$). Tantalisingly, the genome-wide significant variant is in a gene with Na⁺/K⁺ transporting activity and whose protein is known to interact with the protein of one of the three identified familial hemiplegic migraine (FHM) genes.

Extending our 'unrelated' GWA analyses to include 665 affected siblings of the unrelated cases and 865 non-migraine siblings of the unrelated controls identified additional loci significantly associated with migraine.

In addition to results from our ATM GWA study, we present results from additional replication studies in independent cohorts and detailed examination of the relationship between associated variants and migraine symptomatology.

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Long term use of botox (onabotulinum toxin a) for the prophylaxis of migraine in clinical practice in Switzerland

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Aims Botox (onabotulinum-toxin A) has been applied against migraine for approximately 10 years, strictly off label. However, several headache specialists have used botox against migraines. Here we present migraine botox data of 529 patients in the long term course.

Methods Retrospective data analysis of patients treated with botox for migraine in a tertiary care headache center Zurich, Switzerland. Demographics, efficacy and tolerability were analysed.

Results 418 women and 111 male patients received botox against migraine from 2002 to 2009, mainly 100 Units of BoTox (Allergan) in a mixed protocol (fixed dose fixed site and follow the pain) to pericranial muscles commonly treated with botox for migraine. Mean age (both sexes) was approx 50 years (bell shaped distribution), i.e. 49.4 years (range 17 to 79) in women and 51.2 in men, (range 17 to 88) with proportionally more younger males and more older women. Distribution of number of treatments per person: 259 once, 111 twice, 51 three times, 34 pts 4 times, 74 pts 5 times and 46 pts 6 to 21 treatments. We considered responders patients who underwent three or more treatments, N = 159, 30.1% of all migraineurs. Gender distribution of responders was 10% male, 90% female, in comparison to 24% male and 76% female in non responders (one to two treatments). Tolerability was overall excellent and only occasionally mild and fully reversible side effects were reported. No factors were found that would predict responders but middle aged women seem to be more susceptible.

Conclusions The current analysis represents the longest yet published data on botox migraine prophylaxis. The response rate of approx. 30% was similar to other experiences worldwide with women around 50 years old found to be overrepresented in comparison to the normal migraine population. Tolerability and safety were excellent. No problems with long term application were observed.

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Comparison of pain detection thresholds in patients with migraine, tension type headache and asymptomatic controls: generalized or peripheral pain sensitization?

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Background Sensitization is a key phenomenon in headache pathophysiology. To determine the presence of sensitization, pain detection thresholds (thermal and pressure stimuli) of patients with migraine

($n = 39$) and tension type headache (TTH, $n = 21$) were compared with those of asymptomatic controls ($n = 50$ for pressure stimuli, $n = 30$ for thermal stimuli). All patients were diagnosed by an experienced neurologist according to the 2004 criteria of the International Headache Society. Patients mean age and Headache Impact Test score (HIT-6) were $33.9 \text{ y.} \pm 11.7$ years and 66.4 ± 5.6 points, respectively.

Pain detection thresholds were assessed by means of the 'method of limits'. All measurements were performed bilaterally, both on cephalic and extracephalic sites. Cephalic sites were the temple and mastoid process, extracephalic sites were the index and anterior tibial muscle (pressure stimuli) or thenar (thermal stimuli).

Results In comparison with asymptomatic controls, both migraine and TTH patients showed lower pain detection thresholds (both for pressure as well as for thermal stimuli) on cephalic sites but not on extra-cephalic sites.

No significant differences in pain detection thresholds were found between patients with migraine and TTH.

Patients with more than 15 headache days per month showed no statistically significant additional lowered pain detection thresholds, although a trend could be observed for migraine patients only.

Conclusions Reduced pain detection threshold on cephalic sites was found in patients with migraine and TTH. This indicates sensitization of polymodal receptors which, from this study, appears to be peripheral rather than central. The trend for an additional lowered pain detection threshold in chronic migraine patients needs clarification in larger patients samples.

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Predictive factors of migraine outcome in postmenopausal women

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Throughout reproductive life cycle, as hormonal levels are changing, many women experience significant headache changes. Although migraine prevalence decreases with advancing age, migraine can either regress or worsen or remain unchanged at menopause.

Up to now, no certain data exist, predicting the illness' outcome after the onset of menopause. The possibility to predict this outcome could be very useful.

In order to find out some other predictive factor about the development of the illness, we studied the course of postmenopausal migraine focalising the attention on the existence of a possible link between the evolution of migraine after menopause and particular features during reproductive life.

367 post-menopausal women (291 natural and 76 surgical menopause) suffering from migraine according to ICHD-II criteria, were studied. They were asked if and how the characteristics of migraine changed after menopause, and different aspects that were thought to be possible predictive factors of the outcome of the illness after menopause

In 48 (16.5%) natural menopause patients migraine improved after menopause, in 243 (83.5%) worsened or remained unchanged.

44 (91.7%) of the 48 patients whose migraine improved after menopause had migraine attacks correlated to the menstruation, while only 174 (71.6%) of the patients whose migraine worsened or remained unchanged had this correlation ($p < 0.05$). The outcome of migraine after menopause in the majority of cases followed the one of the patients' mothers.

On the basis of these data correlation of migraine attacks with menstruation during reproductive life and the improvement of migraine after menopause in the patient's mother seem to predict a migraine improvement after menopause.

Since at present there are little or no data on this particular aspect of the illness, more studies are needed. If these data will be confirmed this will be a very useful indication for many women approaching the menopausal period.

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Genome-wide association study of 5,957 migraine patients and 50,809 controls identifies a variant on 8Q22.1 with potential glutamate regulatory effects

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We report the results of the first genome-wide association study in migraine, with an initial genotyping phase consisting of 2,748 migraine patients and 10,747 population-matched controls from Finland, Germany and the Netherlands. The initial study was followed by a replication study in 3,209 patients and 40,062 similarly matched controls from Iceland, Denmark, Germany and the Netherlands. In the study, we detected the first common variant associated with migraine, with a genome-wide significant p-value of 5.12×10^{-9} , and OR of 1.23 (95% CI 1.150-1.324). Overall meta-analysis showed a p-value of 1.60×10^{-11} . Patients whose attacks are always accompanied by aura showed the strongest effect size (meta-analysis OR 1.29), and patients without aura the least effect sizes (meta-analysis OR 1.12). The frequency of having migraine among carriers of the variant was increased compared to the general population in ten out of eleven replication study samples (differentiated based on country of origin and migraine type), and the association successfully replicated in six. The variant was found to account for 2.5% of total migraine heritability and 10.7% of the population attributable risk of migraine. A follow-up expression quantitative trait linkage (eQTL) showed that the associated variant shows significant correlation to the expression level of a nearby regulatory gene, *MTDH/AEG-1*, which in turn is known to down-regulate levels of EAAT2, the primary glutamate reuptake transporter in the brain. Our hypothesis is that inappropriate down-regulation of EAAT2 causes glutamate build-up in the brain synapses of a migraine patient, leading to a progressively increasing central sensitisation. Overall, we have detected the first gene for common migraine, estimated to account for a moderate portion of the population attributable risk. This finding provides a potential functional explanation for the association, and provides an interesting hypothesis for a new biological mechanism in migraine.

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Psychopathology in children and adolescents with migraine in clinical studies: a systematic review of the literature

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Background In the last decades, numerous population-based and hospital-based studies have demonstrated a relationship between migraine or headache and psychopathology in children.

Objective To describe and assess all clinical studies on the prevalence and manifestations of psychological functioning and psychiatric comorbidity in children with migraine, and to provide recommendations for its diagnosis and treatment.

Methods A literature search was made in Medline, Embase, PsycINFO and the Cochrane database to identify clinical studies that assessed psychological functioning and/or psychiatric comorbidity in children with migraine. Trial quality was assessed trial for quality according to a standardized and validated set of criteria.

Results Seven studies met the inclusion criteria. Evidence assessment was performed using the best-evidence synthesis method of Slavin. Based on this method, we found strong evidence that children with migraine in a clinical setting do not exhibit more withdrawn behaviour, do not have more thought problems, do not have more social problems and do not exhibit more delinquent or aggressive behaviour than healthy children. Furthermore, there is strong evidence that children with migraine have more somatic complaints and exhibit internalizing behaviour which is, given the construct of the outcome measure used, a consequence of the nature of their disease rather than a sign of psychological dysfunctioning. Finally, compared with healthy children, there is limited evidence that children with migraine in a clinical setting are more frequently diagnosed with oppositional defiant disorder and they are not more frequently diagnosed with ADHD, conduct disorder, dysthymia and depression.

Conclusions Based on this review, we conclude that children with migraine at referral to a specialist do not exhibit more psychological dysfunctioning, and (to a lesser extent) do not exhibit more psychiatric comorbidity compared with healthy controls.

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Information to patients with medication overuse headache - pilot study

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Background At the multidisciplinary Headache center specialist nurses provide detailed education to out-patients with Medication Overuse Headache (MOH) in groups of 6-7 patients or individually before a scheduled 2 months detoxification period. Information is needed on the extent of patients' satisfaction with the given information and applicability.

Aim To evaluate the given information in 2 different strategies, the group sessions (STR1) and the individual approach (STR2).

Method 2 questionnaires on relevance and applicability were created and validated. Patients in both strategies answered 10-14 questions to their readiness before the detoxification and to their satisfaction with the detoxification period and the applicability of the information. Fifty-two STR1 patients and 47 STR2 answered the 1st questionnaire. After the detoxification, 32 STR1 and 21 STR2 answered the 2nd questionnaire. Differences from 1st to 2nd were due to drop-outs, lack of attendance or for detoxification still being active.

Results Overall, 96% of all patients expressed to be Satisfied or Very Satisfied with the information, and 4% reported neither/nor. Seventy-nine percent of STR1 and 95% of STR2 expressed that they were Satisfied or Very Satisfied with the detoxification period. So far, 97% of STR1 and 100% of the 21 completed STR2 claimed that they were Satisfied or Very Satisfied with the applicability of the given information.

Conclusions The vast majority of our MOH-patients were Satisfied or Very Satisfied with the given information and applicability. To motivate patients for treatment, clear and thorough information about MOH and the detoxification period is important.

Both Strategies were positively evaluated. Group sessions are suitable and less demanding with regards to resources. Comparative outcome studies for STR1 and STR2 are important for future MOH-treatment.

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What are the chronic primary headache patients want?The biophysicosocial perspective

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Aim Chronic primary headache is very common in population. The previous studies showed there is complex psychobiology interaction in chronic headache. This study describe the wants of chronic daily headache patients.

Method The data was collected using qualitative method. The subjects of this study were all patients with chronic headache (last more than 3 months), neurological normal, and have not ben investigated by suppoting laboratory and radiology examination in our hospital. The author ask a very simple question " what do you wants with your headache?"

Result There were 18 patients meet the criteria, consist of 16 female and 2 male. The mean age was 23,4 years old. Sixteen of 18 patients answered "I want to know whats wrong with my head", "I want to know what is the cause of my headache", "I am worried there is something wrong with my head". All of this patients willing to be CT scanned and EEG recording. The result of CT scan were normal for all of them. Only 12 from 18 patients answered "I want to be cured", "I want to be free from pain medication". "Do normal CT Scan has placebo effect in this group of patients?" There is a strong need for performing further studies.

Conclusion Most of the chronic headache patients want to know the origin of the pain. The searching of the origin can be very costly in some cases. There is a need of further explorative study.

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Significant headache pain reduction after the application of a special neck massage and manipulation technique in primary headache acute attacks

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Introduction Migraines and tension type headaches constitute the main part in primary headache states. These headache types impose a great suffering to the societies health state and their treatment faces a challenge. The application of simple physical non-pharmacological techniques could greatly reduce the therapeutic costs and side effects in acute onsets of these headache states.

Materials and methods Patients with acute onset of a primary headache according to IHS-2004 diagnostic criteria enrolled in the study. Their headache pain intensity assessed primarily using a verbal

10-point pain assessment scale. A special neck massage and manipulation technique was done as shoulder and neck massage and relaxation and a cervical and upper thoracic intervertebral joints cracking. The pain intensity assessed again after the completion of the therapeutic session.

Results Thirty patients with the complaint of a primary headache onset enrolled in the study. Their mean age was 28.23 ± 9.36 years and just one of them was female. Their post-therapeutic mean headache pain intensity was significantly reduced compared to the primary values (1.72 ± 1.28 vs. 5.28 ± 1.78 , $P < 0.0001$, paired t-test). Average pain reduction value was $67.14 \pm 24.36\%$. None of the measured variables including the headache diagnosis associated with the pain reduction value. No side effects were reported and all of the patients were satisfied with the therapeutic method.

Discussion Our study results showed that the applied cervical and upper thoracic massage and manipulation technique could significantly reduce the headache attack pain intensity in patients with primary headaches. The application of this simple manual technique could reduce significantly the headaches attacks burden. On the other hand, these results more corroborate the role for cervical nerve roots in the arousal of headaches.

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The description of relpax medicine's efficiency dependent of time taking

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Migraine is clinically expressed by periodical repeated acute headache, mostly in one hemisphere of head, which is accompanied by nausea, vomiting, badly bearing of light colors and loud voice.

Since 2008-2009 in medical centre of "Grigor Lusavorich" there have been carried complex studies and treatment of patients suffering from different forms of Migraine.

The aim of investigations were the study of Relpax medicine dependent of time taking on the onset of attack. About 50 people between the age of 30 - 50 were examined, from them 30 women and 20 man, who were suffering from paroxysmal headache, according to diagnostic criteria of migraine.

There were included 22 people in the first group, who had the diagnosis of proved migraine and 28 people created the second group, who had mixed types of headaches (Migraine and Headache of tensions). All the patients got Relpax 40 mg. The first group got the medicine on the onset of headache (1-4 hours). The second group got it between 4-8 hours. The comparative analyze of dates observed that positive results were achieved among the patients of first group between 1-1.5 hours after taking the medicine. It was expressed by improved feeling and opportunity to return to daily life. The improvement was observed among 20% of patients in the second group. The repeated taking of the medicine didn't succeed. Later the patients were given Diazepam 2.0 mg intramuscularly to achieve a deep sleep, after which the attack disappeared.

Conclusion Relpax is mostly effective, when it is taken during the first four hours among the patients, who are surely suffering from Migraine. It helps people to return to their daily activity and improves life quality of patients.

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Photic EEG-driving responses are depressed in migraine without aura within a true interictal interval

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Introduction Increased photic driving has been reported in migraineurs between attacks, but it has not been studied specifically in the preictal interval. Neuropsychological abnormalities tend to accumulate before attacks. Photic responses might have been overestimated in migraineurs as most previous studies have included patients in the preictal phase.

Aim To investigate steady state visual evoked EEG-responses (SSVEPs) in migraineurs before, after, during and between attacks with a blinded and controlled design.

Method We recorded SSVEP for 6, 12, 18 and 24 Hz flash stimuli at three random days from 33 migraineurs without aura, 8 migraineurs with aura and 32 controls. Recordings were retrospectively classified as preictal, ictal, postictal or interictal (more than 72 hours from any attack). Interictal responses were compared pairwise with preictal, ictal and postictal responses and with responses from controls.

Results 12 Hz driving power was increased within 72 hours before the attack ($p = 0.02$). However, driving responses to 18 and 24 Hz were attenuated in migraineurs without aura between attacks compared to controls ($p < 0.02$).

Conclusion Medium-frequency photic responses seemed to be depressed rather than increased in migraineurs without aura in a true interictal interval. Earlier studies may have overestimated the response due inclusion of recordings during the preictal interval and/or habituation among controls. Our results indirectly support the hypothesis of hypoexcitable visual cortices in migraine.

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The effectiveness of using the combined therapy of BOTOX® injection and cervical pulsed radiofrequency in the treatment of cervicogenic headache

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Introduction The treatment of cervicogenic headache is considered a challenge for most clinicians, as symptoms can be similar to migraine, due to its anatomic and pathophysiologic complexities. Successful treatment of cervicogenic headache usually requires multi-faceted approach using pharmacologic, interventional procedures, and others.

Objective To evaluate the effectiveness of using the combined therapy of BOTOX® Injection and cervical pulsed radiofrequency (cervical PRF) in the management of cervicogenic headache.

Design In an attempt to evaluate the best management for treating cervicogenic headache, 64 patients were evaluated according to the IHS

Classification of Secondary Headaches, randomly allocated to receive either BOTOX[®] injection alone, cervical PRF alone, or combination of both. The standard dose of BOTOX[®] was 100 units were injected to cervical muscle region, while cervical PRF was applied to cervical facets, settings including temperature: 42°C, pulse count: 480, rate: 2pps, width: 20 ms, and set: 45v were used. Trial was conducted over an 8-month period in the headache clinic at the International Medical Center, KSA. Patients received single treatment of either BOTOX[®] or cervical PRF, or both. Inclusive criteria including 16 males and 59 females, ages ranged were 17-70 with the mean of 44. Exclusive criteria were Pediatric patients or patients older than 70 with uncontrolled diabetes and blood pressure and other neurological deficits. One-third of these patients had associated migraine symptoms as per IHS criteria. Sample showed that cervicogenic headache was three times more prevalent in females and the mean of age of these patients was 45.

Results An average improvement of 55%, 53%, and 65% had been seen in these patients who were treated with BOTOX[®], cervical PRF, or combination, respectively.

Conclusion Patients who received combined therapy of BOTOX[®] and cervical PRF showed more significant improvement compared to the patients who received either BOTOX[®] or cervical pulsed radio-frequency alone.

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Sensory hypersensitivity is associated with increased resting eeg relative power and decreased photic responses in the theta-alpha range

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Background Migraineurs have increased photosensitivity during and between attacks. Sensory stimuli such as bright light or noise frequently trigger migraine attacks in some patients. The origin of photophobia and the mechanisms behind migraine triggers is unknown.

Aim To study if photophobia and trigger sensitivity in relation to resting quantitative EEG (QEEG) and steady state visual evoked responses (SSVEPs).

Method 41 migraineurs were included (8 with aura, 33 without aura). Resting QEEG and occipitoparietal SSVEPs to 6 Hz, 12 Hz, 18 Hz and 24 Hz flash stimuli were recorded in the interictal phase. Spearman's rho was used to correlate relative resting power and SSVEP components with self-reported photophobia (0-2) and trigger sensitivity (0-4; headache triggered or worsened by light, sound, smell and physical activity, each given one point and summed).

Results Trigger sensitivity correlated negatively with 6 Hz and 12 Hz photic driving ($\rho = -0.7$, $p = 0.00005$, $\rho = -0.4$, $p = 0.04$), positively with interictal temporal theta power and frontocentral alpha power ($\rho = 0.4$, $p = 0.05$ and 0.04) and negatively with frontocentral beta and delta power ($\rho = -0.4$, $p = 0.02$, $\rho = -0.03$, $p = 0.05$). Photophobia correlated negatively with 6 Hz driving ($\rho = -0.4$, $p = 0.03$) and positively with theta power in frontocentral and temporal regions ($\rho = 0.4$, $p = 0.02$ and 0.01).

Conclusion Increased sensory hypersensitivity is associated with attenuated photic driving and increased resting activity in the theta-alpha range. Possibly, increased synchronization in thalamocortical connections predisposes towards aberrant sensory processing.

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A study of the neuroimaging profile of patients referred to a specialist headache clinic

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Introduction Referrals to headache clinics may be for the diagnosis or management of patient with headache disorders and there has been an increase in the number of referrals to such clinics in the UK. There has also been a significant increase in the access to neuro-imaging for GPs in the UK. As part of a larger audit of neuroimaging referrals from the outpatient headache clinic based at the regional headache service in the West of Scotland, we looked at the pre-referral neuroimaging profile of patients seen at the headache clinic.

Methods A prospective study was carried out for 4 months between December 2009 and April 2010. A record of the imaging carried out prior to referral to the clinic was kept in addition to details of the study requested, the date of the study and its results.

Results A total of 400 new referrals were seen at the clinic during the 4 month study duration. 180 of the 400 (45%) had imaging carried out before being referred to the clinic. A CT brain was done in 136 (67%), while an MRI brain was carried out in 63 patients (31%). The imaging had been done from between 3 weeks and 18 years prior to referral at the clinic. 35 (19%) patients had scans within the previous 3 months and 92 (51%) had neuroimaging done in the year prior to referral. 143/180 (79%) of the scans were normal whereas 32/180 (17.7%) showed abnormal findings. 42 of the 180 brain scans (23%) were carried out via the open access service available to GPs.

Conclusions A significant proportion of patients referred to our specialist headache outpatient clinic had neuroimaging studies done prior to referral. Open access CT for GPs is necessary but should be in addition to, not instead of, specialist headache services.

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Surgery for sunct headaches

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Short-lasting, unilateral neuralgiform headaches with conjunctival injection and tearing (SUNCT) is a rare primary headache disorder that is often refractory to medical treatment. The role of surgery for treating SUNCT is controversial. There have been a number of case reports of SUNCT in association with vascular compression of the trigeminal nerve which have responded to surgical intervention. We present two patients who have had complete relief of their symptoms for more than one year after microvascular decompression surgery of the trigeminal nerve. Both patients were males in their fifties with several years of intermittent, often provoked, near daily pain. The pain was strictly unilateral, lasted seconds and was associated with both conjunctival tearing and conjunctival injection. They had both tried a number of different medications, including indomethacin and lamotrigine. Both patients were completely headache free within days of surgery. This data, together with previous reports, suggests that surgery may be an option in some SUNCT cases. All patients with a

likely diagnosis of SUNCT should have an MRI brain scan with particular emphasis on the brainstem and trigeminal nerve as part of their evaluation. If there is evidence of a vascular loop adjacent to the trigeminal nerve and they are refractory to medical therapy, then surgical decompression should be considered.

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The effect of riboflavin and vitamin-E on hippocampal NMDA receptors in rats with glyceryl trinitrate-induced headache

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Objective NMDA receptor activation is a potent stimulus with a depolarizing effect and may stimulate the initiation and propagation of cortical spreading depression.

Methods Sixty rats were administered into 4 groups:

- Group I: sham control (saline),
- Group II: Glyceryl trinitrate (GTN) administered,
- Group III: GTN and riboflavine (RBF); and
- Group IV: GTN, riboflavin and vitamin-E group (RBF + E)

Group I and II were given no drugs. Group III was given riboflavin 100 mg/kg/d p.o and Group IV riboflavin 100 mg/kg/d p.o. and 100 mg/kg i.p on alternate days for a ten day course. Twenty-four hours after the last drug treatment, group I infused with saline and the remaining groups with GTN 10 mg/kg i.p. for 3 hours. After slowing of movements and reaction to tail test was observed, rats were decapitated under ketamin HCl (50 mg/kg) and xylacine (5 mg/kg) i.p. anesthesia. Hippocampal NMDA-NR2A and NMDA-NR2B expression levels were measured with SDS-page and western blotting method.

Results Hippocampal NMDA-NR2A levels was significantly higher in GTN administered group ($435 \pm 19\%$) compared to the control group ($100 \pm 19\%$) ($p = 0,005$). NMDA-2A levels were significantly lower in RBF ($218 \pm 99\%$) and RBF + E ($88 \pm 98\%$) groups compared to GTN group (for both $p < 0.05$). Hippocampal NMDA-2B levels were also significantly higher in GTN group ($180 \pm 20\%$) compared to normal ($100 \pm 38\%$), RBF ($95 \pm 30\%$) and RBF + E ($119 \pm 16\%$) groups. Differences was significant only for GTN-control, GTN-RBF and GTN-RBF + E groups ($p < 0.05$).

Conclusion NMDA receptor activation is reported as an important factor for initiation of cortical spreading depression. It has also been reported that cortical spreading depression propagates amygdala rather than hippocampus. Our results may suggest that exogen nitric oxide exposure activates hippocampal NMDA receptors, and riboflavine and vitamin-E may ameliorate its effect.

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Access to care for headache sufferers, data from the european headache alliance questionnaire in three italian headache centres

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Introduction It's known that primary headaches, especially migraine, do not always receive an appropriate diagnosis and that people with headache have to face, a rather frequent, incorrect diagnostic and therapeutic approach.

Methods 214 patients suffering of headache, having first visit at headache centre of Policlinic of Monza, C.Mondino Foundation, Pavia and University of Insubria, Varese filled a ten items questionnaire, conceived by European Headache Alliance, aimed to collect patients' valuations and observations about the level of knowledge of their disease, the use of drugs and the level of satisfaction with the management and treatment of their condition. Forty-one M (19%) and 173 F (81%) completed the questionnaire.

Results The responders suffered of migraine without aura (45.1%), tension type headache (15.5%) and medication overuse headache (9.2%). Twenty four percent of the patients had more than one type of headache, 58% of the patients used to see regularly a specialist (34.1% of them a neurologist, 31.6% headache clinic staff and 29.7% general practitioner); 62% of patients were not satisfied with the management and treatment of their condition. The reasons were: ineffective treatment (64%), insufficient explanation (17%), next appointment too long ahead (14%) and difficulty to reach a specialist (8%). Patients got to know about the existence of headache centre in 41% of cases by medical experts, in 22% by media and in 17% by other people suffering of headache. These results are partially in consort with those collected by the EHA survey in Europe.

Discussion The questionnaire shows that most of headache patients, visited for first in a headache centre, are not satisfied with their therapeutic treatment and only 31.6% of them are followed by a headache specialist. These results may contribute to focus the necessity to improve the access and quality of care and to spread information in a suitably way.

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Phosphorylation of extracellular signal-regulated kinase occurs in trigeminal ganglion neurons by noxious stimuli

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Introduction The activation of the meningeal nociceptors is considered to play an important role in migraine. Expression of phosphorylated extracellular signal-regulated kinase (pERK) in sensory neurons by noxious stimulation is known to contribute to short-term pain hypersensitivity. We have already observed the phosphorylation of ERK in the trigeminal ganglion (TG) after capsaicin application to the dura mater. In this study, using immunohistochemistry, we investigated the temporal profile of phosphorylation of ERK and localization of pERK-immunoreactivity (pERK-IR) in TG. **Methods** In twelve Sprague-Dawley rats, 10 mM capsaicin was applied to the dura mater. After several survival times (the survival

time after capsaicin stimulation: 1, 3, 5 min, n = 3 each group; 3 min after vehicle application as control, n = 3 each group), the TG were removed and processed for immunohistochemistry. The sections were labeled with anti-pERK antibody. To calculate the proportion of pERK-IR neurons, we counted the total number of TG neurons and the number of pERK-IR neurons. For double staining, slides were double-labeled with anti-pERK and anti-NeuN antibody.

Results The proportion of p-ERK-IR cells was 0.6% in the control animals. Following capsaicin administration p-ERK immunoreactivity was detectable in 1.9% of all the cells examined at 1 minute after capsaicin application, 4.2% at 3 minutes and 2.3% at 5 minutes. The proportions of p-ERK-IR neurons at 3 and 5 minutes after capsaicin application significantly differed as compared to the control animals ($p < 0.05$). This temporal profile of phosphorylation of ERK was similar to that of the findings of western blot analysis. The immunoreactivity of p-ERK was restricted to neurons identified as NeuN-IR cells.

Conclusion These findings indicate that we can use the phosphorylation of ERK as an early phase pain conducting maker in novel animal models of migraine headache.

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Reversible cerebral vasoconstriction syndrome - case report

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Introduction Reversible cerebral vasoconstriction syndrome (RCVS) is an entity which is mainly characterized by the association of severe acute headaches with or without additional neurological symptoms and diffuse, multifocal, segmental narrowings involving cerebral arteries. Cortical subarachnoid haemorrhage (cSAH) occurs in 20–22% of cases and incidental cerebral aneurysm was described.

Methods We presented a case of RCVS physical effort induced, associated with cSAH.

Results A 51 years old woman presented a recurrent thunderclap headache (TCH) physical exertion induced. She had a history of COPD, Diabetes, Dyslipidemia. She had no migraine history and she did not use illicit drug. Her usual treatment consisted in Seretide (salmeterol/fluticasone), Spiriva (tiotropium bromide), Perindopril, Duovent (fenoterol/ipratropium), Fenofibratum, Aspirine, Eucreas (metformin/vildagliptin). Clinical examination was normal. The brain computed tomography was normal. Magnetic resonance angiography (MRA) showed abnormal FLAIR high signals in frontal, parietal and occipital region, suggesting cortical subarachnoid haemorrhage. Therefore, a lumbar puncture was performed and showed 26 red blood cells (RBC) with one RBC crenation. Conventional angiography demonstrated a small (1,5 mm) unruptured aneurysm of right internal carotid and multifocal segmental arterial constriction predominant in parietal, occipital et cerebellar left areas. Reversible cerebral vasoconstriction syndrome was suspected and Nimotop treatment was started with clear improvement of headache. A second angiography (one week later) showed a significant diminution of vasospasm and a later control angiography (six weeks) demonstrated the complete disappearance of vasospasm.

Conclusion It is important to recognise cSAH as a complication of RCVS especially in the presence of a cerebral aneurysm. The finding of an unruptured cerebral aneurysm in RCVS patients is incidental.

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Postprandial, but not fasting insulin secretion is augmented in migraine. are migraineurs at high risk for future insulin resistance syndrome?

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Background There's some evidence that glucose metabolism is altered with impaired insulin sensitivity in migraineurs.

Objective To test the relationship between glucose metabolism, migraine attacks in otherwise healthy migraineurs.

Design and methods 64 nonobese- nondiabetic, normotensive episodic migraine(EM) and 33 chronic migraine(CM) patients, 23 healthy volunteers were enrolled (mean ages 33.0 ± 8.6 , 36.8 ± 8.5 and 36.7 ± 8.4 years). Patients weren't on prophylaxis. Total energy and carbohydrate intake was calculated from a dietary questionnaire completed on three consecutive nonheadache days. After 12hr fasting period 75 g five-hour oral glucose tolerance test(OGTT) was performed. Glucose and insulin levels were measured hourly for and areas under the curve(AUC) were calculated. Symptoms related to reactive hypoglycemia during OGTT were recorded. Homeostatic model assessment insulin resistance(HOMA-IR) index was calculated to diagnose IR. None had IR and metabolic syndrome(IRS) according to the ATPIII-criteria and they didn't differ from controls in terms of diabetes risk factors.

Results The groups did not differ in terms of components of metabolic syndrome, as well as HOMA-IR index. In migraineurs, AUC for glucose was significantly higher compared to controls ($p = 0.016$) as well as AUC of insulin ($p = 0.042$). Total energy intake was significantly different between groups with the highest intake in patients with EM, as well as an increased consumption of carbohydrate containing foods with high glycemic index ($p = 0.036$). Despite no biochemically confirmed reactive hypoglycemia, significantly more patients with EM and CM suffered from hypoglycemic symptoms during OGTT compared to controls. These symptoms were not correlated with glucose or insulin levels and headache was not triggered after oral glucose load.

Conclusion EM patients are prone to consume foods with high GI and energy, which may be a risk for future IRS. Besides, insulin response to oral glucose load is more pronounced and postload glucose levels are significantly higher in migraineurs, suggesting an impaired insulin mediated glucose disposal in migraineurs.

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Clinical features and outcome of headache in a sample of juvenile patients attending a tertiary headache centre

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Introduction Recurrent headaches are significant problems in pediatric populations. Positive family history and disease severity seem to increase headache risk for first degree relatives (1). A better knowledge of pediatric headache may help to identify possible factors of disease progression so this study was conducted to analyze headache clinical features and outcome of a sample of young outpatients.

Patients and methods 508 pediatric subjects attending the Headache Centre, Neurological Clinic, University of Bari were enrolled. International Headache Society criteria were used for the diagnosis (2). Control visits were scheduled every 3 months. Data concerning the drop out group were obtained by a telephone interview. The prevalence of the different headache diagnosis, the follow up duration, the outcome of therapies, the drop out prevalence and reasons were evaluated.

Results Migraine without aura was the most frequent diagnosis. Headache onset age was 9.88 ± 3.62 years in the patients with a positive familial history and 12.03 ± 3.62 years in those with negative familial history ($p < 0.001$). Patient's headache onset age was lower than that of their parents. The most frequent drop out reason was headache improvement or remission. A smaller group dropped out because reassured by diagnosis.

Discussion The headache onset age lower than parental one is a further confirm of a genetic predisposition or an increased environmental susceptibility to headache, as stated previously (1). The drop out reasons show that many patients achieve significant improvement or remission. Tertiary headache centres seem to be important for diagnosis, therapy and the educational work since in a not so small percent of patients dropped out because satisfied by the information concerning their health.

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Effect of yoga therapy on migraine: a clinical and cardiac autonomic function study

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Background Migraine is associated with varied clinical manifestations including autonomic symptoms. Yoga is a traditional Indian psycho-philosophical-cultural method that has multiple health benefits and has shown benefits in various pain syndromes possibly due to its influence on vascular tone.

Objective To study the effect of yoga therapy on clinical and cardiac autonomic function in migraine patients.

Methods Ten chronic migraine patients (age 32.6 ± 2.3 yrs; duration of illness 13 ± 2.9 yrs) fulfilling the International classification of headache disorders (ICHD) II criteria, were recruited from the Neurology department, NIMHANS, Bangalore. In addition to the conventional treatment, patients practiced structured yoga therapy consisting *sookshma vyayama* (light exercises), *pranayama* (breathing exercises), *asana* (yogic postures) and *vishranti kriya* (relaxation technique) for 60 min daily for 45 days. Patients were

assessed before and after yoga intervention by headache impact test (HIT), visual analogue scale (VAS) for pain and cardiac autonomic functions by heart rate variability (HRV) measures. Lead II resting ECG was recorded for 15 minutes and analyzed offline. Baseline HRV parameters in migraine patients were compared with 10 age and gender matched healthy controls to assess autonomic dysfunction.

Results The migraine patients had significant autonomic dysfunction at baseline when compared with the healthy controls. Following yoga therapy, patients exhibited significant improvement in clinical parameters (HIT pre 69.6 ± 2.5 , HIT post 39.8 ± 1.7 ; VAS pre 8.6 ± 0.5 VAS post 1.6 ± 0.3). Cardiac autonomic function parameters also improved significantly (LFnu pre 55.6 ± 4.3 , LFnu post 42.2 ± 4.6 ; HFnu pre 37.27 ± 4.55 , HFnu post 51.05 ± 5.93 ; LF/HF ratio pre 2.94 ± 1.57 , LF/HF ratio post 1.43 ± 0.67).

Conclusion Sympathetic overdrive is integral to migraine and is a negative prognostic marker. Our study shows that yoga therapy enhanced the vagal tone in addition to reducing the frequency and intensity of headaches and thus improving the quality of life in migraine patients. Yoga therapy can be effectively incorporated as an add-on therapy in migraine patients.

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Characterization of cardiac autonomic dysfunction in female migraineurs

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Objective To evaluate cardiac autonomic dysfunction in female migraine patients.

Background Migraine is associated with autonomic symptoms. However, the extent of autonomic dysfunction in the inter-ictal period remains controversial. The present study aimed to characterize cardiac autonomic dysfunction in female migraine patients. Heart rate variability (HRV) is a noninvasive test for autonomic function.

Methods Twenty nine female migraine patients (aged 35.2 ± 9.2 years), fulfilling ICHD-II criteria were recruited from the Neurology outpatient department, NIMHANS, Bangalore, India. Resting lead II ECG was recorded for 15 minute during headache free intervals (recording day ± 2 days). An artifact free 5 minute segment of the ECG was analyzed offline to obtain the HRV parameters in time and frequency domain. The data was compared with 44 age matched (36.0 ± 10.1 years) healthy females.

Results The mean heart rate was significantly higher in the migraine patients (78.8 ± 10.4 /min vs 73.4 ± 9.2 /min) than controls. The time domain parameters of HRV were significantly reduced in migraine patients as compared to healthy subjects [standard deviation of normal to normal intervals (SDNN) 31.4 ± 1.8 ms vs 45.2 ± 3.2 ms; root mean square of successive differences of standard deviation (RMSSD) 25.4 ± 2.2 ms vs 38.5 ± 3.8 ms; number of successive NN intervals > 50 ms (NN50) 27.1 ± 8.1 vs 54.1 ± 8.0 ; percentage of number of successive NN intervals > 50 ms (pNN50) 7.6 ± 2.4 vs 17.1 ± 2.8]. The frequency domain parameters were also reduced in migraine patients compared to healthy subjects [Total power (TP) 1023.1 ± 103.9 ms² vs 2181.2 ± 357.3 ms²; low frequency power (LF) 220.8 ± 19.6 ms² vs 467.2 ± 70.7 ms²; high frequency power (HF) 307.6 ± 51.8 ms² vs 771.4 ± 185.0 ms²].

Conclusion Our study demonstrates distinct parasympathetic dysfunction in female migraine patients and supports the hypothesis of a common neural substrate for migraine and autonomic dysfunction. An enhanced understanding of the autonomic dysfunction in migraine may help to diagnose, prevent, and treat migraine

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Vertigo and dizziness: is an associate or a part of primary headache disorders

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The aim of this study is to evaluate the frequency of vestibular symptoms in primary headache sufferers. Totally 5111 patients with primary headache disorders seen from 1999 to 2010 in Mersin University Hospital Department of Neurology were selected. There were 3231 patients with tension type headache (episodic and chronic) and 1880 with migraine type headache which were 4149 females and 962 males were included. Patients' headache characteristics and accompanying symptoms were analyzed. Among migraine sufferers 1560 subjects diagnosed as migraine without aura (MWOA) and 320 patients diagnosed as migraine with aura (MWA). Data base were evaluated for the following symptoms; dizziness, vertigo, motion sickness, periodical vomiting, abdominal pain and headache relation to menstrual cycles. Dizziness and vertigo were significantly high in patients with MWA (50%, 45.2%, respectively). Motion sickness was also found to be significantly high in patients with MWA (51.4% vs 38.6%, $p = 0.007$). Periodical vomiting and abdominal pain were also significantly high in patients with MWA compared to MWOA (9.7% vs 5.5%, $p = 0.001$; 10.9% vs 7.4%, $p = 0.000$, respectively). All of the associates showed similar frequencies in patients with MWOA and episodic TTH. The significantly high frequencies of dizziness and vertigo in patients with MWA in our study are contrary to the previous studies suggesting that both of the symptoms were significantly high in patients with MWOA. It could be discussed whether vertigo and dizziness is a part of aura period or a separate entity. On the other hand, the continuum hypothesis between MWOA and ETTH could also be questioned.

In conclusion, dizziness, vertigo and motion sickness are found to be significantly high in patients with MWA. As far as we know this is the first study evaluating these symptoms in a tertiary primary headache center.

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Headache in children with chronic rheumatic disease

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Objectives To examine the presence of headache frequency and associated psychological profiles in children with chronic rheumatic disease.

Design and methods Patients of 354 children between ages 4 and 16 were recruited from pediatric rheumatology clinic during routine visits. Among them most frequent types juvenile rheumatoid arthritis (JRA) and familial mediterranean fever (FMF) were included to this study. Headache frequency and characteristics have been recruited using semistructured database by headache specialists, in addition to Child Behaviour Checklist (CBCL) for psychological profile. Patients, reported headache were evaluated additionally by drawing pictures of their headaches. All data was consulted with the specialists (art professor, pedagog, child psychiatrist for CBCL, statistician) and required statistical analysis have been made.

Results Mean age of the subjects was 10.5 ± 3.2 years. Among them 45.4% were boys and 54.6% were girls. Rheumatic disorders diagnosis of patients were JRA (104 subjects, 29.3%) and FMF (250 subjects, 70.7%). Headache prevalences were 43.2% in all subjects without an important gender difference (33.6% for JRA and 42.8% for FMF). Most frequent headache type was migraine for both groups. A higher number of parents of these children described headache history. CBCL showed important frequencies of depressive and anxious features in headache sufferers among rheumatic disorders with a high frequency of internalising disturbances supported by drawing headache pictures of the children.

Conclusion It was concluded that apart from secondary causes of headache in subjects with pediatric rheumatic disorders, primary headache disorders is not rare (totally 43.2%) especially in subjects with FMF and using the following describing features (associated nausea, vomiting, photophobia, phonophobia and aggravation by studying) it can differentiate each others. In order to reach best life quality these subjects should be consultate to neurologist and psychiatrist for the best performance and diagnostic procedure include the drawing picture performance in addition to standardised tests.

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Application of bioinformatics in headache: the I2B2-pavia project

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A detailed clinical interview is the basis of a correct diagnosis of headache disorder, particularly of a primary form; indeed, instrumental examinations are required only for the symptomatic forms. All headache disorders are classified according to the International Classification of Headache Disorders, in which there are major groups, each of which is then subdivided one, two or three times into headache types, subtypes and subforms. To support a diagnosis of primary headache, details of pain characteristics, time of onset, and associated symptoms have to be collected; extensive information about family history, comorbidities and biogenetic markers often sheds light on the aetiopathogenic basis of different subforms of

primary headache. However, to analyse all these variables it is essential to use informatics software.

In order to exploit the information available in discharge summaries, we exploited a Natural Language Processing (NLP) system that, after a lexical and syntactical analysis of textual files, is able to extract different types of clinical concepts, like principal diagnosis, comorbidities, therapies, etc. These data are then stored in a database suitable for a further data exploration and analysis. As the framework for processing such reports we implemented an NLP system inspired by the one available within the i2b2 project, with substantial modifications and extensions to cope with the Italian language and with our specific tasks. We have currently analyzed more than 474 discharge summaries. To date, system evaluation has been performed on the principal diagnosis extraction task on the basis of a *gold-standard* provided by the physicians composed of 150 documents. The diagnosis extraction task has a precision of 96.75% and a recall of 94.25%.

This method showed precision evaluation of simple Word file and could be an easy method for collecting a great number of clinical data allowing extension of an analysis to a larger headache population.

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Vitamin D levels in migraine and headache patients compared with pain patients

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Objective We measure Vitamin D (25-OH) levels in our migraine and headache clinic population and compared them with our patients who had chronic pain disorders without any headache.

Background Vitamin D levels have been found to be low in musculoskeletal, fibromyalgia and other pain syndromes. We tried to separate, as much as possible clinically, headache/migraine patients from patients with chronic pain syndromes to measure Vitamin D levels in both groups individually.

Methods Serum Vitamin D levels [total Vitamin D level = D2 + D3] were drawn on over 1500 migraine and headache patients, as well as in chronic pain disorders of many types, (fibromyalgia, rheumatologic disorders and neuropathic pain disorders (TN, CRPS, TMD, lumbar and cervical radiculopathies). We present data on 100 patients with migraines/headaches and pain disorders.

Results We compared 100 patients with headache and pain conditions [55 with migraines/headache, 45 with pain syndromes with regard to their Vitamin D levels. The average Vitamin D level in patients with predominantly migraine and mixed headache disorders, including CDH, was 26.3 ng/ml. Only 15% had any other remote pain disorder in their history. This compared to Vitamin D levels of 25.2 ng/ml in a variety of pain patients, with no headache symptoms. No statistical significance was found between the 2 groups of patients ($P < .8$). Neither group was compared to persons without either of the clinical conditions.

Conclusions We conclude that Vitamin D levels are low in both migraine and headache patients and are comparable to low levels seen in our chronic pain patients. This potential biomarker should be studied in double-blind trials, both for epidemiological and clinical reasons, and for potential treatment effects. Vitamin D may play some yet unknown role in multiple painful and possibly headache and migraine disorders.

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Overlapping features of migraine and tension-type headache. new insight to continuum hypothesis

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Objectives To investigate the overlapping features of tension type headache (TTH) and migraine in tertiary based headache centers common database.

Background Question of whether TTH and migraine represent two point of continuum has been debated before. Definitions of International Headache Society attempt to make distinction between migraine and TTH based on pattern, duration and severity of attacks. However; patients may present with characteristics of both headache disorders and continuum concept is a possible key to the understanding of this association.

Methods Totally 7184 patients with headache aged between 18 and 67 were included. Information of sociodemographics and clinical features was gathered in all patients by face to face interviews by headache specialists using semi-structured web-based questionnaire. Primary describing characteristics of these two headache disorders were analyzed using standardised tests and most important discriminant features were evaluated using classification and regression tree method.

Results Groups composed of 3317 subjects with migraine and 3,996 subjects with TTH. They showed important difference in the aspect of headache duration (60 months vs 24 months), frequency of attacks (5 vs 15 per month), duration of attacks (24 hr vs 6 hr), quality of attacks (pulsating vs pressing), location of attacks (unilateral vs suboccipital), frequency of associated features (77.2% vs 35.5%). On the other hand both headache type showed similar frequencies in the aspect of headache timing (commonly at the evenings), associated dizziness and nausea in addition to previous positive history of atopic disorders and travel sickness.

Conclusions Although migraine and tension type headache are considered two different entities with different pathophysiology, however these disorders exhibit more similarities than differences. They may exhibit similar associated features, share similar demographics and may be more intimately related than would be suggested by their diagnostic criteria. The most differentiating features of these disorders are associated nausea and dizziness in contrast to previous reports.

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Injections of the greater occipital nerve in episodic and chronic cluster headache - efficacy and safety of 113 injections

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The infiltration of the greater occipital nerve with local anaesthetics and corticosteroids is a treatment option in patients with cluster headache. We retrospectively analysed efficacy and safety of 113 consecutive injections in 64 different patients with episodic and chronic cluster headache. The data was collected from the patients files from 2005 to 2009 at the headache and pain unit, Department of Neurology, University Hospital Zurich.

More than 80% of these infiltrations had been effective. The effect was maintained for 4 weeks on average in chronic cluster headache, and 6 weeks in episodic cluster headache.

No major side effects have been reported. In 18 infiltrations (14%) mild to moderate side effects have been reported, all of which have been transient. Nevertheless, two patients decided to stop the infiltrations despite the beneficial effect of their previous injections.

Our data shows that GON-infiltration is a valuable and safe option to treat patients suffering from cluster headache. Especially patients with the episodic form benefit from an injection of the greater occipital nerve on the side of pain.

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Primary headaches: epidemiologic and clinical aspects in the neurology department of the central hospital Yaounde -Cameroon

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Introduction Headaches constitute the first presenting complaint in neurological practice in western countries. However, rather few studies have been done on headaches in Africa in general and Cameroon in particular.

Methods To evaluate the frequency and clinical presentation of primary headaches, 276 patients with headaches were interviewed and examined based on the 2004 IHS criteria in the Neurology Department of the Central Hospital in Yaoundé.

Results/discussion Primary headache was found in 84.42% of the patients. 65.22% of the patients suffered from tension-type headache (TTH) and 13.04% from migraine whilst 6.16% had an association of TTH and migraine. Three patients had an association of chronic TTH and probable analgesic overuse headache. The mean age of patients with TTH was 36.40 ± 13.63 years as against 25.47 ± 9.08 years for migraine patients. The F/M ratio of the patients with TTH was 1.90 as against 5.0 for migraine patients. About $\frac{1}{4}$ of the patients with TTH and $\frac{1}{2}$ of the migraine patients were students. Among the patients with TTH, 53.2% presented with frequent episodic TTH and 46.8% with chronic TTH. Of the patients with migraine, 83.33% had no aura. Insomnia was present in 42.2 % of TTH patients. Primary headaches affected mainly the active youths, females dominating.

Conclusion This is the first report of the prevalence of headache in Cameroon, and shows that primary headaches are frequent in Yaounde - Cameroon, TTH been the most frequent. The prevalence of TTH seems to be higher than in western countries.

Keywords Headache, prevalence, tension-type headache, migraine, Cameroon.

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Thunderclap headache: the clinical features, diagnosis and management: a 6 months prospective study

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Thunderclap Headache (TCH) is a severe and explosive headache whose maximal intensity at or within 60 seconds of onset. Primary thunderclap headache lasts from 1 hour to 10 days and diagnosis can be made only after exclusion another disorder. First every thunderclap headache has to be considered as symptomatic headache, such as subarachnoid hemorrhage, cerebral venous sinus thrombosis, cerebral artery dissection, reversible cerebral vasoconstriction, meningitis and other primary headache such as cough, exertional and sexual headache. For diagnosis we used ICHD-II criteria of International Headache Society and a cerebral CT scan, lumbar puncture, magnetic resonance imaging, CT angiography, MR angiography, cervical and transcranial ultrasound examination. The first step of diagnosis procedure was to obtain a history of present and previous headaches. We monitored pain intensity, location of headache, quality of headache, time and duration of headache. During 6 months we included 21 patients (11 women, 10 men), mean age 52 (standard deviation 17; median age 53) with clinical pictures of TCH from 211 patients with headache who were in emergency at our clinic. 10 patients had diagnosis of primary headache (2 patients had primary TCH, 3 patients had organic headache, 1 patient had exertional headache, 2 patients had first attack of migraine with aura). 13 patients suffered from secondary headache (5 patient suffered from ischemic stroke, 1 patient had hemorrhagic stroke, 2 patients had subarachnoid hemorrhage, 2 patients had meningitis, 1 patient suffered from posterior reversible encephalopathy syndrome, 1 patient had psychosis, 1 patient had lymphadenitis of neck). Mean score of pain intensity on a pain scale of 0-10 were 8,4 (standard deviation 2,1 median 9) and mean time of duration of headache was 131 hours (standard deviation 378, median 24).

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The increase in the calcitonin gene-related peptide immunoreactivity following the CSD activation in the serotonin depleted state

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Objective This study aimed to investigate whether the calcitonin gene related peptide (CGRP) involves in the facilitation of trigeminovascular nociception induced by cortical spreading depression (CSD) in the serotonin depleted state.

Methods Male Wistar rats were separated into 3 groups of eight animals each as following: control, cortical spreading depression (CSD), and low serotonin with CSD groups. Serotonin was depleted by administration of para-chlorophenylalanine. CSD was used to activate trigeminal nociception. In all experimental groups, the immunoreactivity of the calcitonin gene related peptide (CGRP) was investigated in the sections obtained from the cerebral cortex, trigeminal ganglion (TG) and the trigeminal nucleus caudalis (TNC) using the immunohistochemical technique.

Results The depletion of serotonin caused an increase of the CGRP immunoreactivity in both TG and TNC as compared with the CSD group. In the cerebral cortex, the perivascular immunoreactivity of CGRP after CSD activation was more prominent in the serotonin depleted group than in the CSD group.

Conclusion The results of this study indicate that the increase of the CGRP release after CSD activation could be one explanation for the facilitation of the trigeminal nociception observed in the serotonin depleted state.

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Lacosamide in the prophylaxis of chronic headache and migraine disorders

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Objectives We studied a new anticonvulsant, lacosamide, in the prophylaxis of chronic daily headaches [CDH] and mixed chronic migraine disorders.

Background Lacosamide is a new anti-convulsant with a unique mechanism of action that enhances the slow inactivation of voltage-gated sodium channels in nerve.

Because other sodium channel agents have been shown to have efficacy in the prophylaxis of chronic headache disorders, we chose to study this agent in our clinic population who had failed multiple other medication trials for their headaches.

Methods We studied 22 patients who had failed up to 6-7 other prophylaxis agents for chronic migraines, CDH and mixed headache disorders with neck/TMD pain. 22 Patients were treated with daily lacosamide in increasing doses, averaging 10-14 days between dosage changes. Average lacosamide dosage per day was 165 mg. 14 patients (64%) had neck pain or TMD co-existent with migraines and CDH.

Results Average lacosamide treatment was 94 days at the above dosage. The number of headache and migraine days per month at onset of lacosamide treatment was 21.4 (12-30 days per month). After therapy, the average headache and migraine days per month reduced to 13 per month ($p < .05$, 2 tailed t test). 4 patients had no response, mainly due to side effects such as nausea, cognitive complaints or drowsiness. 11 of 14 (79%) patient with co-existent pain also reported a reduction of about 47% of their symptoms.

Conclusions We conclude that lacosamide may offer a newer approach to prophylaxis of CDH and chronic migraine. It has a novel mechanism of action on sodium channel function in nerve, and should be studied rigorously in a double-blind manner.

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IV tramadol treatment for chronic daily headaches and migraines in the outpatient clinic

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Tramadol is used orally for chronic pain in the USA but no IV form is available. We prepared an IV sterile preparation of tramadol for treating chronic daily headaches (CDH) and chronic migraines (CM).

Method Tramadol was given IV in the headache clinic to patients with CDH and CM, following failed treatment with usual medications. 112 patients were treated with IV tramadol (37 had chronic migraines or migrainous features with CDH), An IV line with normal saline and with pulse oximetry monitoring and with monitoring of headache status by the patient on a 0-11 numeric rating scale (NRS). The study was done in an outpatient headache clinic setting.

Results All but 4 patients treated had some response to IV tramadol. Average dose of tramadol was 499 mg (range = 250-1,200 mg), given over 108 minutes in the clinic. Average reduction in severity of CDH (0-11 NRS) was 7.12/10 to 1.65/10 after treatment [$p < .001$ by two-tailed t test]. No side effects other than transient drowsiness or nausea were noted in 15 patients. 52 patients were subsequently placed on oral tramadol for their CDH. Headaches returned within 24 hours in 22 patients not treated with oral tramadol.

Conclusions IV tramadol is very effective in treating CDH/CM and mixed headaches acutely in the clinic. It has virtually no toxicity IV and can be the starting point for oral treatment. Tramadol IV offers a new possibility in treating CDH/CM effectively and safely and should be studied in a double-blind manner. Tramadol has mu opioid receptor activity and reuptake blockade of norepinephrine and serotonin. No other example of a medication administered IV with these latter mechanisms has ever been shown to be effective in treating CDH and other headaches with this rapidity and effectiveness.

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Evaluation of habituation patterns in cluster headache

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Background Cluster headache (CH) is a rare primary headache disorder, which is characterized by strictly unilateral severe headache attacks. Hypothalamic dysfunction and alteration of habituation patterns were suggested to play a pivotal role in the pathophysiology of CH.

Objective To determine habituation patterns of trigeminal nociceptive processing in patients with CH using the nociceptive blink reflex (nBR).

Methods Sixty-six patients with CH (18 episodic CH inside bout; 28 episodic CH outside bout, 20 chronic CH) and 30 healthy controls (HC) were investigated. NBR was performed following nociception

specific electrical stimulation on both sides of the forehead (first division of the trigeminal nerve: V1). Habituation of the R2 response was determined by analyzing the mean regression coefficient (MRC).

Results In healthy controls the MRC was -1.4 following right-sided stimulation and -1.9 following left sided stimulation. In episodic CH inside bout the MRC was -2.2 after stimulation of the headache side (HA) and MRC = -1.2 of the non-headache side (non-HA). Outside bout the MRC was -1.6 on the HA and MRC = -1.2 on the non-HA. In chronic CH MRC = -1.4 after stimulation of both sides of the head. The differences between HA and non-HA as well as CH and HC were not statistically significant. In episodic CH inside bout the R2-response was significantly increased on the HA compared to the non-HA.

Conclusion Our data did not detect a habituation deficit in CH, regardless of the course of the disease (episodic inside and outside bout, chronic) compared with healthy controls. These results contradict prior studies that showed an even pronounced habituation deficit of brainstem reflexes in CH compared with migraineurs. Increased R2 responses on the HA, however, point to a facilitation of the trigeminal nociceptive processing in CH patients inside bout.

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Normal levels of circulating trace amines in tension-type headache

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Trace amines, such as tyramine and octopamine, are neuromodulators related to classic biogenic amines. They are present in plasma at very low physiological concentrations. Tyramine, which is derived from the amino acid tyrosine through tyrosine decarboxylase enzyme activity and from tyramine containing food (cheese and chocolate), is rapidly metabolized by dopamine- β -hydroxylase into octopamine, which is the most stable among biogenic trace amines. Levels of these amines are altered in various disorders such as migraine, cluster headache, psychiatric state and Parkinson's Disease. There are no data available in the literature regarding plasma trace amine levels in tension-type headache.

Therefore we assessed the plasma levels of tyramine and octopamine in 15 patients affected by chronic tension-type or high frequency episodic tension-type headaches, without history of migraine, and 15 healthy control subjects. For the detection of tyramine and octopamine levels we used a multi-channel electrochemical HPLC system (Coulchem II, ESA).

We found detectable levels of octopamine and tyramine in all subjects. Plasma levels of octopamine and tyramine of patients [octopamine 2,3 ng/ml \pm (0,14-8,55) and tyramine 1,17 ng/ml (0,03-4,1)] were not statistically different from those of controls [octopamine 1,63 ng/ml (0,05-8,8) and tyramine 0,59 ng/ml (0,03-3,1), $p = 0.45$ and $p = 0.32$ respectively].

Our very preliminary results, in contrast to the data in migraine and cluster headache patients, could indicate that these two neuromodulators do not play a role in tension-type headache. If confirmed, this different pattern between migraine and cluster headache, on one side, and tension-type headache, on the other side, may indicate different biochemical and pathophysiological grounds.

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Vitamin D levels in chronic migraine

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Chronic migraine affects 3% of persons worldwide (1). The mechanisms and causes of chronic migraine are not well understood (1). There is a positive relationship between chronic migraine and greater distance from the equator (2). The importance of adequate vitamin D has been highlighted recently in the pain literature (3-7). Several studies suggest vitamin D supplementation is helpful in the management of chronic pain including non-specific musculoskeletal pain, back pain and diabetic neuropathy (3-5). There is evidence that migraine prevalence correlates to northern latitude and colder climates (2), suggesting that a deficiency of vitamin D may be involved (2, 7). This study examines the correlation of Vitamin D levels with pain disability measures, age, sex, BMI, and season of the year, for new patients presenting to a headache clinic at 42.3 degrees latitude with a diagnosis of chronic migraine. A retrospective medical record review was done on 882 new patients seen from January 1, 2009 to January 1, 2010. 123 subjects thus far were found to have a diagnosis of chronic migraine with recorded vitamin D level measures, pain disability index, and body mass index. These measures were then compiled into an excel spread sheet. Preliminary data results are average vitamin D level 25.88, average pain disability index 34 and average age 43. Vitamin D levels below 20 are usually considered low and pain disability index scores vary from 0 being no disability to 70 as the maximal disability of pain. Further correlations will be presented to make the connection between vitamin D levels and chronic migraine apparent.

Citations available upon request.

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Burden of disease in cluster headache

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Introduction Cluster headache (CH) belongs to the most excruciating headache syndromes known. However, relatively little is known about the burden of cluster headache regarding its various subtypes (chronic and episodic CH in and out of the active period). The implications of

headache can be differentiated into diverse economic (e.g. impaired work life) and non-economic burdens (e.g. disability and psychiatric complaints).

Patients and methods In a multicentre prospective study patients with chronic CH ($n = 27$), with episodic CH in the active period ($n = 26$) and outside the active period ($n = 22$), migraine patients ($n = 24$) and controls without a history of primary headaches ($n = 31$) were included. Apart from epidemiological data, the German version of the Headache Disability Inventory (HDI) and screening questions for psychiatric complaints were applied.

Results About 25% of chronic CH patients received invalidity allowance due to headache. HDI scores (total and the subscales emotion and function) indicated a statistically significant severe headache-specific disability in the chronic and active episodic CH patients. Patients with inactive CH and migraine were less affected than the former group but still more impaired than healthy volunteers. Symptoms suggestive of psychiatric comorbidity were found predominantly in the chronic CH group. Depressive symptoms (56%) and signs of agoraphobia (33%) prevailed. Interestingly, 22% of the chronic CH patients reported thoughts about death and suicide.

Discussion In conclusion, a massive headache-specific disability in patients with chronic and active episodic CH could be found. Job life was severely affected with a surprisingly high proportion of early retirement in chronic CH. Lastly, psychiatric comorbidity and suicidal tendencies were highest in chronic CH. Therefore, patients with chronic CH have a severe and disabling condition that warrants special medical and further supportive care.

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Comorbid conditions with migraine

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Background and objectives Comorbidity refers to coexistence or concomitancy with an unrelated pathological or disease process of separate conditions in the same individuals. Migraine may be associated with various medical, neurological and psychiatric diseases. The aim of this study was to evaluate the comorbidity in migraine patients.

Materials and methods Patients' data from Turkish Headache Database Study Group were evaluated in this retrospective study. The study group consisted of 3414 cases based on The International Classification of Headache Disorders, 2nd edn diagnostic criteria. Migraine comorbidity in the patients were assessed according to their self reports.

Results Mean age was $43,3 \pm 12,6$ (min 14–max 90). The patients were divided into four groups; migraine with aura, migraine without aura, probable migraine, complications of migraine. Psychiatric comorbidities (depression in 31.5%, anxiety disorder in 11.7%, obsessive-compulsive disorder in 1.9%, psychosis in 0.8%), non-headache pain in 31.0%, vascular comorbidities (hypertension in 14.5%, atherosclerotic heart disease in 8.5%, transient ischemic attack and stroke in 0.3%), atopic disorder in 1.5%, and epilepsy in 1.1% of patients were detected.

Conclusion Migraine is a complex disease that requires a multidisciplinary disease management approach. Comorbid disorders have been found to affect migraine progression and treatment strategy. The presence of these disorders can impose therapeutic challenges and limit treatment alternatives.

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Migraine and epilepsy - a shared genetic region on 14Q13-Q23

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Migraine and epilepsy are paroxysmal disorders of the brain. Patients are typically symptom-free between the attacks. Decrease in level of consciousness (severe in epilepsy, milder in migraine), presence of auras, post-ictal drowsiness, aphasia and attacks that may be triggered by either visual or hormonal stimulus are all characteristics shared by both migraine and epilepsy. Epidemiological and clinical studies have demonstrated a high degree of co-morbidity between migraine and epilepsy. We performed a genome-wide linkage scan in search for shared loci for migraine and epilepsy.

A large Finnish family with a high prevalence of migraine and epilepsy was identified and clinically characterized. Data on IHS-defined attack symptoms was collected using the validated Finnish Migraine Specific Questionnaire for Family Studies. Of 46 individuals, 27 had migraine and eight generalized tonic-clonic seizures (GTCS). All GTCS patients had migraine (five patients with and three without aura). Genome-wide genotyping was performed using 382 microsatellite markers with an inter-marker distance of 9.4 cM. Multipoint non-parametric linkage and haplotype analyses were performed using SimWalk v2.96.

A shared region on chromosome 14q13-q23 was identified for migraine and GTCS. Suggestive evidence of linkage (p -value 0.0018) was found between migraine and marker D14S70. This marker also indicated suggestive evidence of linkage to GTCS (p -value 0.0025). Significant evidence of linkage (p -value 0.0005) between migraine and marker D14S70 was detected after fine-mapping. A haplotype analysis identified a shared segment of 21 Mb for both migraine and GTCS.

Our finding indicates a shared region on chromosome 14q13-q23 for migraine and GTCS. Furthermore, our study confirms results of two previous studies indicating linkage of migraine without aura (Soragna et al., 2003) and epilepsy (Sander et al., 2000) to this locus. Future work will show whether there are shared or separate susceptibility variants for migraine and epilepsy in this region.

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Top-down control of visual cortex in migraine populations

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The pathophysiology of migraine includes a heightened excitability of visual cortex that persists between headache events and that has been linked to impaired inhibitory intracortical processes. Here we examined the implications of this cortical pathophysiology for the top-down attentional control of visual cortex. We asked two groups of participants – migraineurs (N = 29) and non-migraine controls (N = 29) – to perform a probabilistic spatial orienting task as we measured visual sensory cortical responses via event-related potentials (ERPs). Data were then analyzed as a function of whether the ERP-eliciting stimulus was in the fovea vs. parafovea, and whether the stimulus' location was attended or unattended. In this regard, we found two key between-groups differences in the effect of attention on sensory-evoked visual-cortical activity. First, relative to controls, migraineurs showed a larger attention effect in the visual N1 ERP component for events at the fovea. Second, unlike controls, migraineurs showed no early-phase attention effect in the P1 ERP component for events in the parafovea. Taken together, our results suggest that migraineurs have an abnormal top-down modulation of visual cortex leading to a lack of normal suppression of unattended information.

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Headache as a manifestation of spontaneous cervical artery dissections

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Background Spontaneous cervical artery dissection (sCAD) is a well recognized cause of stroke, particularly in the young, with a wide spectrum of clinical presentations. Patients may present with local manifestations, ischemic signs or both. Headache and neck pain are thought to be frequent symptoms of sCAD.

The aim was to evaluate headache occurrence associated with cervical artery dissections as well as clinical characteristics of headaches in sCAD.

Methods A study was done on 37 neurological inpatients with spontaneous internal carotid (sICAD) or vertebral artery dissections (sVAD) who were treated at stroke unit and department for cerebrovascular disorders and headache at the Institute of Neurology Clinical Center of Serbia. Diagnosis of arterial dissection was established by CT or MR angiography, and confirmed by extracranial Doppler ultrasound. Headache characteristics (localization, intensity, duration, pain quality) were analyzed as well as accompanying features in patients with headache.

Results In a group of 37 patients with sCAD, 26 were males (75%), with mean age of 42.5 years. Headache occurred in 17 patients (46%) and in 2 was the only symptom of disease, lasted from 3 hours to 15 days. Headache was an initial symptom in 9 patients, and preceded stroke or TIA up to 4 days. Unilateral localization was present in 7 and bilateral in 10 patients. 2 patients with sICAD presented with intensive continuing retro-orbital unilateral pain with ipsilateral autonomic signs (semiptosis, miosis, eyelid swelling, lacrimation). Unilateral throbbing pain in occipital region accompanied with vertigo, nausea and vomiting was found in 4 patients with sVAD.

Conclusion Headache is often the initial sign of sCAD. Clinical presentation may vary in intensity, duration and localization and it can mimic primary headache disorders.

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Headaches and medical doctor education in Serbia

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Introduction Fact that there is insufficient number of Medical Doctors specialized in headaches as well as their insufficient education often introduces wrong diagnosis, and improper treatment of different headache entities.

Objective Study is focused in determination of the quality level of Medical Doctors specialized in different areas in order to make the proper diagnosis of the different types of Headaches.

Method This retrospective study analyzed referral diagnosis that was conducted by the group of Medical Doctors of different specializations, who have referred the patients to a Headache Center. Diagnosis were compared with the ones provided by the Neurologists specialized in headaches and in accordance to the standards specified by the International Headache Society differentiating the variety of headaches. Referral and final diagnosis were compared for 1,200 of consecutive patients (M:F = 330:870) taken from the specialized protocols for evaluation used in the Headache Center. 1200 analyzed patients, are divided into three groups. First group, 976 patients referred by the General Practitioners, second, 32 patients referred by the Neurologists, third 192 patients referred by the Medical Doctors specialized in different areas.

Results Referral diagnosis from General Practitioners were confirmed in 30.3%, from Specialized Neurologists in 62% and from Medical Doctors specialized in different areas in 37.5% cases. Biggest problem to define the proper diagnose, for all the groups was the Cluster Headache, that has been properly diagnosed just in 16% of all the cases and Migraine with Aura that has been properly diagnosed in just 23% of all the cases.

Conclusion This study results, indicates the problem of assigning the right diagnosis for different types of headaches, especially within the group of patients checked by General Doctors. Organization of the supplementary education in this area would significantly improve the way of treatment, and would also impact the economy factor in reducing the costs.

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Evaluation of sleep disorders among migraineurs and tension-type headache and control group

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Headache is one of the most common complaints of patients visiting neurologists. More than 90% of individuals experience headache at least once in their life time which may be exacerbated by various risk factors including sleep disorders. Sleep disorders related to headache are of different types such as insomnia, polysomnia and circadian rhythm disturbances. Considering the above, determination of sleep

disorder pattern among headache sufferers and appropriate approach to these disorders may remit or cure headache.

This case-control study was conducted on 3 separate groups consisting of migraineurs, tension-type headache and control group in 1388-89 in Tehran. Twenty hundred and ninety eight participants completed Sleep Disorders' and Epworth Questionnaires and 8 sleep disorders including hypersomnia, insomnia, restless leg syndrome (RLS), excessive daytime sleepiness, somnolence, sleep talking, nightmare, and bruxism were evaluated. Chi-square analysis was performed to compare groups.

Out of the 298 participants 72.1% were female and 27.9% were male. Mean age of participants was 38.3 years. Ninety two participants were in the control group and according to HIS criteria 124 individuals were migraineurs and 82 were classified as having tension-type headache. Results of this study show significant difference in 3 of the sleep disorders including insomnia ($p = 0.036$), restless leg syndrome ($p = 0.034$) and nightmare ($p = 0.027$) between headache and control group. No other significant difference was found between the two groups. In addition, no significant difference ($p > 0.05$) was found between migraineurs and tension-type headache group.

Considering the results of this study it is suggested that evaluating risk factors and clinical symptoms and treating sleep disorders, specially insomnia, restless leg syndrome, and nightmare, can be effective in migraineurs and tension-type headache sufferers.

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Posttraumatic headache in former military men: clinical picture and age differences

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Posttraumatic headache in former military men: clinical picture and age differences.

Background Traumatic brain injury (TBI) ranging from 30 to 50% of all types of injuries and increasing to 60-80% in case of traffic accidents. The number of TBI in warzone is really high and about 80% of them are mild brain injuries very often leads to posttraumatic headache. Soldiers with TBI often have symptoms and findings affecting several areas of brain function. Among 5,000 soldiers who returned from deployment to Fort Lewis, Washington 19% had had a concussion, and more than 90% of this group reported having headaches during the previous three months (Theeler BJ, Erickson JC, 2009).

Material We had investigated 60 veterans of local wars with posttraumatic headache. Patient age ranged from 21 to 59 years.

Results Posttraumatic headache could be characterized as bilateral pain which was mainly located in frontotemporal (42.6%) and occipital region (24.6%), prompted by a bad dream, accompanied by vertigo (18.0%) and fluctuating blood pressure (26.2%). 59.0% of patients suffered from it for ten years or more. Patients were divided into two subgroups are compared with each other: First subgroup - patients under 40 years, 26 men, mean age 33.9; Second subgroup - patients older than 40 years, 34 men, mean age 46.7. The intensity of headache according to visual and analog scale of pain and other clinical characteristics was not statistically differed in both subgroups. However, people older than 40 years, significantly more often complained about the presence of other pain syndromes: 47.1% - for vertebrogenous pain syndromes, 20.6% - heart pain, 8.8% for joint pain, 5.9% - epigastric pain. 65.4% of men from the first subgroup, and only 38.2% from the second complained only of a headache.

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Cluster headache-like headache in an eight-year-old girl: case report

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Cluster headache (CH) is a primary episodic headache clinically characterized by extreme unilateral orbital or periorbital pain, cranial autonomic symptoms and periodic occurrence. The prevalence of CH in the general population is 0.1% and is threefold more common in men. CH mostly occurs in the second and third decade of life; however, cases of its occurrence in the first decade of life have also been reported. A case is presented of an 8-year-old girl, previously healthy, with a one-week history of clinically typical daily CH attacks, with motor hyperactivity for about one hour of falling asleep, persisting for hours. The administration of analgesics (paracetamol, ibuprofen) proved inefficient. The attacks were only interrupted by cold winter air inspiration. Diagnostic work-up including C-reactive protein, complete blood count, general biochemistry, neurologic examination with electroencephalography, and ophthalmologic examination (vision, fundus, biomicroscopy and tonometry) yielded normal findings. ENT examination with paranasal cavity x-ray and sinusoscopy pointed to inflammation of the ipsilateral maxillary sinus with the respective ostium obstruction. Upon topical endoscopic treatment with decongestants on two occasions at a week interval and topical therapy with corticosteroid and antibiotic drops, pain attacks subsided in severity and frequency, to regress completely in the second week of therapy. The subsequently obtained magnetic resonance of the head was normal. The case presented points to the need of additional diagnostic work-up in children with CH irrespective of a typical clinical picture, in order to exclude the secondary treatable causes.

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Neck-tongue syndrome: a Turkish patient

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A syndrome, unilateral upper nuchal or occipital pain with or without numbness in these areas, accompanied by simultaneous ipsilateral numbness of the tongue is explicable by compression of the second cervical root in the atlantoaxial space on sharp rotation of the neck as published justly by Lance JW and Anthony M in 1980. Since then totally 25 papers were published about this syndrome. Now we are presenting probably the first Turkish neck tongue syndrome patient. The patient is 15 years old girl and she has been suffering from ipsilateral numbness and pain on the neck and tongue during sharp rotation of the neck for ten years. She has no history of neck trauma.

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Clinical characteristics of primary headaches and the efficacy of prophylactic therapy in out-patients

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Department for Clinical Neurophysiology and Epilepsy,
Institute of Mental Health, Belgrade, Serbia**Objectives** To assess the clinical characteristics of primary headaches, prior to initiation of prophylactic therapy as well as the response to treatment.**Background** Successful management of primary headaches - migraine and tension type headache, a highly prevalent disorder, is based upon timely and appropriate choice of prophylactic medication.**Method** We studied 120 subjects in an out-patient setting using post-hoc analysis of: the age of occurrence (before or after 30); number of years with headache (more or less than 10), number of headache days per month (more or less 15). Diagnosis of headache was made according to IHS-classification (2004). Clinical diagnosis of depression (ICD-10) was supported by the BDI-scale. We initiated prophylactic treatment according to guidelines of headache treatment, as a step-by step and stratified care.**Results** The sample of 120 patients contained 93 females and 27 males, ages 16 - 70. There was low therapeutic efficacy in 23 of 120 patients (19,16%). It was observed that the characteristics of the non-responders were: headache that started after the age of 30 in 13 out of 50 (26%); headache duration more than 10 years in 19 out of 85 (22%) and over 15 headache days per month in 16 out of 60 (26%) . We had low therapeutic efficacy in 6 out of 46 (13%) migraine patients, 10 out of 33 (30%) with tension type headaches and in 7 out of 41 (17%) with co-existence of the two types. 16 out of 64 patients (15%) who also suffered from depression did not respond to prophylactic treatment.**Conclusion** We concluded that later onset of headache, more headache days per month (chronic course), tension type headache and co-existing depression were conditions that led to low therapeutic response in patients with primary headaches.

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Co-existing depression in primary headaches - clinical characteristics in an out-patient sample

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Institute of Mental Health, Belgrade, Serbia**Objectives** We wanted to study the possible influence of certain clinical characteristics of primary headaches on the co-existence of depression.**Background** Depression, the most prevalent co-morbid condition in patients with migraine and tension type headache, worsens the clinical course and demands much greater therapeutic effort.**Method** In the sample of 120 out-patients we followed the age of onset (before and after 30), duration (more or less than 10 years), number of headache days per month (more or less than 15) and the efficacy of prophylactic treatment. Diagnosis of headache was made according to IHS-classification (2004). Clinical diagnosis of depression (ICD-10) was supported by the BDI-scale.**Results** In the group of 93 females and 27 males, ages 16 - 70 (mean 45,61 yr.) - 64 patients (53,3%) suffered from depression. Depression was more prominent in those who started headache after the age of 30

yrs. - 32 out of 50 (64%), but similarly distributed in those whose headache lasted more and less than 10 years, as well as in those with more and less than 15 headache days per month. Depression co-existed in 18 out of 46 (39%) migraine patients, 24 out of 33 (73%) with headache of tension type and 22 out of 41 (54%) that had both types. Depression was founded in 16 out of 23 patients that did not respond to prophylactic therapy (69%), and was equally present in the group of responders.

Conclusion We found more depression in patients with later onset of headache, while the duration and the number of headache days per month did not affect the emotional state. Tension type headache and low therapeutic response to prophylaxis could be signed as the risk factors of co-morbid depression in primary headaches.

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Adolescent migraine: long-term health outcomes following treatment with a single tablet formulation of sumatriptan and naproxen sodiumE.M. Pearlman¹, M.C. Runken², P. Winner³, N. Richard⁴,
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West Palm Beach, FL, USA;⁴Neurosciences MDC, GlaxoSmithKline, Research Triangle Park,
NC, USA**Objective** To measure long-term patient-reported health outcomes (≤ 12 months) in adolescents treating migraines with sumatriptan and naproxen sodium (SumaRT/Nap).**Methods** A prospective, open-label, single-arm, multi-center study was conducted to evaluate SumaRT/Nap acute treatment of migraine in adolescents 12-17 years old. Trial design reported elsewhere (McDonald 2010). Quality of Life (QoL) was measured using the Migraine-Specific QoL Questionnaire for Adolescents (MSQ-A) at baseline and at 3 month intervals. Overall medication satisfaction was measured at baseline and monthly following treatment using the global subset of items from the Revised Patient Perception of Migraine Questionnaire (PPMQ-R).**Results** The ITT population was used for these analyses and was defined as subjects taking ≥ 1 dose of SumaRT/Nap and completing an eligibility-treatment assessment: 591 [12-14 yrs: 273; 15-17 yrs: 318]. Subjects were primarily Caucasian (86%), females (60%), with a 5-year history of migraine without aura (69%) and experiencing 4 attacks/month. 67 (11%) withdrew due to adverse events or lack of efficacy. 333/591 subjects remained in the study for at least 6 months treating on average ≥ 1 attack/month within the first 6 months (6mo-Completers); 181/591 remained in the study for 12 months treating ≥ 1 migraine attack/month (12mo-Completers).In the ITT and 12mo-Completer groups, mean MSQ-A scores improved significantly from baseline in all three QoL dimensions ($p \leq 0.0001$ for ITT; $p \leq 0.005$ for 12mo-Completers) and on average exceeded the Minimal Clinically Important Differences in the Role-Restrictive(7) and Role-Emotional(6) dimensions at all time points. PPMQ-R data indicated that 82%, 84% and 85% of the ITT, 6mo- and 12mo-Completer groups were either 'Satisfied' or 'Very Satisfied' with the Overall Efficacy, while 86%, 87% and 89% respectively, were 'Satisfied' or 'Very Satisfied' with the Overall Treatment of SumaRT/Nap.

Conclusions Adolescents migraineurs using SumaRT/Nap reported improved quality of life compared to baseline and were generally satisfied with their treatment.

Conflict of interest M. Chris Runken, PharmD is full time employee of GlaxoSmithKline, Research Triangle Park, North Carolina, USA.

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Paroxysmal hemicrania and visual aura: a case report

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A 48 years-old healthy female patient presented to our outpatient clinic in December 2008. Since the age of 20 the patient had experienced severe left side orbital, supraorbital and temporal headache pain lasting about 15-20 minutes, associated with ipsilateral symptoms and signs (lacrimation, ptosis and nasal congestion). Attacks had a frequency above 6 per day and occurred in periods lasting about one month with subsequent pain free period lasting more years. In December 2008, she experienced another headache period with daily attacks with average frequency of 8 per day, always characterized by the same unilateral headache pain and ipsilateral located signs on the left side. The physical and neurological examination was normal. The attacks stopped with indomethacin 100 mg BID by injection for 3 days and later with 150 mg orally for maintenance, supporting the diagnosis of paroxysmal hemicrania.

The patient returned at our observation after 3 months, reporting a complete remission of headache.

A MRI and angio-RMI of the brain was performed in february 2009, showing a small, right intracranial carotid artery aneurysm.

In July 2009, she reported a three month history of visual disturbance typical for migraine aura (characterized by gradual onset of binocular scotoma lasting 15-30 minutes) without subsequent headache, occurring four-five times in a month. One month ago she was operated upon the aneurysm with endovascular coiling; she started treatment with double antiaggregation drugs after which she referred no other episode of migraine aura.

This is a case in which two different diagnosis, paroxysmal hemicrania and migraine aura without headache, seem coexisting. Since visual disturbance was clearly reported as binocular and typical for aura, carotid aneurysm could be considered a casual finding as well as also episodic unilateral headache pain located in left head seems not to be related with right carotid alteration.

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Characteristics of headache: a clinico-epidemiologic study

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Background Headache disorders are extremely common and are a common complaint among patients seeking care. The prevalence of

headache has long been a subject of discussion. As with all disorders, the key to diagnosis is a good history.

Patients and methods The objective of this study was to describe the epidemiology, clinical presentation of chronic headache in 96 patients.

Results The mean age was 39 years, 61 patients were female and 35 were male. The onset of headache is acute in 8%, fast progressive in 20.8%, progressive in 66.1%. The prodromes are vomiting in 17.7%, anxiety in 5.2%, irritability in 18.7%, others in 29% and without prodromes in 18%. The headache is localised in 18.7%, diffuse in 8.3%, unilateral in 19.8%, bilateral in 17.7%, holocranial in 11.4%, hemicranial in 29%, orbital in 18.7%, occipital in 20.8%, vertex in 26%, frontal in 26%, parietal in 8.3%, temporal in 22.9%, hemi facial in 2%, cervical-occipital in 2%, a bascule in 6.2%.

The neurological examination was normal in all patients and the diagnoses were migraine with in 8.3% and without aura in 39.7% and psychological headache in 52%.

All the patients are treated with analgesics; NSAID, Triptan, Amitriptyline, Oxétorone and the outcome are variable.

Conclusion The different headache symptoms may be causally related to age, but an influence of medication or other factors must also be considered. The use of specific coping strategies as well as non-pharmacological or pharmacological prophylactic therapies needs further support in daily clinical practice.

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Demographic characteristics of out-patients with primary headaches and the clinical course of illness

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Objectives We wanted to estimate the possible importance of the age, sex, academic level and employment of patients with primary headache for the efficacy of prophylactic medication.

Background Migraine and tension type headache are highly prevalent chronic disorders, that affect general population in their most active and productive period of life, with consequences to their functioning, also important for economic cost and burden of the illness.

Method In the sample of 120 out-patients, diagnosed according to criteria of ICD-10 (2007) and IHS (2004) - as migraine, tension type headache and co-existence of migraine and tension headache - we marked demographic characteristics and their possible influence on the success of prophylactic medication.

Results Patients were both sexes, 93 females and 27 males, ages 16 - 70 (mean 45 years). There were 20 patients (16,7%) with elementary, 66 (55%) middle and 34 (28,3%) high education level. 58 patients (48,3%) were employed, while the other 62 (51,6%) did not work - pupils, students and retired. There were 31 unemployed persons that is 26% in the whole sample and 35% among 89 subjects in work active period. Prophylactic therapy was not successful in 23 out of 120 patients (19,2%), worse in males (8 out of 23 or 34,8%), older subjects (mean age 52 years), middle education level (16 out of 23 or 69,5%), non-working individuals (14 or 60,8%) and unemployed, but in work-active period of life 7 or 30%.

Conclusion We found that the factors of worse clinical course of primary headaches could be: male sex, more than 50 years of age, middle education level and non-working population, specially unemployed.

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Quality of life in Tunisian headache sufferers

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Objective To assess quality of life in Tunisian headache sufferers.

Methods We studied 50 consecutive patients presenting with headache and consulting in Neurology department of Habib Bourguiba Hospital (Sfax, Tunisia). Data collection included patient characteristics, characteristics of headaches, neurological exam and radiographic findings. Headaches were diagnosed according to the New International Classification of Headache Disorder. The quality of life was assessed using the SF-36 questionnaire, including physical functioning, social functioning, role physical, role emotional, bodily pain, vitality, mental health and general health. For better interpretation of our results we proceeded to the standardisation of initial average scores of eight domains to an average of 50 in accordance with the study in general population (USA 98). According to Lean, the quality of life was compromised if mean score of eight domains was ≤ 66.7 .

Results Patients included 42 women and 8 men, aged 17–82 years. Thirty-two percent of headache sufferers had a poor quality of life (mean score ≤ 66.7). They reported diminished functioning and well-being on all eight domains. The daily frequency of headache was significantly associated with role physical ($p = 0.01$), role emotional ($p = 0.01$) and vitality ($p = 0.035$). Throbbing headache types were correlated with bodily pain ($p = 0.02$) and vitality ($p = 0.032$).

Conclusion Tunisian headache sufferers often report compromised physical, mental and social functioning because pain changes quality of their lives.

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The effect of incident cranial neuralgia on pre-existing migraine

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Objectives To describe the impact and characteristics of incident cranial neuralgias (CN) in patients with pre-existing migraine.

Background A subset of episodic migraine (EM) patients progress to chronic migraine. A variety of risk factors have been identified for this transition, including comorbid pain conditions and temporomandibular dysfunction (TMD). A shared mechanism may be the development of cutaneous allodynia, a clinical marker of central sensitization.

Results Co-existing CN and migraine were identified in 5 patients, all women. Three patients developed trigeminal neuralgia (TN), 1 developed glossopharyngeal neuralgia (GN), and 1 developed both. In all patients, migraine onset preceded CN onset, mean time between the two was 34 years. Comorbidities included TMD in 2 patients, depression in 1 patient, and anxiety in 1 patient. Three patients reported worsening of their migraine following incident CN, 2 with TN and 1 with both TN and GN. In the year following CN onset, monthly days of headache increased by a mean of 7 days (range 3 to

15 days). In the other 2 patients, headache frequency was unchanged. After CN onset, patients were started on oxcarbazepine ($n = 2$), topiramate ($n = 2$), or venlafaxine ($n = 1$). Allodynia was present in 3 patients, mean ASC score of 6 (range 4–8). Patients with prominent allodynia had a higher likelihood of developing worsening migraine after CN onset. All 3 patients who progressed had a history of using abortive medications > 10 days a month, including meperidine, ibuprofen, and butalbital/acetaminophen/caffeine.

Conclusions Three of five patients reported worsening of long-standing migraine after the new onset of CN. Migraine worsened despite treatment with preventive medications for CN. We hypothesize that CN may be associated with migraine progression through the mechanism of central sensitization. Analytic epidemiologic studies are required in larger series of patients to further elucidate this relationship.

Conflict of interest Dr. Grosberg serves on a scientific advisory board for Kowa Pharmaceuticals American Inc. and Merz Pharmaceuticals; has received honoraria for speaking engagements or educational activities from Merck and Nautilus Pharmaceuticals; and received institutional research support from Allergan Inc., Merck, GlaxoSmithKline, Endo Pharmaceuticals, Boston Scientific, Neuralieve Inc., Advanced Bionics, ProEthics, Minster Pharmaceuticals, and Capnia.

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Pathogenic mechanism in familial hemiplegic migraine 2 (FHM2) involves disruption of local and global Ca^{2+} signaling

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Point mutations in the $\alpha 2$ isoform of the Na, K-ATPase (ATP1A2 Na pump) cause FHM2, an autosomal dominant migraine phenotype identical to that caused by CACNA1A P/Q calcium channel mutations in FHM1. Although FHM2 alleles produce diverse effects on pump kinetics, all FHM2 mutants tested, unlike WT, similarly disrupt intracellular Ca^{++} signaling in stable transformant human SH-SY5Y neuroblastoma cells. Ca^{++} signals evoked by 100 μM carbachol were diminished in mutants, Ca^{++} oscillations were suppressed and local Ca^{++} puffs, representing quantal IP3R release events evoked by photoreleased inositol trisphosphate (IP3) occurred with similar frequency, yet lower amplitude than in WT. These effects of FHM2

mutations were evident without inhibiting normal endogenous human Na pumps, simulating the mix of pumps present in the heterozygous disease state. The changes are observed in the absence of changes in cellular proliferation, basal calcium levels or ER calcium stores. Given these mutations affect ATPase kinetics in different ways, yet lead to similar disease and disruptions in Ca⁺⁺ signaling, we propose that regulation of IP₃-mediated Ca⁺⁺ signaling is a critical physiological function of $\alpha 2$ and that calcium signaling alterations are a central component of the pathogenic mechanism of FHM.

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Depression in Tunisian headache sufferers

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Objective To detect depression in headache sufferers.

Methods We studied 50 consecutive patients presenting with headache and consulting in Neurology department of Habib Bourguiba Hospital (Sfax, Tunisia). Data collection included patient characteristics, characteristics of headaches, neurological exam and radiographic findings. Headaches were diagnosed according to the New International Classification of Headache Disorder. Depression was defined as a Beck scale ≥ 4 .

Results Patients included 42 women and 8 men, aged 17–82 years. Depression was observed in 50% of Tunisian patients with headache. There were correlations between depression and some characteristics of headache such as its higher frequency ($p = 0.05$), the existence of preamble ($p = 0.047$) and associated blurred vision ($p = 0.024$). Moreover, the presence of depression was correlated with persistence of headache ($p = 0.01$) despite treatment.

Conclusion Depression is a frequent co-morbidity in Tunisian headache patients. Therefore, the systematic use of depression scale in such patients would allow readjusting their treatment and bettering their management.

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Skeletal scintigraphy of craniocervical structures: clinical significance in cervicogenic headaches

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Objective To investigate the relevance of morphological changes in the main stabilizing structures of the craniocervical junction in persons with cervicogenic headache (CEH).

Material and methods A case control study of 46 consecutive persons with CEH, 22 consecutive with headache attributed to whiplash associated headache (WLaH) and 19 consecutive persons with migraine. The criteria of the Cervicogenic Headache International Study Group (CHISG) were used for diagnosing CEH, otherwise the criteria of the International Classification of Headache Disorders (ICHD II) were applied. All participants had a clinical interview, and a physical and neurological examination. The skeletal bone scintigraphies were evaluated in a blinded fashion.

Results Is analyzed at the time

Conclusion Will be presented at the congress.

Keywords Cervicogenic headache, skeletal scintigraphy, cervical spine,

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Depression comorbidity in patients with tension-type headache at the neurology outpatient consultation in Yaounde-Cameroon

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Introduction Tension-type headache (TTH) is the most frequent type of primary headache. In advanced forms, it is associated with psychiatric comorbidities which have a high impact on the quality of life of patients.

Objectives To determine the frequency, assess the severity and analyse the symptoms of depression in tension-type headache during outpatient neurology consultations in Yaounde.

Patients and methods One hundred and thirty-six consenting patients with TTH (2004 IHS criteria) were recruited and answered the BDI-II questionnaire (Beck Depression Inventory, 2nd edition).

Results The F/M sex-ratio was 1.68. The main age of the patients was 33.51 ± 11.35 years. Most patients (94.12%) had a formal level of education of more than 7 years, and the majority lived in an urban setting. The mean duration of evolution of the headache was 4.14 ± 5.74 years (range: 0.08 to 28). Chronic TTH was found in 70.40 % of the patients while 29.70% of the patients had frequent episodic TTH. Probable analgesic-overuse headache was associated to TTH in 14.81% of patients. Severe depression (BDI score of 29–63) was diagnosed in 35.29% of patients, and moderate depression in 32.35% of them (BDI score of 20–28). The mean depression score was 26 in men as against 23 in women ($p = 0.221$). Depression was more present in the chronic form of TTH than in the frequent episodic form ($p = 0.096$). The most frequent symptoms of depression were sleep disorders and concentration difficulties with means scores of 3/6 and 1.53/3 respectively.

Conclusion Depression is a frequent comorbidity in patients with TTH in Yaounde. An assessment of these patients from an affective perspective needs to be systematically carried out and integrated in their management.

Keywords Headache, Tension-type, depression, comorbidity, Yaounde.

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Three-dimensional analysis of the cervical range of motion in cervicogenic headacheH. Knackstedt^{1,2}, D. Bansevicius^{1,2}, M.B. Russell^{2,3}¹Department of Neurology, Innlandet Hospital Trust, Elverum, Norway;²Head and Neck Research Group, University Hospital Akershus, Oslo, Norway;³Faculty Division Akershus University Hospital, University of Oslo, Nordbyhagen, Norway**Objective** To investigate the physical impairment of the cervical range of motion in persons with cervicogenic headache (CEH).**Material and methods** A case control study of 46 consecutive persons with CEH, 22 consecutive with headache attributed to whiplash associated headache (WLaH) and 19 consecutive persons with migraine. The criteria of the Cervicogenic Headache International Study Group (CHISG) were used for diagnosing CEH, otherwise the criteria of the International Classification of Headache Disorders (ICHD II) were applied. All participants had a clinical interview, and a physical and neurological examination. The active and passive cervical range of motion was evaluated with a 3D ultrasound-based device.**Results** Are analyzed at time**Conclusion** Will be presented at the congress.**Keywords** Cervicogenic headache, active and passive cervical range of motion, cervical spine

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Heat pain threshold habituation in migraine and tension-type headacheT. Sand^{1,2}, M. Engstrøm¹, M. Stjern¹, G. Gravdahl³, K. Hagen^{1,3}, L.J. Stovner^{1,3}¹Department of Clinical Neuroscience, NTNU, Trondheim, Norway;²Department of Neurology and Clinical Neurophysiology, Trondheim, Norway;³National Headache Centre, St.Olavs Hospital, Trondheim, Norway**Objectives** Sensory allodynia has been reported by some migraine (MIG) patients. Lack of habituation to sensory stimuli has also been described for several sensory modalities.. The aim of our study was to measure pain threshold habituation for thermal stimuli in migraine compared to tension-type headache (TTH) and healthy controls (CO).**Materials and methods** 60 MIG (mean age 38.4 years, 15 with aura, 46 women), 23 patients with TTH (mean age 39.5 years, 12 women) and 43 healthy controls (mean age 39.3 years, 27 women) were recruited. Heat pain (HPT) thresholds were recorded for three consecutive stimuli with five second intervals by the method of limits in frontal and volar hand regions. ANOVA with repeated measures was applied. Habituation effect was defined as the percentage change in the third compared to the first threshold.**Results** HPT stimulus x group interaction was significant in the frontal region ($p = 0.008$), but not in the hand ($p = 0.85$). Mean frontal habituation effects were 4.5% in controls, 2.5% in migraine and 3.0% in TTH (Tukey post-hoc test for MIG vs CO: $p = 0.01$). Frontal HPT-habituation tended to correlate with photophobia ($r = 0.27$, $p = 0.05$).**Conclusion** Patients with migraine had less heat-pain habituation in the frontal region compared to healthy controls. This result supports the theory about a trigeminal brainstem hypersensitivity in migraine.

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Trigeminal neuralgia as a consequence of temporal bone epidermoid cyst: case reportS. Ljubisavljevic¹, J. Ljubisavljevic², M. Spasic¹, S. Lukic¹, D. Savic¹, Z. Peric¹, A. Prazic¹¹Clinical Center Nis, Nis, Serbia;²Medical Faculty Nis, Nis, Serbia**Introduction** Trigeminal neuralgia has been described to as one of the most painful conditions of humanity. Heterogenous causes include traumatic disorders of the trigeminal nerve by neoplastic or vascular anomalies, infectious agents and intracranial tumors or demyelinating conditions. Here we report a case of a patient diagnosed with trigeminal neuralgia to epidermoid cyst at the pyramid part of temporal bone.**Case report** Fourthly six years old women, cook, was treated in Clinic of Neurology of Nis because of headache and eyes movements impairment, especially during the turning eyes on right side, without diplopia. Two years ago she had hypacusis and tinnitus without complete recovery. Also, she had a very big pain on temporal and parietal head side usually by night. In neurological finding it is evidence right hemifacial restricted to the innervations of the areas of all trigeminal branches. Magnetic resonance fided in the top of temporal bone on right side sign as a consequence of inflammation process. Hyperdense structure noted also on a computer tomography scan with destruction of bone part and bone wall of carotid channel, without density changes after contrast application. Described structure probably is genetic cholesteatoma (epidermoid cyst) which is related to carotid artery. The patient is suited for surgical intervention.**Conclusion** Trigeminal neuralgia may be an unique or initial clinical presenting symptom of epidermoid cyst. It is very important that appropriate imaging be undertaken to help in identifying the underlying cause of the pain and also its management.**Keywords** Trigeminal neuralgia, epidermoid cyst

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Cyclical methysergide in the treatment of menstrual migraineW. Mowafi¹, R. Mir², A. Al Din²¹Leeds General Infirmary, Leeds, UK;²Neurology, Pinderfields General Hospital, Wakefield, UK

Menstrual migraine is a recognised clinical diagnosis that is responsible for 3% of migraines in its pure form and upto 50% of women with migraine as a menstrually related migraine. The headaches are more severe, last longer, are more likely to be associated with nausea, tend not to be associated with aura and are more resistant to treatment than non menstrual migraine. The role of cyclical triptans in the acute treatment and prophylaxis of these headaches has been clinically validated. The use of methysergide has fallen out of favour to other treatments in recent years due to its side effects and the clinical monitoring required. We present a 52 year old women who has suffered from menstrual migraines

without response to a multitude of acute and abortive therapies over the years, including triptans, who responded to low dose cyclical methysergide.

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Sleep quality in migraine and tension-type headache

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Objectives Sleepiness and fatigue is reported by migraine (MIG) patients. EEG studies have suggested a sleep dysfunction in migraineurs. Little is known about sleep in tension-type headache (TTH). The aim of our study was to measure sleep quality with polysomnography (PSG) in primary headache compared to healthy controls (CO).

Materials and methods Subjects slept unattended in a single-room in our patient-hotel. 52 patients with migraine (mean age 38.1 years, 15 with aura, 40 women), 20 patients with tension-type headache (mean age 40.1 years, 10 women) and 37 healthy controls (mean age 39.6 years, 23 women) were analysed. Kruskal-Wallis test was applied.

Results No differences in age, height, weight, neck circumference, apnea-hypopnea index, or desaturation was found. Group differences were found for stage III + IV sleep time (mean MIG 100 min, TTH 106 min, CO 85 min; $p = 0.009$) and relative stage III + IV sleep in percent (MIG 23%, TTH 25%, CO 21%; $p = 0.04$). Differences were not found for wake after sleep onset or the number of awakenings.

Conclusion Patients with primary headache had more slow-wave sleep than healthy controls, suggesting prior sleep deprivation or hyperactivity in thalamic inhibitory networks. Increased headache-related arousal was not detected in macro-sleep parameters.

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Novel powder device significantly improves nasal deposition compared to liquid spray; implications for absorption and clinical effects of nasal sumatriptan?

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Objectives Rapid initial rate of absorption across the nasal mucosa is regarded the main explanation for the faster onset of 20 mg sumatriptan nasal spray as compared to 100 mg delivered orally. However, only 10% of the sumatriptan spray is absorbed nasally. Clinical trials with the OptiNose nasal powder device (Opt-Powder) have shown faster and more extensive nasal sumatriptan absorption and excellent clinical efficacy. We compare the deposition patterns of a nasal spray and Opt-Powder and discuss how deposition patterns may influence PK-profiles and clinical outcomes

Methods The regional deposition and clearance patterns of the device used in the Phase I&II studies were compared to a conventional liquid

spray pump in 7 healthy subjects by gamma camera imaging after administration of either ^{99m}Tc-labeled lactose powder or liquid ^{99m}Tc-DTPA-aerosol. The gamma camera images were aligned with sagittal MRI's to identify nasal regions. Deposition results were compared to published PK-profiles and efficacy data for the two nasal sumatriptan formulations.

Results The Opt-powder device achieved a sevenfold larger initial deposition in the upper posterior third of the nose (Opt-Powder: 18.3% ± 11.5 vs. Spray: 2.4% ± 1.8; $p < 0.02$) and threefold deposition in the upper posterior 2/3 of the nose (Opt-Powder: 53.5% ± 18.5 vs. Spray: 15.7% ± 13.8; $p < 0.02$). Cumulative exposure for 32 minutes following delivery shows a similar pattern. The ratio for cumulative exposure in the upper posterior third is 3.7 (Powder/Spray), ($p < 0.04$) and 2.2 for the upper posterior 2/3rd ($p < 0.04$).

Conclusions The more widespread nasal deposition achieved with the Opt-powder device compared to a liquid spray is the most obvious explanation for the faster and greater nasal absorption of sumatriptan. However, based on efficacy data and recent animal studies we speculate that the improved deposition of Opt-Powder may contribute to the clinical effects also by blocking pain signaling in the trigeminal nerve directly involved in the pathophysiology of migraine.

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Analysis of a relationship between smoking and headache in working population

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Smoking represents, to put it mildly, a bad habit, but at the same time it represents a risk factor for many diseases, and sometimes it can be viewed as an addictive disease. The aim of this research was to establish the relationship between smoking and headache occurrence, as well as the occurrence of certain headache types and sub-types in working population in our environment. The research has been conducted on a sample of 1022 employed examinees of both sexes and between 20-65 years of age. The data have been collected via general questionnaire in which one of the questions was related to nicotine use. The data that have been collected were processed by corresponding mathematical-statistical methods. The results show the prevalence of a non smoking population (59% of examinees) in our working population. Although the number of non-smokers is greater among the healthy, the difference is not a relevant one, and using the method of a χ^2 - test, the correlation between the presence of headaches and nicotine use has not been proven. In the group of examinees who have headaches, and who have been divided in those suffering from migraine, tension-type headache and other types of headaches, the largest number of smokers was within the group of those with migraine with very low correlation between the type of the headache and nicotine use. In relation to observed sub-types of headaches, which have been divided into migraine with, and without aura, rare episodic tension-type headache, frequent episodic tension-type headache and chronic tension-type headache, the greatest number of smokers was among those with chronic tension-type headache. A very low correlation between nicotine use and sub-type of a headache has been established. Although low, the correlation between nicotine use and certain types and sub-types of headaches harms the patients and quitting the habit would be strongly recommended.

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Correlation between circle of Willis and migraine

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Background Migraine is already classified among the diseases with cerebrovascular risk, based also on the white matter alterations seen in the MRI. Relating to the fact that vascular abnormalities can trigger cerebral hypoperfusion, in this study we assessed the correlation between the variations of the Circle of Willis and Migraine.

Methods In this study were included 50 patients which underwent CT angiography or MRI angiography from March 2007 until March 2009. 23 of the patients were diagnosed as migraineurs (46 %) 27 patients had other neurologic disorders (54 %). In the migraineurs group 12 had migraine without aura and 11 had migraine with aura. In 8 of the migraine patients were seen abnormalities of the white matter (5 had migraine with aura and 3 without aura). 60 % of the total number of the patients presented abnormalities of the Circle of Willis (30 patients), from which 18 belonged to the group of the migraineurs (60%) and 12 (40%) to the other group. The abnormalities were related to hypoplasia or aplasia of the posterior communicating artery, or other vascular abnormalities.

Results It was shown an evident correlation between the abnormalities of the circle of Willis mainly with hypoplasia or aplasia of the posterior communicating artery with the migraine patients.

Conclusion Our comparative study despite being conducted in a small number of patients showed a strong correlation between the abnormalities of the circle of Willis and migraine.

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Clopidogrel (PLAVIX) in the prevention of typical migraine aura without headaches - a case report

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Aims Treating and preventing frequent migraine auras is known to be very challenging, be it with frequent auras as part of migraine with aura attacks or as freestanding auras without headaches. Clopidogrel may have a relatively specific role in the prevention of migraine auras. Subanalysis of the Migraine Intervention With STARFlex Technology (MIST) trial (Dowson et al, 2008) seemed to point to a relatively specific role of clopidogrel (with and without combination of acetyl salicylic acid). Wilmshurst reported in 2005 a highly significant reduction of migraine with aura attacks after addition of clopidogrel to aspirin after transcatheter closure of pending foramen ovale. This case report supports the possible specific role of clopidogrel in the prevention of migraine auras.

Methods Case report.

Results A 74 year old lady with moderate cardiovascular disease was seen at the Headache Center Zurich Hirslanden for frequent visual migraine auras without headaches. Her major concern were worries about pending cerebrovascular infarction. Persistent open foramen ovale was ruled out by echocardiography. Several migraine prophylactic substances were tried without success until she was switched by

her cardiologist from aspirin to clopidogrel leading to an immediate disappearance of her visual auras. Auras recurred during three episodes of several weeks. During each of these episodes clopidogrel had to be stopped for orthopedic surgery of large joints.

Conclusion Clopidogrel seems to play a relatively specific role in the prevention of migraine auras, here typical visual auras without headaches. This case further seems to point to an independent role of clopidogrel with no need for a combination with aspirin although in some cases the combination may be needed to prevent auras.

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Subcutaneous occipital nerve neurostimulation; treatment for refractory headaches

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There are many primary headache in which the involvement of the trigeminal system in the entire etiopathogenic process has been identified. We know the importance of such a system and through intervention on it, we can determine a change in the activation humbral. There are many articles describing the Occipital Nerve Stimulation as a treatment for some types of refractory headaches. Despite the results, which in general are encouraging, we still can not reach statistically significant conclusions.

In this paper, we analyze the results of our experience in the treatment by placing occipital stimulation systems in patients with refractory cluster headache. Data has been collected from 14 patients through pre- and post-surgery diaries. All of them chronic and refractory to medical treatment during a previous period of monitoring in our unit for 3 years. Two subcutaneous electrode system were implanted and located by anatomical references and looking for a suitable stimulation area as directed by the patient during surgery. During the first 24 hours the system was tested and turned on. Monitoring visits were arranged during the first and third month, biannually and annually, in which the parameters were adjusted again if needed. The clinical response was satisfactory in all patients, with a reduction of at least 50% in the number of crises in all of them. 7 patients had no more seizures after surgery and medical treatment could be completely removed in 10. The stimulation parameters used were variable (300-700 cms, 40-80 Hz, 1.5 to 6 mA). During follow-up the most frequent complication was the rejection and infection of the system, which forced the withdrawal of the system in three patients. There were no major complications. Therefore we conclude that occipital nerve stimulation is an effective and safe treatment for some selected patients with chronic and refractory cluster headache.

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Onabotulinum toxin, type A, for treating co-morbid migraine/headaches and TMD symptoms

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Objectives Onabotulinum toxin, type A, intradermally, [BontA] was used to treat headaches and migraines of facial origin (IHS criteria) for migraine in patients with temporomandibular disorders (TMD). Intradermal application was used, a novel injection technique.

Background Botulinum toxins can play a role in reducing pain and headache disorders and recent evidence suggests that there is migration of BontA to the CNS from peripheral injection sites.

Methods 48 patients [35f, 13 m] were entered. All received intradermal BontA, 100 units, given on the side of predominant side of TMD/migraine involvement. All patients were followed monthly. Migraine frequency and severity, along with TMD symptom severity, were assessed monthly.

Results BoNTA showed statistically significant reductions of migraine frequency and severity both at 1 month and at 3 months. Headache/migraine frequency was 17.2 headaches per month, as compared with 3.6 headaches per month after BontA treatment. ($p < .001$, 2-tailed t test). Reductions in migraine severity continued at $p < .002$ compared to baseline data after 3 months. TMD pain reduced 73% VAS) after BoNTA treatment for an average of 12.6 weeks (6.4–21.7). Reductions in migraine severity continued at $p < .002$ compared to placebo over 12.5 weeks. No side effects were noted with BontA, other than minor discomfort at injection sites. Safety and tolerability of intradermal BontA were excellent.

Conclusions Intradermal dosing may involve mechanisms of action that do not utilize cholinergic motor nerve elements and may involve alterations in pain transmission pathways.

Intradermal BontA reduced significantly the frequency and severity of migraines and TMD symptoms, including pain. Safety and tolerability of intradermal BoNTA was excellent. Intradermal BontA dosing may involve mechanisms of action that do not utilize motor nerve elements and may involve alterations in pain transmission. Double-blind studies are needed for intradermal BontA for face pain and migraine disorders.

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A randomized controlled trial evaluating the efficacy of tailored migraine self-management tools

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Background Migraine is a chronic disease with attacks that vary in frequency. A hallmark of chronic disease management is patient self-management. In order for patients to optimize migraine management and prevention they need knowledge and tools. Tailoring self-management materials for migraine management and prevention would enhance personal relevance and in theory be more efficacious than generic materials.

Objective This randomized controlled trial evaluated the impact of tailoring migraine self-management (miSelf-T) vs. generic miSelf (miself-G) and compared these groups to those keeping daily diaries (DD) or usual care (UC). The following outcomes (12 weeks post-baseline) were considered:

- headache days per month;
- number of days modifiable migraine triggers (sleep, stress, skipping meals) were elevated;
- headache-related disability; and
- whether cognitive factors moderated efficacy.

Methods 119 individuals with migraine (91% female; Age $M = 41.66$, days with headache per month $M = 9.83$) were randomized to one of 4 conditions (miSelf-T, miSelf-G, DD, UC). The

miSelf program consisted of 8 newsletters and provided education and tools for “managing triggers, managing medication, and managing life”. Materials were tailored on demographics, risk of triggers, self-efficacy/locus of control (LOC), and disability. Individuals kept a daily web-based diary.

Results The miSelf-T group showed the greatest improvement, especially among those with high efficacy/LOC at baseline. MiSelf T or G showed significant improvement at 12 weeks relative to those in the DD or UC group for disability ($p < .05$) and headache days relative to UC ($p < .05$). Relative to UC, all other conditions showed significant improvement in managing triggers ($p < .01$). Cognitive factors also showed improvement, especially among those in miSelf-T.

Conclusions Providing self-management materials improved migraine management, especially among those with high efficacy/LOC at baseline. Tailoring these materials enhanced the efficacy of the materials and suggests that more elaborate tailoring be researched to evaluate its added benefit.

Conflict of interest Nicholson R.A. Funded by NIH grant NS048288. Provided consultative services for Endo Pharmaceutical, Merck & Co during the past 12 months.

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Evidence for CGRP re-uptake in rat dura mater encephali

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Background and purpose Calcitonin gene-related peptide (CGRP), a potent vasodilator, is distributed in trigeminovascular sensory nerve fibres and CGRP is released upon its activation.

Release of CGRP is thought to be one of the underlying mechanisms of migraine pathogenesis. Uptake and re-release of peptide signalling molecules is generally not believed to occur, but we have previously found functional evidence for uptake in a guinea pig basilar artery preparation. We investigated CGRP release as well as uptake in the intact dura mater.

Experimental approach The hemi-sected skull model was used to study CGRP release and uptake from rat dura mater. The released CGRP was measured using an enzyme-linked immunoassay. We used four successive capsaicin challenges to deplete CGRP followed by CGRP incubation to allow uptake. Immunohistochemistry was performed to visualize the depletion and uptake of CGRP from sensory nerves.

Key results Capsaicin-induced CGRP release was attenuated by the TRPV1 antagonist capsazepine and by calcium ion free environment. Subsequent to depletion of CGRP skull halves were incubated with exogenous CGRP which caused an increase in capsaicin-induced CGRP release as compared to the challenge just prior to incubation. The CGRP uptake was not influenced by a Ca^{2+} -free environment. Sumatriptan, olcegepant and CGRP₈₋₃₇ did not affect the uptake of CGRP. However, a monoclonal CGRP-binding antibody decreased

CGRP uptake significantly. Release of CGRP after incubation was attenuated by Ca^{2+} free environment and by capsazepine. Immunohistochemistry experiments also indicate CGRP uptake in rat dura mater.

Conclusion We provide evidence that CGRP can be taken up and subsequently released in response to chemical stimuli in a calcium

dependent manner. This new phenomenon may have considerable influence on CGRP signalling. Deciphering the exact mechanism and site of uptake and how it can be used to manipulate CGRP release may be of interest for future treatment of migraine.