INVITED SPEAKER PRESENTATIONS

11 The epidemiology of migraine genetics: recent findings, implications, and future directions
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There is little doubt about the strong contribution of genetic factors to migraine occurrence. However, while specific genes have been identified for the rare familiar hemiplegic migraine form, the contribution of genetic factors to more common forms of migraine on the population-level remains challenging. The complex heterogeneous clinical presentation, multifactorial triggering factors, and involvement of other disorders contribute to the difficulties identifying specific genetic variants for common migraine forms. Candidate gene association studies did not show convincing results and replication often failed. Recent collaborations of clinic- and population-based studies have identified several genetic variants in specific migraine subgroups but also on the population level. In addition, several studies have evaluated the role of genetic factors in the interrelationships of migraine and specific comorbidities. Some of the variants point towards involvement of biological reasonable mechanisms while the role of others remains unclear. This talk will summarize recent advances in migraine genetics in clinic- and population-based settings, discuss potential implications and pitfalls, as well as outlines future directions.

12 Analgesic drug development: time to break the mould
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Success in the introduction of novel, effective and safe analgesics has been notably limited over the past ten years even though existing treatments have low responder rates and a high side effect burden. The pipeline of compounds acting on novel targets is very restricted and there have been many disappointments with drugs that appeared promising in preclinical studies, failing repeatedly in clinical trials. We have to recognize that something is fundamentally wrong with the industry standard approach to the selection of targets, identification of hits, validation of leads and proof of concept clinical studies. A radically alternative strategy is required, one that is driven by the patient and focused on disease phenotype. I will discuss what such an approach may look like and how it may contribute to new therapeutics.

13 Headache research - where are we heading?
Rigmor Jensen
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Since the pioneering work with the IHS-classification in 1988 and the triptan era in the early nineties, the field of headache research has expanded exponentially. Slowly but steadily headache has been moved from a trivial and neglected disorder to be respected and acknowledged as illustrated by the nomination of 2012 as The Year of Headache in The International Association of Pain. Almost all areas of headache research are now flourishing from genetics, experimental animal and human research, epidemiological and costs studies to new treatments and optimized care. Despite this scientific explosion, why are millions of headache patients still suffering from severe headaches, overuse of medication, significant disability and limited access to proper headache care? What have we achieved and is it relevant for the individual headache patient? When will we find the underlying mechanisms, genetic and diagnostic markers, stratify patients and individualize their treatment? With proper animal models for both primary and secondary headaches we may understand the mechanisms and their interfaces. The pharmaceutical industry has to raise their interest in the headache and new targeted drugs should be developed. If patients at risk of chronic headache could be identified, effective prevention could be initiated in this subset of patients leading to optimization of resources. In a world with major demographic challenges and limited ressources, education and organization in headache care are absolute essentials. These challenges and exciting possibilities will be discussed in respect to the outstanding work of Professor Jes Olsen and his generation of headache pioneers.

14 Effects of glyceryl trinitrate and calcitonin-gene-related peptide on BOLD signal and arterial diameter – methodological studies by fMRI and MRA
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Introduction: Over the last decades MRI has proved to be very useful in the field of drug development and discovery. Pharmacological MRI (phMRI) explores the interaction between brain physiology, neuronal activity and drugs [1]. The BOLD-signal is an indirect method to investigate brain activity by way of measuring task-related hemodynamic changes. Pharmacological substances that induce hemodynamic changes can
therefore potentially alter the BOLD-signal that in turn falsely can be interpreted as changes in neuronal activity. It is therefore important to characterize possible effects of a pharmacological substance on the BOLD-response per se before that substance can be used in an fMRI experiment. Furthermore MR-angiography is useful in determining the vascular site-of-action of vasoactive substances.

Methods: Four substances; Acetazolamide, Glycerol Trinitrate (GTN), CGRP and sumatriptan has been examined using a 3-Tesa MRI scanner in three double-blind placebo-controlled crossover studies in normal volunteers.

Results: Acetazolamide depresses the BOLD-signal by increasing cerebral blood flow (CBF). GTN had surprisingly no effect on the BOLD-signal even though it is known increase cerebral blood volume (CBV) [2]. Infusion of CGRP induces immediate headache and dilates the middle meningeal artery (MMA) but contrarily to previous belief does not dilate the middle cerebral artery (MCA) [3]. Nor does CGRP increase brain activity per see [4]. Sumatriptan ameliorates headache, contracts MMA and marginally constricts MCA [3] without altering brain activity [4].

Conclusion: Acetazolamide depresses the BOLD-signal while GTN does not alter the BOLD-signal. Neither CGRP or sumatriptan has a direct effects on brain activity. Instead it seems that both the migraine provoking peptide CGRP and the anti-migraine drug sumatriptan exert their actions outside of the blood brain barrier. These studies show that pHMRI can be a powerful tool in understanding mechanisms and site-of-action of pharmacological compounds. And can have important implication for implementation of fMRI in headache research.

References

15
A multidisciplinary approach to the functional abnormalities of the migraineous brain and non-invasive interventions to treat them
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Background: Migraine is characterized pathophysiologically by an intertial habituation deficit of information processing, responsible for cortical hyperresponsiveness, which normalizes during attacks [1]. Furthermore, descending pain control systems (DPCSs) can be impaired in episodic and chronic migraine [34]. Noninvasive neuromodulation of the cerebral cortex may be effective in migraine prophylaxis [2] including, in chronic migraine, modulation of the dorso-lateral prefrontal cortex (DLPFC) that is part of the DPCSs [5].

Aims: To identify targets and neuromodulation interventions for migraine treatment by exploring the role of DLPFC in heterotopic noxious analgesia and by using transcranial magnetic stimulation (TMS) and direct current stimulation (tDCS).

Methods: To this purpose, we performed the following studies:
1) we studied the modification of visual cortex (VC) responsiveness, as assessed by visual evoked potentials (VEPs), induced by excitatory intermittent theta-burst TMS (iTBS) [6] or anodal (i.e. excitatory) tDCS (AtDCS) [7] in healthy volunteers (HV) and in episodic migraineurs (EM)
2) we used AtDCS on VC (twice/week for 8 weeks) in a pilot study of migraine prevention.
3) we used fMRI to explore the role of DLPFC in heterotopic noxious analgesia induced by painful cold in EM during and between attacks.

Results: iTBS induced a sustained increase of 1st block VEP amplitude and habituation in HV (n=13), AtDCS increased habituation in HV (n=11) and EM (n=12).

In the prophylactic trial (n=7), AtDCS reduced significantly migraine frequency (-40%), and attack duration (-43.25%).

In migraineurs, interictally, cold-induced analgesia, which was related to baseline autonomic arousal, was proportional to cold-induced BOLD responses in the DLPFC. During an attack, BOLD responses induced in the premotor cortex by cold application on the foot were also significantly increased.

Conclusions: Excitatory neuromodulation (both iTBS or tDCS) of the visual cortex in HV induces changes in cortical responsiveness that should be able to normalize the interictal abnormalities found in migraineurs. Our pilot therapeutic study suggests that excitatory anodal tDCS could have a preventive anti-migraine effect. Finally, the impaired descending analgesia that characterizes migraine could be amenable to AtDCS or iTBS neuromodulation targeting the DLPFC and premotor cortices.

References

I6
Cortical modulation of thalamic function during cortical spreading depression- Unraveling a new central mechanism involved in migraine aura
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The thalamus is a key structure in migraine pathophysiology [1]. Direct cortico-thalamic connections provide important interactions on both cortical and thalamic structures [2]. Cortical spreading depression (CSD), believed to underlie the pathophysiology of migraine aura [3], would be expected to influence sensory responses of thalamic neurons, through such corticothalamic interactions.

To investigate this, a CSD was induced while recording neuronal activity from ipsilateral thalamic neurons responding to electric stimulation of dural vessels. CSD induced a transient increase of spontaneous activity for 30-150s. Following this activity, in 43% of the studied neurons, spontaneous neuronal activity, as well as, A6- and C-fiber activity in response to dural vessel stimulation, was significantly enhanced for 25-90min by 94±17%, 27±6% and 109±33%, respectively. In 38% of neurons, spontaneous neuronal firing, A6- and C-fiber activity were significantly decreased following CSD by a maximum of 44±3%. Interestingly, none of the short or long-lasting effects of a single CSD within the thalamus were altered following trigeminal ablation. In a different experimental group, multiple waves of K+ induced CSDs significantly inhibited neuronal activity, compared to a single CSD. Thalamic recordings during a single CSD were further compared to CSD-evoked responses in the ipsilateral and contralateral trigeminocevical complex (TCC). CSD induced both inhibitory and excitatory responses on ipsilateral and contralateral second order neurons, through different mechanisms of action, as previously described [4]. In comparison, CSD induced a higher degree of neuronal activation within the ipsilateral sensory thalamus, compared to the facilitated evoked-activity of CSD within
the TCC (ipsilateral spontaneous activity: 94±17% vs 27±11%; C-fiber activity: 109±33% vs 36±5%).

The data demonstrate that CSD markedly alters neuronal firing of ipsilateral third order thalamic neurons, independent of peripheral trigeminal inputs. This provides a new mechanism by which CSD may indeed induce central head pain via cortico-thalamic circuits and may shed more light on the relationship between aura and headache.

References

ORAL PRESENTATIONS

O1
Treating primary headaches – management of migraine
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Migraine is a common chronic neuronal disorder with episodic attacks affecting the one tenth of the general population with enormous social impact. The management of the disorder includes several approaches, both behavioral and pharmaceutical interventions, preventive or symptomatic ones. Exceptionally, invasive treatments may be required as well. A plentiful pallet of pharmacological agents covers symptomatic treatment, further divided into specific and non-specific anti-migraine agents. Apart from triptans, ergot alkaloids are also included in the specific anti-migraine drugs. Triptans, share a common pharmacological profile targeting to 5-HT1B/1D/1F receptors with different pharmacokinetic and pharmacodynamic properties resulting to slight diverse efficacy and safety that may be important for the treatment goals. Triptans are recommended as initial treatment for moderate to severe migraine attacks, or when other agents failed to reach the expected therapeutic benefit in less-disabled patients. For migraine prophylaxis valproate, topiramate and flunarizine are recommended. In the case of chronic migraine, a disabling subgroup of migraine, with or without medication overuse, onabotulinumtoxinA and topiramate are suggested. A variety of behavioral treatments are available for those patients they experience increased stress in particular. Although numerous, the above treatments may not be enough to manage migraine appropriately even in the right hands, rising needs for future treatments with improved efficacy and safety profile. CGRP antagonists and specific 5-HT1F agonists are potential future symptomatic agents for migraine.

O2
Tension type headache
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Tension-type headache is a common primary headache with high socioeconomic impact. Establishment of an accurate diagnosis is important before initiation of any treatment. Non-drug management is crucial. Information, reassurance and identification of trigger factors may be rewarding. Psychological treatments with scientific evidence for efficacy include relaxation training, EMG biofeedback and cognitive-behavioural therapy. Physical therapy and acupuncture are widely used, but the scientific evidence for efficacy is sparse. Simple analogies are the mainstays for treatment of episodic TTH. Combination analgesics, triptans, muscle relaxants and opioids should not be used, and it is crucial to avoid frequent and excessive use of simple analogies to prevent the development of medication-overuse headache. The tricyclic antidepressant amitriptyline is drug of first choice for the prophylactic treatment of chronic TTH, while the antidepressants mirtazapine or venlafaxine are drugs of second choice. Treatment of chronic TTH may be difficult and multidisciplinary treatment strategies are recommended.

O3
Headache in children
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One in 30 children who attend primary school have a headache problem which has an impact on the child and family. However, the problem is under recognised and under treated. In children, identifying a primary headache syndrome can be challenging. However, it can be achieved in a focussed consultation undertaking appropriate history and examination. The course aims to cover the common pitfalls and red flags in the diagnosis of primary headache disorders in childhood and treatment strategies.

O4
Reflections on NICE Headache Guidelines
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The presentation illustrates the process for the development of the recent NICE Headache Guidelines and the importance of careful topic selection. The methodology, timescale, and the role of the Expert Group including patient representatives are described. The Guidelines are intended for the non-specialist in Primary Care where most patients present and can be safely diagnosed and managed. The Guidelines provide support with the diagnosis of primary headache including the value of neuroimaging which evidence suggests should not be used only for reassurance. The importance of excluding secondary causes, in particular medication overuse which is found among migraine sufferers is emphasised. Specific advice is given for management of the three most common types of primary headache; migraine, tension headache and cluster headache. Changes are recommended to current practice including prescribing combination therapy in acute migraine and indications for prophylactic topiramate. The management of female migraine sufferers of child baring potential also receives attention and caution is advised in the use of combined hormonal contraception for patients with aura due to increased risk of stroke. There are also recommendations for perimenstrual prophylaxis with frovatriptan or zolmitriptan.

O5
Menstrual migraine, migraine and contraceptives, migraine and pregnancy and migraine triggers
Anne MacGregor
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More than 50% of women with migraine report an association with menstruation. Attacks are most likely to occur during the two days before menstruation and the first three days of bleeding and are typically without aura, even in women who have attacks with aura at other times of the cycle. The majority of menstrual attacks can be controlled with symptomatic treatment alone. If this is inadequate, pre-emptive treatment with perimenstrual estradiol, triptans or non-steroidal anti-inflammatory drugs (NSAIDs) may be effective. Suppression of the menstrual cycle with anovulatory contraceptive agents is an additional option for management, particularly for women who also require contraception. Using combined hormonal contraception
continuously, without a break, can prevent estrogen “withdrawal” migraine during the hormone-free interval. Limited research suggests that high levels of estrogen, such as occur with use of combined hormonal contraceptives (CHCs), can trigger migraine with aura. Since aura and CHCs are independent risk factors for ischemic stroke, the appropriateness of CHCs solely for contraception in women who have migraine with aura needs careful consideration.

During pregnancy, migraine follows a benign course with improvement in migraine without aura likely by the second trimester. However, the high oestrogen state is associated with increased migraine aura in susceptible women. In these women, hypertensive disorders of pregnancy and stroke are more likely to occur although the absolute risk remains small. Women benefit from early advice on drugs that can be continued during pregnancy in order to optimize control and avoid unnecessary concern.

06
Novel techniques and developments in migraine research
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Advancing our understanding of the pathophysiology of migraine is one of the key ways that researchers can help provide answers to the many questions that migraineurs have. More importantly it is the only way that tailored therapeutics can be developed that can provide relief to all sufferers, not just those that are lucky enough to respond to existing therapies. It is therefore crucial that we in headache research continue in our efforts to find these answers, through continued development of our methods and providing open-minded thinking to embrace new techniques and ideas into our field. There is much important research in migraine being conducted throughout the world at this time, research that will hopefully help us to find some of these answers. It is the aim and focus of this teaching session to try to introduce the audience to some of the more recent findings and developments in migraine research, and some of the novel approaches researchers are trying to take to understand the dynamics of the migraine pain experience, from a fully translational point of view.

Dr. Akerman will provide an introduction to the topics that will be highlighted and briefly discuss our current understanding of the pathophysiology of migraine and how this may drive migrainous symptoms. It is well known that migraine involves activation of the trigeminovascular system, but it is what and how other areas of the brain and periphery may drive this activation in patients to impact migraine that still requires further investigation. These areas may include the peripheral meningeal nociceptors, the brainstem and the diencephalon, but also interaction of these areas with the cortex, and the respective importance of both the neuronal and vascular components. We know that thalamocortical function is very important in the processing of nociceptive information. Altered cortical function has long been thought to be at the root of migraine aura, and maybe even trigeminovascular activation. Dr. Holland will use preclinical data to discuss how alteration of normal cortical function can result in symptoms such as migraine aura, but also how uncoupling of the normal neurovascular relationship in the cortex, thought to drive aura, can also impact other symptomatic aspects of migraine that results in migraine as a global brain disorder. Dr. Sprenger will discuss this issue of cortical function from a clinical perspective. He will try to address how imaging is helping us understand the role of the cortex in migraine, and how migraineurs may present cortical function that is different from the non-migrainous brain.

Another very important issue for the headache researcher is in actually understanding the dynamics of the pain experienced by the migraineur. Other forms of pain research, away from the headache, have for a long time relied on animal behavioural models to observe nociceptive behaviours as a marker of pain. These models are used to study, preclinically, the different dynamics of pain that may be experienced in the clinic and also to test pharmacological agents for therapeutic efficacy. It is only recently that headache research has begun to embrace these techniques. Dr. Romero will discuss some of the methods and techniques that can be used to assess pain in the head and facial region in migraine. She will address the importance of measuring spontaneous (non-evoked) nociceptive behaviours in animals, something which the migraine patient complains of mostly, and how one can do this. Also, as we have seen in our understanding of migraine pathophysiology and the role of sensitisation, how this physiology can be interpreted in the measurement of evoked behaviours in animals. Finally, for a clinician, understanding the pain experienced by their patients is of the utmost importance in diagnosing and treating them, as well as aiding us in understanding the pathophysiology. Therefore, having the tools available to understand this is crucial. Dr. Geber, using this clinical approach, and his skills and experience in allodynia and sensory testing in experimental pain models and pain patients, will describe how these techniques can be used in patients to understand the quality of the pain symptoms related to the headache and facial region. Also, how they can be used experimentally as a research tool to aid us in understanding more about the pathophysiology of migraine and other head pain disorders.

07
Therapeutic Strategies
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Treatment strategies for childhood headache involves a multi faceted approach. Once a diagnosis is achieved. Management choice should include-treatment strategy for acute attacks and prevention. Lifestyle management-diet, exercise and sleep, psycho social factors, trigger identification and avoidance, pharmacological agents and neuromodulators, biofeedback and alternative therapies are discussed.

08
Comorbidity of headache in children and adolescence
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In its first part, this presentation will cover a short review of the features of migraine and tension-type headache in children and adolescents, which is a fascinating chapter and will especially focus on migraine aura, confusional migraine and chronic headache.

It the second part somatic and psychiatric comorbidities in children and adolescents with migraine will be reviewed covering asthma and allergies, vascular disorders, sleep disturbances, depression and anxiety as well as Tourette syndrome and attention deficit hyperactivity disorder.

09
Efficacy of multidisciplinary rehabilitation of patients with chronic headache
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Chronic headache is a challenge for general physicians and neurologist, too. In a distinctive number of patients exclusive medical drug therapy is not sufficient. Therefore multidisciplinary headache treatment concepts are an option to optimize treatment and to merge medical and non-medical treatments in a comprehensive therapeutic concept. Recently data on efficacy of multidisciplinary treatment programs are published. The combination of drug therapies including substances like topiramat, amitriptyline and Onabotulinumtoxin A which shown some efficacy in chronic migraine with behavioral psychology, psychiatry, psychosomatic medicine, physical therapy, and sport therapy may outperform a single therapy. Such a therapy can be offer in an outpatient department or as inpatient treatment. Interdisciplinary concepts are needed, which integrate these disciplines in congruent program including patient education and therapy. Multidisciplinary rehabilitation for headache patients should include a follow-up care after treatment in a headache center therefore innovative technologies and collaboration between disciplines, and between hospitals and neurologists or therapist in private practice are necessary.
These preliminary results showed a significant proportion of patients to various professional sports and the impact of headache conditions on elite athletes we are undertaking a joint study together with the Faculty of Sports and Exercise Medicine UK. The prevalence of primary headache and its association with sporting activities has increased substantially. Several chronic musculoskeletal pain disorders may be explained by alterations in central nervous system processing. More specifically, the responsiveness of central neurons to input from unimodal and polymodal receptors is augmented, resulting in a pathophysiological state corresponding to central sensitization, characterized by generalized or widespread hypersensitivity. Central sensitization encompasses altered sensory processing in the brain, impaired functioning of top-down anti-nociceptive mechanisms, and (over)activation of top-down and bottom-up pain facilitatory pathways which augment nociceptive transmission. Importantly, a different ‘pain signature’ arises in the brain of those with chronic musculoskeletal pain and central sensitization.

Given the increasing evidence supporting the clinical significance of central sensitization in those in a wide variety of disorders, including chronic whiplash associated disorders, chronic tension-type headache and migraine among others, the awareness is growing that desensitising the central nervous system should be a treatment target in these patients. Besides pharmacological options, rehabilitation (consisting of pain physiology education, stress management and exercise therapy) and neurotechnology options (e.g. Transcranial magnetic stimulation, TENS, virtual reality) offer interesting perspectives.

**POSTER PRESENTATIONS**

**P1**

A rare case of persistent visual aura in a 12 year old girl

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Introduction: Migraine is a common neurological disorder affecting between 3% and 10% of children [1]. In up to 30% of sufferers [2], the headache is preceded or accompanied by a complex of neurological symptoms known as an aura. When aura symptoms persist beyond 7 days without evidence of infarction, the International Headache Society characterizes the condition as persistent migraine aura without infarction [3].

Purpose/objectives: Persistent visual aura symptoms are rare, and only two published cases describe the condition in children [45]. We use this case to exemplify the condition and how it has been managed in our specialist clinic. We highlight the need for further insight to allow effective management in the paediatric population.

Methods: The case of a 12 year old girl who has experienced persistent visual aura symptoms continuously since May 2010 is described, including the results of investigations and treatment history. The patient’s illustration and verbal description of symptoms provides a unique insight into her ordeal.

Results: Our patient’s aura symptoms have so far been resistant to pharmacological therapy.

Conclusion: Aura persistence in children lasting months is unusual. Our specialist clinic has only seen 2 previous cases, in which the aura lasted less than a week, and resolved with treatment for the migraine. As advances are made in our pathophysiological understanding, further treatment options may be discovered. Until a proven treatment is identified, it is important that clinicians share their experiences to help guide patient management.

References

**P2**

London 2012 - a survey of the impact of headache on UK elite athletes

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Background: It is well understood that to maximise performance in sport it is important to optimise all possible variables. Headache is a very common symptom, while migraine affects between 10-15% of the population. Although athletes are frequently subject to large numbers of potential migraine triggers (exertion, stress, fatigue, dehydration), there are relatively little data examining the impact of headache conditions on elite athletes.

Objectives: In order to investigate the prevalence and impact of headache on the performance of elite athletes we are undertaking a joint study together with the Faculty of Sports and Exercise Medicine UK.

Methods: A questionnaire has been formulated together with the British Association for the Study of Headache (BASH), and the Faulty of Sports and Exercise Medicine. It will be submitted to various professional sports and athletic associations. To date the British Lawn Tennis Association, British Horse Racing Authority and Football Association (UK) have been approached.

Results: At present, preliminary results are available from 30 questionnaires recently received via the British Lawn Tennis Association and British Horse Racing Authority. 57% (17/30) of respondents reported that headaches limited optimal performance in their sport (12/22 males; 5/8 females), although only one respondent fulfilled ID migraine criteria.

Conclusions: The results of this preliminary study highlights the need for further research into the relationship between headache and elite athlete performance.

References
Objective: The aim of this study was to estimate the prevalence of headache among children in Lithuania in 2010 and describe the association between headache and socio-economic factors. This study was a part of the Cross-National Survey on Health Behaviour in School-aged Children--World Health Organization Collaborative Study (HBSC).

Methods: The research was carried out according to the methodology of the HBSC study using the anonymous standardized questionnaire. In total, 5,323 students (2,740 (51.5%) boys and 2,583 (48.5%) girls aged 11, 13 and 15 years from Lithuania were surveyed in the 2010 school-year.

Results: The total prevalence of frequent headache (at least once a week) among children 11, 13 and 15 years of age was 33.7% 31.9% and 34.4%, respectively. Pain was most frequent among older girls (13 and 15 years of age) (χ² = 43,529 ; df = 2; p<0.005). The headache prevalence was slightly higher in low-income families and divorced or one parent families compared to those of high status and two parent families. Multivariate analysis revealed that having a good relationship with parents and peers, associated with less headache cases.

Conclusion: Headache is more common among children with lower socioeconomic groups. Social causation can play a role in the pathogenesis of headache and should be considered by health promoters.

Reference

P4
The clinical characteristics of abdominal migraine and risk factors for developing migraine later in childhood
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The Journal of Headache and Pain 2013, 14(Suppl 1):P4

Objective: Abdominal migraine (AM) is an idiopathic recurrent disorder occurring primarily in children. Because their abdominal pain may be so intense to interfere with their normal activity and AM is recognized as migraine prodrune, it is important to make the exact diagnosis, appropriate managements and close follow-up the symptoms. We therefore analyzed the clinical characteristics of AM and risk factors for developing migraine later.

Methods: The 923 children with recurrent abdominal pain (RAP) visited our hospital from Jan 2006 to Dec 2010. Among them we retrospectively studied 84 children fulfilled ICHD-II criteria for AM. Through chart review and telephone interviews, we evaluated the clinical characteristics of AM and divided them into two groups by developing for migraine (group A) or not (group B). By comparing the groups, we tried to find the risk factors for developing migraine later.

Results: About 8.9% of patients with RAP were diagnosed as AM. Their mean age was 7.1±3.0 years (boys, 24, 28.6%; girls, 60, 71.4%). The frequency of abdominal pain was 4.3±2.4/week and the duration of abdominal pain was about one hour (0.5~2.0). The symptoms associated with abdominal pain were anorexia (n=35, 15.5%), nausea (n=58, 69.0%), vomiting (n=26, 31%), pallor (n=12, 14.3%) and headache (n=64, 76.2%). 27 (32.1%) patients with AM were suffer from migraine 1.7±0.8 years later from onset of AM, and their mean age was 8.3±3.2 years (boys, 8, 29.6%; girls, 19, 70.4%). When the clinical characteristics were compared to each other between group A (n=27) and group B (n=57), there were no differences in age, gender, frequency, duration etc. But AM patients with headache significantly developed migraine later (P=0.003). AM patients who needed drug therapy significantly developed migraine later (P=0.034).

Conclusion: 32.1% of AM patients developed migraine. And the risk factors for developing migraine were headache associated with AM and general impression by physician that need pharmacologic therapy.

References

P5
Frequency and pattern of migraine among medical and nursing students at Enugu, South East Nigeria
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Introduction: Headache may be the commonest neurological disorder in the community and may impose a substantial burden on sufferers and on society. Although data from the last century revealed that primary headaches were rare among Africans, newer data have shown higher prevalence in the continent. Few studies have addressed the frequency of migraine among students in South East Nigeria.

Objective: To ascertain the Frequency and pattern of migraine among young Nigerians as represented by medical and nursing students in two Teaching Hospitals and two Nursing Schools in Enugu, South East Nigeria.

Methods: This was a cross-sectional descriptive interview-based study using structured headache questionnaire. Consent was obtained and the results interpreted following the guidelines of the International Headache Society (IHS).

Results: The one year frequency of primary headache of any type was 86.3% (85.4% in males and 86.7% in females). The frequency of migraine was 13.1% (males 10.8%, females 14.8%). Frequency of migraine was highest below 20 years (16%) (males-8%, females 18.8%). The peak frequency for males was from the ages of 20 to 26 (15.3%) and below 20 years for females (18.8%). Most, migraine attacks were unilateral (89.8%), moderate/severe (67.8%), pulsating 96.6%) with phono/ photophobia (83.1%) and stress as the commonest triggering factor (61%). Migraine attacks were frequent in 66.1% and affected the quality of life of the sufferers in 40.7%.

Conclusion: There is a high frequency of headache of migraine among medical and nursing students in Enugu. Migraine was 1.4 times commoner in females than in males. Migraine affected the quality of life of more than 40% of its sufferers.

P6
The effect of sleep duration in clinical features and impact of migraine: Result from a population-based study
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Background: Although sleep disturbances are a common complaint in migraine patients, the role of sleep habits such sleep duration in clinical features and impact has been poorly analyzed.

Objective: To assess the influence of sleep duration on clinical features and impact of migraine.

Methods: We selected a stratified random population sample of Koreans over age 19 and evaluated them with a 60-item semi-structured interview designed to identify headache type using ICHD-2 criteria and sleep status such as sleep duration and sleep onset time. We also included items for demographics and HIT-6.

Results: Of 2,836 all participants, 152 were diagnosed as having migraine. The mean sleep duration similar between migraineurs (7.1±1.5 hours) and non-migraine controls (7.1±1.3 hours). Among migraineurs, 15 (9.9%) participants slept <5 hours, 83 (54.6%) slept 5-7 hours, 44 (28.9%) slept 7-9 hours, and 10 (6.6%) slept>9 hours in weekdays. Migraineurs with sleep duration of ≤5 hours reported higher migraine attack frequency
(9.8±11.3 attacks per month) comparing to a sleep duration of >5 hours (3.8±6.3 attacks per month, p=0.001). Migraineurs with ≤5 hours sleep duration showed a tendency of increased HIT-6 score (59.7±9.9) comparing to sleep duration of 7-9 hours (53.1±5.8, p=0.088). Unilateral pain was more prevalent among migraineurs with sleep duration of >5 hours comparing to sleep duration of ≤5 hours. Headache severity, pulsating quality, aggravation by movement, nausea, vomiting, photophobia and phonophobia was not significant according to sleep duration.

Conclusions: High attack frequency is associated with sleep duration of ≤5 hours among migraineurs.

References

P7 Excessive daytime sleepiness and migraine: A population-based study
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Background: Excessive daytime sleepiness is a common symptom, with a prevalence of 10-20% in general population and is reported to be with associated with migraine. However, the prevalence, clinical features, and impact of excessive daytime sleepiness among migraineurs in population-based setting have only rarely been reported.

Objective: To assess the influence of excessive daytime sleepiness on clinical features and impact of migraine.

Methods: We selected a stratified random population sample of Koreans over age 19 and evaluated them with a 60-item semi-structured interview designed to identify headache type using ICHD-2 criteria. We assessed the Epworth sleepiness scale (ESS) for assessing sleepiness and excessive daytime sleepiness (EDS) was defined as ESS ≥10. We also included items of HIT-6 to assess impact of headache.

Results: Of 2,836 all participants, 152 (5.1%) were diagnosed as having migraine. EDS was more prevalent among migraineurs comparing to non-migraine controls (25.7% for migraineurs vs. 16.3% for non-migraine controls, p=0.003). Migraineurs with EDS reported higher attack frequency per month (7.0±9.7 attacks for migraineurs vs. 3.5±5.8 for non-migraine controls, p=0.000), higher VAS score for pain intensity (7.1±1.8 for migraineurs vs. 6.0±1.9 for non-migraine controls, p=0.006), and higher HIT-6 score (60.6±10.3 for migraineurs vs. 52.8±8.3 for non-migraine controls, p=0.000) comparing to migraineurs without EDS. Migraineurs with EDS showed more of depression (OR=5.67, 95% CI 2.5-12.7), insomnia (OR=2.98, 95% CI 1.1-8.4) and sleep disordered breathing (OR=2.78, 95% CI 1.1-7.3) than migraineurs without EDS. Unilateral pain, pulsating quality, aggravation by routine physical activity, nausea, vomiting, photophobia and phonophobia were not significant according to EDS.

Conclusions: EDS is prevalent among migraineurs in general population. Attack frequency, severity and impact by headache increase with EDS.

References

P8 Adolescents with chronic headaches - mental health problems and coping patterns
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Introduction/purpose: Most studies on chronic headache have focused on adults, but chronic headache is also a major problem in children and adolescents [1]. There are gaps in knowledge of coping and mental health problems in adolescents with chronic headaches [2]. The aim of the present study is to get a better understanding of the relationship between different coping strategies and the presence of chronic headache either alone or in combination with mental health problems.

Methods: This study is based on a self-report cross-sectional study undertaken in Akershus County in Norway in 2002. A total of 19,985 adolescents were included in this study, covering lower secondary and upper secondary students, aged 13-19 years. Mental health was assessed by using the Strengths and Difficulties Questionnaire (SDQ). Chronic headache was measured with a single item, defined in close accordance with the classification of the International Headache Society (ICHD-2). Internal and external coping strategies were assessed through seven items, based on the question: What do you do/what happens when you are burdened by painful thoughts and feelings?

Results: Adolescents with chronic headaches showed more symptoms of mental health problems overall compared to those without chronic headache or with mental health problems alone. Logistic regression analyses showed that those adolescents having both chronic headaches and comorbid mental health problems to a greater extent used internal coping strategies, such as keeping feelings inside (OR 2.05), using drugs (OR 1.79) and talking oneself out of problems (OR 1.55), compared to those with chronic headache alone.

Conclusion: We suggest that attention should be paid towards coping strategies used by a high risk group that have both headaches and mental health problems.

References

P9 Major life events, stress appraisal, and migraine: results of the American Migraine Prevalence and Prevention (AMPP) study
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Objective: To assess cross-sectional differences among persons with chronic migraine (CM) versus episodic migraine (EM) in major-life-events (MLE) rates and appraisal of events as stressful (SLE).

Methods: AMPP is a longitudinal, US-population-based study for which questionnaires were mailed to 24,000 severe headache sufferers and followed annually. Respondents with ICHD-2 migraine were stratified as either CM (≥15 headache-days/month) or EM (<15 headache-days/month). MLE occurrences were defined as moving, change in significant-other, other deaths, other over preceding year. For endorsed MLEs, respondents were asked to assess stress level on a 5-point Likert scale (1=not at all to 5=very much). To identify a SLE, responses were dichotomized with a cut-score of ≥74. Ordered logistic regressions used to model odds of reporting more SLEs. Results: In 2007, 14,069 individuals responded and 557 had CM and 748 had EM. 80.1% of CM reported ≥1 MLE in preceding year vs 78.6% of EM.
The proportion of CM vs EM reporting no MLEs (18.2% vs 21.4%), 1 MLE (26.3 vs 27.5%), 2 MLEs (27.8 vs 25.1%) or ≥3 MLEs (27.8 vs 25.1%) revealed more MLEs for CM. 76.5% of CM reported vs 71.4% of EM. Proportion of CM vs EM reporting no SLEs (19.3% vs 23.3%), 1 SLE (32.9 vs 34.1%), 2 SLEs (27.2 vs 25.2%) or ≥3 SLEs (30.7 vs 17.4%) revealed more SLEs for CM. Unadjusted odds ratio (OR) comparing those with stress scores ≥5 vs lower score was ~25% greater for CM vs EM (OR=1.25, 95%CI 1.04-1.49). Adjusting for age, gender and race produced similar results: (OR=1.27, 95%CI 1.07-1.52).

Discussion: CM persons reported more MLEs in the preceding year and were more likely to perceive events as stressful. Longitudinal analyses are required to assess whether MLEs/SLEs are risk factors for CCM.

Funding: The AMPP study was funded through a research grant to the NHF from Ortho-McNeil Neurologics. Additional analyses were supported by Allergan, Inc.

P10
Cerebral venous hemodynamic disturbances in children with different types of headache. The role of transcranial ultrasonography methods
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Materials and methods: 1,340 patients aged from 3 to 17 years who complained of headache have been examined. Ultrasonic Transcranial Doppler (TCD) of “BIOSS”and “SPECTROMED” companies (Russia); transcranial color-coded duplex (TCCD) by “Logic P-5”.

Results: All children with headaches were separated according the clinical complaints: migraine, tension type of headache, headache with increase or reduction of arterial pressure, headache caused by cerebral venous dysfunction. 30% of them had cerebral anomalies (of craniovertebral junction and deep brain veins). The children complained of headaches (100%) and also vegetative dysfunction (80%), nasal bleeding (60%), vomiting (40%), dizziness and noise in ears (35%). Venous outflow in the cavernous sinus, straight sinus, great cerebral vein of Galen have been registered by TCD, TCCD. Cerebral venous hemodynamic disturbances (“markers”) revealed in all groups children: migraine – 35 %, tension type of headache – 40%, headache with increase or reduction of arterial pressure – from 25 % to 55%. Thus a venous outflow is stimulated and makes influence on intracranial venous circulation. The estimation of cerebral venous hemodynamic disturbances in literature is described mainly in adults, but they are of great importance in clinical manifestations, especially in children. Diagnosis of such disturbances in children is not detected in time, though they often turn out to be one of the main evidence of cerebrovascular pathology. The complex research of cerebral venous hemodynamics presents new possibilities for revealing disturbances of cerebral venous blood circulation. The conservative treatment which has been performed under ultrasonographic control (TCD, TCCD) in children with disturbances of cerebral hemodynamics, led to objective improvement in 85% of children.

P11
Unraveling migraine susceptibility in females: the involvement of GABA genes
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Migraine is a common neurological disorder with a global prevalence around 10% [1]. Several studies showed that migraine is influenced by genetic and environmental factors [2]. The female-to-male ratio of migraine prevalence is 3- to 4-fold higher among women than men [3]. The role of common variants of GABA genes in the X-chromosome in migraine susceptibility was assessed, aiming to explain the differences in disease frequency between males and females. An association study with 188 unrelated cases and 287 migraine-free controls age- and ethnic matched was performed. The case-control ratio was 1:1.5. Candidate genes were selected based on their possible role in pathophysiology of migraine. Thirty-two tagging SNPs were selected in three genes (GABRE, GABRA3 and GABRQ) and genotyping was performed by SNaPshot. Allelic, genotypic and haplotypic frequencies were compared between cases and controls and multiple testing corrections were performed. Also, gene-gene interactions were analyzed. The Results for allelic associations revealed five nominal significant associations and three trends for association. In what concerns genotypic frequencies, four noteworthy results were found in GABRE and GABRA3 genes. After multiple testing correction, two allelic associations remained significant (GABRA3 and GABRE) and one genotypic association resisted to Bonferroni correction (GABRE), all in the females group. No significant results were found in the haplotypic analyses but an additive effect was observed between two SNPs of GABRA3 and two of GABRE. These findings show, for the first time, evidence of a possible involvement of common variants in GABA receptors in migraine susceptibility and in gender-specific liability.

References

P12
The relationship between headache and chronic musculoskeletal complaints: an 11-year follow-up in the Nord-Trøndelag Health Study (HUNT)
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Background and aim: Chronic daily headache (CDH) and chronic musculoskeletal complaints (CMSCs) are associated disorders, but whether there is a causal relationship between them is unclear. The aim of the study was to determine whether CMSCs are associated with the subsequent development of CDH and vice versa.

Methods: This longitudinal population-based cohort study used data from two consecutive surveys in the Nord-Trøndelag Health Study (HUNT 2 and 3) performed in 1995–1997 and 2006–2008. Amongst the 51 383 participants aged ≥20 years at baseline, 41 766 were eligible approximately 11 years later. Of these, 26 197 (63%) completed the questions regarding headache and CMSCs in HUNT 3.

Results: A bidirectional relationship was found between headache and CMSCs. In the multivariate analyses adjusting for potential confounders, a nearly twofold risk (OR 1.8; 95% CI 1.5–2.3) for developing CDH was found for those with CMSCs at baseline. Vice versa, a similarly elevated risk of CMSCs (OR 1.8; 95% CI 1.2–2.6), and even higher risk of chronic widespread MScs (OR 2.7; 95% CI 1.6–4.7), was found at follow-up amongst those with CDH at baseline.

Conclusion: Chronic musculoskeletal complaints predispose to CDH and CDH predisposes to CMSCs 11 years later. This may have relevance to understanding the pathophysiology of these disorders. CMSCs should be treated not only to relieve them but also to prevent the development of CDH, and vice versa.

P13
Risk factors for MOH and chronic daily headache: an 11-year follow-up study. The Nord-Trøndelag Health Studies (HUNT)
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Background: Medication-overuse headache (MOH) is relatively common, but its incidence has not been calculated and there are no prospective
population-based studies that have evaluated risk factors for developing MOH. Aim of the study: This was to estimate incidences of and identify risk factors for developing chronic daily headache (CDH) and MOH.

**Method:** This was a longitudinal population-based cohort study using data from the Nord-Trøndelag Health Surveys performed in 1995-1997 and 2006-2008.

**Results:** Among the 51,383 participants at baseline, 41,766 were eligible approximately 11 years later. There were 26,197 participants (responder rate 63%), among whom 25,296 did not report CDH at baseline in 1995–1997. Of these, 201 (0.8%) had MOH and 246 (1.0%) had CDH without medication overuse (CDHwoO) 11 years later. The incidence of MOH was 0.72 per 1000 person-years (95% confidence interval 0.62-0.81). In the multivariate analyses, a 5-fold risk for developing MOH was found among individuals who at baseline reported regular use of tranquilizers (odds ratio 5.2 (3.0-9.0)) or who had a combination of chronic musculoskeletal complaints, gastrointestinal complaints, and Hospital Anxiety and Depression Scale score ≥11 (odds ratio 4.7 (2.4-9.0)). Smoking and physical inactivity more than doubled the risk of MOH. In contrast, these factors did not increase the risk of CDHwoO.

**Conclusion:** In this large population-based 11-year follow-up study, several risk factors for MOH did not increase the risk for CDHwoO, suggesting these are pathogenetically distinct. If the noted associations are causal, more focus on comorbid condition, physical activity, and use of tobacco and tranquilizers may limit the development of MOH.

**Reference**

**P14 Developmental coordination disorder and migraine in childhood**
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**Purpose:** Migraine without aura (MoA) could be considered the most frequent form of primary headache in children, associated with many known comorbidities, but only the recent literature has begun to consider the importance of motor impairment linked to the attacks. The developmental coordination disorder (DCD) is a very common problem among children, with a prevalence ranging up to 19%. The aim of this study was to evaluate the presence of motor coordination impairment in a population of children affected by MoA, and its role as putative risk factor for motor skills impairment.

**Methods:** This observational study was performed in the Clinic of Child and Adolescent Neuropsychiatry of the Second University of Naples. MoA was diagnosed according to the International Classification of Headache Disorders (ICHD-2) criteria. The study population consisted of 27 patients affected by MoA (16 females, 11 males) (mean age: 8.7±2.15 years) and 59 typically developing children (34 females, 25 males) (mean age: 8.0±2.1 years). The whole population underwent a clinical evaluation in order to assess the Total IQ level, the visual motor integration skills and the presence of DCD.

**Results:** Our results showed that MoA children had more impairments in motor coordination (p<0.001) and visual motor integration (p<0.001) than control group.

**Conclusion:** To our knowledge this is the first study to assess the association of poor motor coordination and MoA in children using.

**References**
Introduction: Children with tension-type headache (TTH) might have an altered pain perception. Some of these children suffer from the chronic form of TTH. It is not yet known if central sensitization plays a role in chronicization of TTH in children.

Objectives: The aim of this study was to use stimulus-response functions for pressure versus pain to test the difference in pain perception between children 7-17 years of age with frequent episodic tension-type headache (FETTH), chronic tension-type headache (CTTH) and controls.

Method: From May 2009-May 2011 we included 22 children with FETTH, 36 children with CTTH and 57 controls into this case-control study. We applied pressure of 5 increasing intensities to M. Temporalis and M. Masseter respectively with a Somedic Algometer II. The child rated pain on a VAS-scale.

Statistical methods: Area under the curve (AUC) was calculated and represents the tenderness of the muscle. Whereas factor analysis showed that AUC represents only one dimension common for both muscles, an average AUC in each person was used as outcome variable in further univariate multiple linear regression analysis.

Results: Stimulus-responses functions were different between the control group and CTTH. CTTH had a significant higher AUC (median 180-406) than the control group (median 191, IQR 83-286) P<0.001. However AUC in the FETTH group (median 281, IQR 202-371) was not significantly different from either the control group (P=0.084) or CTTH (P=0.283), indicating that this group does not represent an intermediate state between the two extreme groups. Sensitivity (AUC) did not change with increasing age, headache years, headache intensity, headache frequency or sex.

Conclusion: Pain perception for pressure versus pain in children with CTTH is altered. These changes seem to be a continuum of changes with the FETTH representing an intermediate state between controls and children with CTTH.
Objective: To investigate the genetic cause of FHM in a Spanish four-generation family.

Methods: We assessed the clinical features in the four affected family members by direct interview (proband and her offspring) and from heteroanamnestic information from the proband about her father. We performed direct sequencing of the FHM genes. After exclusion of mutations in the CACNA1A and ATP1A2 genes, direct sequencing of the SCN1A gene was performed.

Results: The proband had life-long hemiplegic migraine attacks. At age 69, she had a prolonged episode of hemiplegia, which gradually resolved completely over the course of a month. Her father, one of her three children, and one of her grandsons were also affected by hemiplegic migraine, but with a much lower attack frequency. We identified a novel missense mutation (c.4460G>C; p.Ile1498Met) in exon 24 of the SCN1A gene in all tested FHM patients of the family. The mutation is located in the intracellular loop of the protein and affects the IFM (4 amino acids) motif, which is essential for inactivation of the encoded Nav1.1 sodium channel.

Conclusion: p.Ile1498Met is only the sixth SCN1A mutation identified thus far. It is the first mutation in the IFM motif that causes pure FHM without additional symptoms, albeit with a large variability in severity and frequency of hemiplegic migraine attacks among mutation carriers.

P20
A meta-analysis of psychological factors in children with migraine and tension-type headache

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Introduction: Headache affects many children and adolescent causing disability. Many studies underline the role of psychological factors in children’s headache. A recent review [1] questioned the existence of psychological difficulties in migraine children, concluding that they don’t exhibit neither more psychological dysfunctions nor more psychiatric comorbidity than healthy controls. It is not clear how psychological factors effect on different kinds of headache. We wanted to clarify if there is a difference in the influence of psychological factors on migraine compared to healthy subjects and tension-type headache (TTH).

Methods: We selected 10 studies that were comparable, had a control group, a sufficient sample size, sufficient data reporting and that used CBCL as a psycho-diagnostic tool. Internalizing and Externalizing disorders in different sub-types of headache and in healthy subjects were studied. Data were analyzed using Comprehensive Meta-Analysis Software version 2. The Hedges’g was adopted as a measure of effect size. We compared migraine patients vs controls, non-migraine patients vs controls and migraine vs TTH in 3 meta-analysis using Externalizing/ Internalizing scales scores as a categorical moderator factor.

Findings: Both migraine and TTH patients showed more psychopathology than healthy controls (respectively p < .001; p=0.0002). Both the sub-types showed more marked difference with the healthy controls at the Internalizing than at the Externalizing scale (TTH respectively p=0.009, 0.051). There was no significant difference between the two sub-types (migraine, TTH).

Conclusion: Psychological factors influence headache in children, both migraine and TTH. We suggest to investigate this area and to treat children and adolescent in order to prevent a chronic evolution of the pain syndrome. CBCL may be a useful tool for a psychological evaluation.

Reference

P21
Migraine without aura: genome-wide association analysis identifies several novel susceptibility loci

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Introduction: Genome-wide association studies (GWAS) are a novel and promising method to study genetic susceptibility factors for common disorders, including migraine.

Objective: Here we performed the first GWAS in migraine without aura (MO), which is the most common form of migraine.

Methods: To identify common genetic variants for this migraine type, we analyzed genome-wide association data of 2,326 clinic-based German and Dutch patients and 4,580 population-matched controls. Loci with two or more SNPs with P-values < 1 x 10^-5 were selected for follow-up in 2,508 Dutch, Spanish, Finnish and Norwegian patients and 2,652 controls.

Results: Meta-analysis of the discovery and replication data yielded four genome-wide significant (P < 5 x 10^-8) MO susceptibility loci in or nearby MEF2D, PHACTR1, ASTN2 and TGFBR2. In addition, SNPs in two loci (in or near TRPM8 and LRPI) that were previously identified in a GWAS on population-based migraine were significantly replicated in our clinic-based MO cohort.

Conclusion: This study reveals the first susceptibility loci for migraine without aura, thereby expanding our knowledge of this debilitating neurological disorder.

P22
Influence of Tohoku-Pacific ocean earthquake on headache cases in the affected area

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Introduction: On March 11, 2011, Tohoku-Pacific Ocean Earthquake with a magnitude of 9.0 occurred in East Japan, affecting a part of our hospital located in Sendai causing serious damage. The tsunami struck 4 km away from our hospital. This disaster caused considerable damage to various lifelines including food and medical supplies. Some transportation networks were also paralyzed for several weeks. Although there were such limitations, our hospital continued to conduct medical examination of patients including outpatients.

Purpose: The aim of this study was to examine how the disaster influenced the headache (HA) medicine at our hospital. Method: We compared the situation of outpatient consultation for HA cases, severity of pain, impact on daily life, and types of HA, which included migraine, tension-type HA (TTH), cluster HA (CH), and medication-overuse HA (MOH).

Results: The number of outpatient HA cases before the disaster was 9.5 persons/day, and the occurrence rates of the HA types were 62.2% for migraine, 38.6% for TTH, 3.0% for CH, and 10.6% for MOH. The number of HA cases decreased remarkably after the disaster (1.6 persons/day) in March, after which it increased gradually (8.1 persons/day) in July. After the disaster, although the severity of pain did not change, the impact on daily life because of migraine became significantly worse (p < 0.001). The occurrence rate of migraine increased and that of TTH decreased significantly (p < 0.001). The occurrence rate of MOH increased slightly, and a change was seen in the occurrence rate of CH.

Conclusion: After the disaster, although the HA outpatient consultation rate fell evidently, the occurrence rate of severe migraine increased at our hospital. Although it was difficult to visit a hospital due to difficulties as a result of the disaster, an HA patient particularly with the high impact on daily life visited hospital to seek help.

References:

P24
A loss-of-function CACNA1A mutation causing benign paroxysmal torticollis of infancy
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Introduction and background: Benign paroxysmal torticollis of infancy (BPTI) is a rare paroxysmal disorder characterized by recurrent episodes of head tilt and variable behavioural and autonomic changes, usually disappearing after age 2 years and often evolving into benign paroxysmal vertigo or common migraine. A few reports have linked BPTI to mutations in CACNA1A.

Patients and methods: A 2-year-old boy was referred with a history of recurrent episodes of torticollis starting at the age of 9 months and occurring twice per month ever since. During the episodes, which lasted from minutes to 2 hours and were relieved by sleep, the patient became irritable, unsteady and held onto his mother. After age 2 years the patient appeared drowsy and apathetic during the episodes. His psychomotor development and interictal examination are normal. Her 10-year-old female sister experienced similar attacks between ages 13 months and 3 years. They occurred monthly and lasted from 30 minutes to 24 hours and some reportedly associated upgaze deviation and severe global hypotonia. Carbamazepine did not help. No overt migraine attacks have developed. We performed direct sequencing of the 47 exons and flanking introns of the CACNA1A gene in the nuclear family and a maternal aunt affected with epilepsy.

Results: A heterozygous G-to-A transition in exon 12 (c.1597G>A) of CACNA1A, bringing about a p.Glu533Lys change, was found in both patients and their asymptomatic mother. The change involves a highly conserved glutamate on the S2 segment of domain II of the protein. Analysis of the mutant channel expressed in HEK 293 cells reveals that the mutation produces both a huge decrease in current density and a significant shift to higher voltages of the current activation curve that was accompanied by the alteration of activation kinetics. A previous report has shown cosegregation of p.Glu533Lys with familial episodic ataxia type-2 (EA-2).

Conclusion: This is the first report of a childhood periodic syndrome being caused by a loss-of-function CACNA1A mutation.

References:

P25
Circadian preference in children and adolescents with migraine - a controlled study
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Introduction: Research on chronobiological aspects of neurological disorders has gained influence in recent time. Besides epilepsy, dementia and movement disorders [1] migraine was identified to be influenced by the circadian clock [2].

Purpose/background/objectives: The aim of the present study was to investigate the circadian preference of children and adolescents with migraine.

P23
Self-reported efficacy of complementary and alternative medicine in chronic headache subjects in the general population
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Background: Chronic headache is associated with disability and high utilisation of health care including complementary and alternative medicine (CAM). We have previously shown that 62% of primary and 73% of secondary chronic headache sufferers from the general population have tried CAM for their headache but the efficacy of this use as treatment for chronic headache is not known.

Methods: An age and gender stratified cross-sectional epidemiological survey included 30,000 persons aged 30-44 years. Respondents with self-reported chronic headache were interviewed. The International Classification of Headache Disorders was used. Participants with primary or secondary chronic headache were asked about previous use of CAM and efficacy for their headache. Modalities of CAM queried were acupuncture, chiropractic, homeopathy, naprapath, physiotherapy, psychologist, and psychomotor physiotherapy.

Results: The questionnaire response rate was 71%, the interview participation rate 74%. Of 405 subjects with primary chronic headache, 253(62%) had used CAM for their headache. Of 113 subjects with secondary chronic headache, 82(73%) had used CAM. The self-reported efficacy ranged from 15-35% and 6-38%, respectively for primary and secondary chronic headaches depending on CAM modality being used. Generally, there were no significant differences in self-reported efficacy of CAM depending on gender, co-occurrence of migraine, medication overuse or physician contact. Of the most commonly used CAM modalities, subjects with primary chronic headache reported greatest efficacy of psychomotor physiotherapy(35%) > chiropractic(26%) > physiotherapy(25%). Of the most commonly used CAM modalities, subjects with secondary chronic headache reported greatest efficacy of physiotherapy(38%) = chiropractic(38%) > acupuncture(32%).

Conclusion: Self-reported efficacy of different CAM modalities in chronic headache subjects from the general population is modest.
Methods: We compared circadian preference of patients with migraine according to the criteria of ICHD-2 with that of headache-free controls matched for age and sex. For differentiating morning-, intermediate and evening-types we applied the Morningness-Eveningness Questionnaire.

Results: We included 67 children (age 6-11) and 78 adolescents (aged 12-18) with migraine as well as a total of 244 headache-free controls. In children, we found significant differences between patients and controls ($\chi^2=37.075, \text{df}=2, \text{p}<0.001$). Morningness as well as eveningness tendencies were more common in subjects with migraine than in controls. In contrast, the circadian preference of adolescents with and without migraine did not differ from each other ($\chi^2=0.833, \text{p}=0.659$).

Conclusion: Children with migraine tended towards extremr circadian orientation, but this was not the case in adolescents. As eveningness is connected with sleeping and emotional problems and morningness seems to have a protective function concerning the development of sleeping and emotional problems, these findings may be seen as starting point for possible new therapeutical interventions such as specific psychological, educational strategies, light- and chronotherapy in children with migraine.

References

P26
Screening of cacna1a and ATP1A2 genes in hemiplegic migraine: clinical, genetic and functional studies

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The Journal of Headache and Pain 2013, 14(Suppl 1):P26

Introduction: Hemiplegic migraine (HM) is a rare and severe subtype of autosomal dominant migraine, characterized by a complex aura including some degree of motor weakness. Mutations in three genes (CACNA1A, ATP1A2 and SCN1A) have been detected in familial and in sporadic cases. This genetically and clinically heterogeneous disorder is often accompanied by permanent ataxia, epileptic seizures, mental retardation, and chronic progressive cerebellar atrophy.

Objectives: To perform an exhaustive mutational screening of the CACNA1A and ATP1A2 genes in 18 HM patients.

Methods: Direct sequencing of PCR amplicons, Multiplex Ligation-dependent Probe Amplification (MLPA), Quantitative Multiplex PCR of Short Fluorescent fragments (QMPSF), heterologous expression and electrophysiology, ouabain survival assay.

Results: We identified four previously described missense CACNA1A mutations (p.Ser218Leu, p.Thr501Met, p.Arg583Gln and p.Thr666Met) and two missense changes in the ATP1A2 gene, the previously described p.Ala606Thr and the novel variant p.Glu825Lys. Additionally, a quantitative analysis was performed to detect exonic duplications or deletions in the CACNA1A gene using MLPA and QMPSF, with negative results. Functional studies were performed for the CACNA1A p.Thr501Met mutation and the ATP1A2 p.Glu825Lys change, the first having been previously described only in association with the EA2 phenotype.

Conclusion: This genetic screening allowed the identification of more than 30% of the disease alleles. Functional studies performed with two of the identified changes suggest that they are disease-causing.

References

P27
A clinical study on medication overuse headache in childhood and adolescence

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The Journal of Headache and Pain 2013, 14(Suppl 1):P27

Introduction: There are few studies on Medication Overuse Headache (MOH) in children and no epidemiological studies on an Italian population. We evaluated the prevalence of MOH in patients referred to our Center in 2011.

Methods: We studied 118 patients looking for correlations between age of onset, sex, age at first contact, headache type, presence of Chronic Daily Headache (CDH), pain frequency, severity and prevalence of MOH (according to the revised criteria [1]). By Student’s t test, Pearson’s Chi Square and Mann-Whitney’s test were used to analyze data.

Results: 44.9% of the sample had a diagnosis of CDH. Among this group the prevalence of medication overuse was 20.8%. After 2 months of drug withdrawal 45.4% of the patients reported a significant improvement. No significant correlation was found between the presence of MOH and age of onset, sex, age at first contact, headache type, pain frequency and severity.

Conclusion: About 1/5 of children with CDH afferent to our Headache Unit are at high risk of worsening because of medication overuse. No previous studies showed a role for medication overuse in the etiopathogenesis of CDH in children and adolescents [2]. We suggest to keep in mind the possibility of medication overuse in children with headache and to investigate it carefully. Further studies are required to define a specific treatment protocol.

References
The impact of migraine on children education, school attendance, and social life and relationships was assessed by filling a special questionnaire designed for this purpose by the two groups of children. Data were stored and analysed on Excel.

Results: Questionnaires were fully completed by 506 children (257 had migraine and 249 controls). Twenty-three questionnaires were partially completed and were excluded. 70% were females and age range was 1–18 years (83% between 10-16 years). Children with migraine missed on average 9.7 days of school due to illness over the past 3 months compared to 2.7 days in children without migraine. 85% of children with migraine were prevented from taking part in activities and hobbies on at least one occasion, 69% missed at least one special family event and 80% had to cancel plans with friends at least once. Over 50% of children with migraine felt less confident, felt it was hard to carry out homework or chores and felt that migraine stopped them doing well at school.

Conclusions: The impact of migraine on children and adolescents is often underestimated and a better management of childhood migraine may help improve children’s quality of life.


**P32**

**Headache and wine. Are all wines the same?**

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**The Journal of Headache and Pain 2013, 14(Suppl 1)p32**

**Objectives:** Classically, most migraineurs refer some relationship between drinking wine and headache. There are few previous studies confirming this. Our aim is to confirm (or not) this relationship and find out if all kind of wines have the same effect producing headache.

**Methods:** Based in previous data we have designed a simple and structured questionnaire. All patients attending a headache clinic (one day/week) during 6 months have been required to fill it. Age, gender, headache type (IHC-2004 criteria) are recorded. Questions referring to usual intake of wine, wine producing headache, kind of wine (red/white, sweet/cava-champagne) were asked. Questions about other alcoholic beverages producing headache and hangover headache also were presented. In this paper we describe the Results.

**Results:** 397 patients filled the questionnaire. Mean age 44.4 years, 79.6% females. Mean headache days, 11.5 per month. Migraine was the commonest headache type (74.8%). Just 9.1% drink wine usually. 166 patients (41.8%) affirm drinking wine produces headache. Some interesting differences were found between headache types and migraine subtypes: 55.6% of chronic migraine vs just 19% of MAura patients. Patients referring headache due to wine consumption (most with little quantity) appoints red wine in 60%, cava-champagne 47%, white 36% and sweet 32%. Most of them have stopped drinking wine due to this headache-producing problem. Other alcoholic beverages (mostly high-alcohol-degree) induces headache in 26.7%, 4/5 of them having also wine-induced headache. Hangover headache was recognised by half of the patients along their lifetime, but just 30% of them referred this headache to be similar to their usual headache.

**Conclusions:** Headache due to wine consumption seems to be frequent, at least in migraine patients. Not all kinds of wine are referred as headache inducers, there’s some special sensitivity to different wine types in different patients. Hangover headache feels different to usual headache by the majority.

**Reference**


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**P33**

**Childhood’s chronic headache in children national hospital of Albert Royer in Dakar**

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**The Journal of Headache and Pain 2013, 14(Suppl 1)p33**

**Introduction:** Children’s headaches are frequently primary. Their diagnosis is difficult because of anamnesis discomfort. Aetologies are numerous, above all functional. As in adults, symptomatic headache has to be taken into account among these.

**Purpose:** Our aim is to determine the clinical and aetiological features in a sample of children suffering from headache.

**Methods:** This was a prospective study conducted at the Children National Hospital Albert Royer (CHNEAR) in Dakar. We included children aged 5–15 years, received in out-patient department for chronic headache. The marital status, personal and family past medical history, headache characteristics, physical examination data were searched and supplemented with additional tests according to the clinical context.

**Results:** We collected 43 children. The sex ratio was 1.05 in favour of girls. The mean age was 10.68. Fifty-five point eight percent of them had familial past medical history of chronic headache in at least one of the two parents. It was localized headache in 76.19% of the cases and diffused in 21.42% of them. The most frequent localized headaches were frontal or fronto-occipital (35.71%), temporal (19.4%), hemiconciliar (16.66%). The main triggering factors were noisy atmosphere (60.4%), light (37.20%), fatigue (35%), heat (28%), and nervousness (25.50%). The brain CT-scan was performed in 25.50% of children and had returned normal except in one case. The EEG performed in 14 patients did not find any abnormality. Migraine was present in 58.13% of cases, non specific headaches in 41.80% of cases, hypertension induced headache in one case (2.3%). Associated pathologies were psychomotor developmental delay (11%) and seizures (11.6%).

**Conclusion:** Children chronic headaches are frequently primary ones, above all migraine. Sensory and psychic factors are the most frequent among triggering factors. As in adults, atypical features must lead to cerebral lesion research.

**References**


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**P34**

**Elucidating the molecular genetic basis of cluster headache:**

**delination of the genetic architecture by exome sequencing**

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**The Journal of Headache and Pain 2013, 14(Suppl 1)p34**

**Introduction:** A genetic predisposition to cluster headache (CH) has long been debated. Genetic epidemiological studies have reported an increased risk of CH in relatives of CH sufferers. The familial clustering supports a model of autosomal dominant inheritance with reduced penetrance. Some candidate gene studies have been performed, detecting associations with HCRTR2 and ADH4, but these have been limited by small sample size. We have established a large cohort of CH families in which we have previously reported a genome-wide linkage scan, isolating a number of putative linkage loci [1]. Despite this, a single causative gene is yet to be identified, largely due to substantial genetic heterogeneity.

**Purpose:** To further delineate the genetic architecture underlying CH, we have used an exome sequencing strategy in a subset of Northern European families.

**Methods and results:** Exome target enrichment and paired-end sequencing were performed for ten probands. Annotated variants were filtered to exclude known polymorphisms, leaving a total of 1711 novel variants. Exome data from related affected subjects were examined to limit the analysis to variants segregating with the CH phenotype. Segregation analysis by Sanger sequencing in all family members reduced the candidate list to a total of 45 genes (range: 1–13 genes per pedigree). These genes are now being screened in our extended cohort to provide further insight into the role of each gene in CH pathogenesis.

**Conclusion:** Whilst exome sequencing for rare monogenic disorders is now well-established, approaches to detect pathogenic variation with complexities such as locus heterogeneity and incomplete penetrance remain challenging. We have combined exome and Sanger sequencing to isolate novel coding variation segregating across CH families, highlighting the need for large homogeneous cohorts to elucidate the molecular genetic basis of CH. The significance of these variants in CH pathogenesis remains to be determined; however these results provide further evidence for a potential genetic predisposition to this debilitating disorder.

**Reference**

P35
Naturalistic study of the joint presence of headache and pets
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The Journal of Headache and Pain 2013, 14(Suppl 1)p35

Introduction: Pet Therapy is our first choice intervention for the therapy of children's headache, since in the majority of children in growing up age headache is often linked to a situation of psycho-social discomfort [1]. On the basis of several works, which had found that just the simple presence of pets was an improvement factor of the physical conditions of several patients [23], we wanted to ascertain whether also the simple presence of pets (mammals) could be related to the development of childhood headache.

Methods: In a sample chosen in compulsory schools of our district we administered a questionnaire that would use (IHS, 2004) for the diagnosis of headache in the fifth year of primary school. The questionnaire, in addition to the data relating to the number of brothers and sisters and social conditions, indicated the presence of pets (mammals) in the family nucleus. results 477 children participated in the study (279f.198m. range 10-12 years), with diagnosis of Migraine 10.3%(8.4%Mwa, 1.9MWA)Tension Type Headache17.4%(FTHH4 %, CTTH 3.5%). No significant differences were found in the number of brothers and sisters, and in the social conditions. The presence of pets was equal to 18.4% of healthy children, whilst it was 4.3% in migraine sufferers, compared to 4.8% in children suffering from tension type headache.

Conclusion: The presence of animals in the house is significantly concurrent with a lower incidence of migraine and tension headache. The presence of pets in the house seems to be a factor of prevention of the onset of headache. From an epidemiologic standpoint, the interaction with a pet presupposes a difference of family lifestyle and a consequent development in the coping modality, enabling to mitigate the arising of those etiological cognitive factors, which can promote headache suffering.

References

P36
A translational in vivo model of trigeminal autonomic cephalalgias – therapeutic characterization with brainstem stimulation
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The Journal of Headache and Pain 2013, 14(Suppl 1)p36

Introduction: Trigeminal autonomic cephalalgias (TACs) are highly disabling primary headaches that involve activation of trigeminovascular neurons and their reflex connection with the parasympathetic outflow to the cranial vasculature, via the superior salivatory nucleus (SuS) in the brainstem. Our understanding of TAC pathophysiology, and how and when central modulatory factors influence these autonomic responses is still limited. To further characterize the role of the autonomic nervous system in the pathogenesis of trigeminal autonomic cephalalgias, we have recently developed a translational in vivo animal model of TACs, which we have used to evaluate the role of brainstem responses in the generation of TAC-like symptoms.

Methods: Rats were anesthetized with pentobarbital (60 mg/kg) and prepared for physiological measurement. Electrophysiological techniques were used to record neurons of the trigeminocervical complex, using SuS stimulation, to activate the trigeminal-autonomic reflex. We compared the effects of specific TAC treatments with those of similar class used for other primary headaches. We also looked at autonomic responses through blood flow observations around the lacrimal duct.

Results: SuS stimulation resulted in two distinct populations of TCC neurons. Shorter latency neurons were unresponsive to 100% oxygen and the autonomic ganglion blocker, hexamethonium bromide. Longer latency responses were inhibited by oxygen (P < 0.05, n=20) and hexamethonium (P < 0.05, n=16). These longer latency responses were also preferentially inhibited by indomethacin and a triptan. Similarly 100% oxygen (P < 0.05, n=9) and hexamethonium (P < 0.05, n=7) inhibited evoked blood flow changes in the lacrimal duct. Likewise these responses were also inhibited by indomethacin and a triptan, but not naproxen or the CGRP receptor antagonist, olcegepant.

Conclusion: This is the first in vivo characterization of both trigeminovascular and cranial autonomic manifestations present in TACs and demonstrates that brainstem activation may drive both sensory and autonomic symptoms. Both manifestations were specifically inhibited by highly effective TAC treatments, and some part of their locus of action is via the parasympathetic pathway.

References

P37
Long-term efficacy of Boswellia serrata in 4 patients with chronic cluster headache
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The Journal of Headache and Pain 2013, 14(Suppl 1)p37

Background: Cluster headache (CH) is an extremely severe and debilitating trigemino-autonomic pain syndrome. About 10% of patients with CH manifest a chronic form (CCH). Extracts of Boswellia serrata have been clinically studied for the treatment of many inflammatory conditions such as osteoarthritis and rheumatoid arthritis (3). The resin from Boswellia Serrata contains a number of biological actives called pentacyclic triterpene acids, which give the extract its anti-inflammatory and analgesic properties, with boswellic acid the major active ingredient (4). These acids have been demonstrated to interfere with the body’s natural inflammatory response by inhibiting cytokines and leukocyte activity. The present study aims to evaluate the long-term efficacy of Boswellia Serrata (Sallaki H15) on headaches and disturbed sleep in patients with CCH.

Results: In an open-label study, 4 patients with CCH and disturbed sleep received oral Boswellia Serrata.

Conclusion: The effects were long-lasting in 3 patients (mean 15 months) and transient (6 months) in one patient. The rapid improvement of nocturnal pain within weeks is similar to the analgetic effect observed in recent trials using Boswellia Serrata in cancer pain (5) of how Boswellia Serrata reduces pain in CCH remains unclear. Boswellic acids, constituents of Boswellia extract have subsequently been identified as selective redox independent noncompetitive inhibitors of both 5-lipoxygenase, the key enzyme in leukotriene biosynthesis and human leukocyte elastase. Proinflammatory cytokines, such as leukotrienes, are known to play a role in the pathophysiology of CH. This study provides Class IV evidence that oral Boswellia Serrata (Sallaki H15) reduces the intensity and frequency of headaches in patients with CCH.

Conflict of interest: None

References

P38
Common diagnostic/therapeutic errors in trigeminal autonomic cephalalgias and hemicrania continua: a systematic review
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The Journal of Headache and Pain 2013, 14(Suppl 1)p38

Introduction: Trigeminal autonomic cephalalgias (TACs) and Hemicrania Continua (HC) are relatively rare but clinically well-defined primary headaches. Despite the current clear-cut diagnostic criteria (2nd edition of the International Classification for Headache Disorders - ICHD-II) and...
several therapeutic guidelines, errors in work-up and treatment are frequently encountered in clinical practice.

Objective: The aim of the present study is to investigate all published data dealing with mismanagement of patients affected by TACs and HC in order to understand and avoid the causes of such behaviors.

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

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

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

Conflict of interest: None.

References

P39
Characteristics of primary exertional headache in Korean marine corps BH Cho*, YUN Choi, TS Nam*, SM Choi*, SH Lee*, MS Park*, MK Kim*

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Introduction: Primary exertional headache is included in “Other Primary Headaches” (Group 4) in the International Classification of Headache Disorders, 2nd edition (ICHD-II) with primary cough headache, primary sexual headache, and idiopathic stabbing headache. The prevalence of primary exertional headache showed about 1-30.4%.

Purpose: We investigated about prevalence and characteristics of primary exertional headache in Korean marine corps.

Methods: 704 patients were treated due to headache. 79 patients of them suffered from exertional headache. We assessed characteristics of patients, comorbidity of migraine, nature of headache, Visual Analog Scale(VAS), neurologic symptoms, exercise which prompted the headache, and effect of medication. Effect of medication also evaluated with VAS.

Results: 10.38% of headache group was diagnosed as primary exertional headache. Average age was 20.6 year old and only 1 of 73 patients was female because of homogeneity of military corps. Most quality of headache is pulsating nature (93%) and most location of the headache is bilateral (84%). 3 patients had history or comorbidity of migraine (4%). 16 patients had accompanied symptoms, such as nausea(13 patients), photophobia (1 patient), dizzy sense (2 patients). In analyses of provoked factor, an aerobic exercise is most prompted cause of the headache (67%). 15 patients were provoked due to swimming, and other patients suffered from headache after running, or other aerobic exercise. Average of VAS score was 8.48. After treatment, the score was decreased to 3.40.

Conclusion: Prevalence of primary exertional headache in Korean marine corps is similar to previous population-based studies. Low rate of comorbidity of migraine and neurologic symptoms was differed from these studies. Anaerobic exercise and swimming are revealed frequent inducing factors of primary exertional headache. Because of significant lowering VAS scale, ergotamine might be useful drug to treat the headache.

References


P40
The efficacy of neurotropin in treating patients with nummular headaches
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The Journal of Headache and Pain 2013, 14(Suppl 1):P40

Introduction: A nummular headache is a headache that is characterized by pain localized to a small, circumscribed area of the head, typically measuring 2 to 6 cm in diameter in the absence of any lesion of the underlying structures.

Purpose: Neurotropin is a non-protein extract isolated from the inflamed skin of rabbits inoculated with the vaccinia virus that is used to treat neuropathic pain. In this study, we reviewed three cases retrospectively to assess the possible efficacy of neurotropin in patients with nummular headaches.

Methods: Three nummular headache patients participated in this study. For each patient, the diagnosis of nummular headache was made based on the ICHD - II nummular headache diagnostic criteria. We prescribed neurotropin at a dose of 16 NU/day to the patients during the clinical course of this study.

Results: Case 1: A 39-year-old male developed bifocal pain one week previously in a circumscribed area of the left temporal region measuring 4 cm in diameter. Treatment with NSAIDs was determined to be invalid. Treatment with neurotropin relieved the patient's pain, and the headache resolved after four days. Case 2: A 57-year-old female developed bifocal pain one week previously in a circumscribed area including both temporal regions measuring 3 cm in diameter. Treatment with neurotropin relieved the patient's pain slightly; however, the headache remained. Case 3: A 71-year-old male developed pain more than one year previously in a circumscribed area of the left parietal region measuring 3 cm in diameter. Treatment with NSAIDs was determined to be invalid. Treatment with neurotropin relieved the patient's pain, and the headache resolved after three months. In two of the three cases of patients with nummular headaches, treatment with neurotropin was found to be very effective for pain reduction.

Conclusion: The present results suggest that prescribing neurotropin may be a possible choice for treating patients with nummular headaches.

References

P41
Diagnostic distribution of 100 strictly unilateral headaches consulting in a specialised clinic
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The Journal of Headache and Pain 2013, 14(Suppl 1):P41

Introduction and objectives: Pain location is an important point in the diagnosis of headaches. Our aim was to analyse the diagnostic distribution of the first 100 patients consulting in our specialised headache clinic due to strictly unilateral headache.

Patients and methods: Headache diagnoses for all patients sent to our headache clinic in the last year and referring to strictly unilateral headaches were analysed according the current ICHD-II classification. We receive patients aged 14 or older.

Results: The 100 collected patients with strictly unilateral headaches accounted for the 18.9% of the 528 patients seen in our clinic in the study period. Strictly unilateral headaches were more frequent in males (58%). Age ranged from 19 to 81 years. Diagnostic distribution was as follows: cluster headache (38 cases)> a variety of secondary headaches (14 cases)> migraine (11 cases)> cervicogenic headache (9 cases)> hemicrania continua (8 cases)> nummular headache (6 cases)> psychogenic
headache (5 cases)> paroxysmal hemicrania (4 cases)> SUNCT syndrome
(3 cases)> stabbing headache (1 case)> and probable hemicrania continua (1 case). Mean, median and mode of age at onset felt between 47 and 58 years for several diagnoses (cervicogenic headache, nummular headache, psychogenic headache, hemicrania continua and paroxysmal hemicrania), between 25 and 35 years for cluster headache, below 25 for migraine and, in general, were older than 55 for secondary headaches.

Conclusions: Strictly unilateral headaches account for almost 20% of headaches attending a headache clinic. Trigemino-autonomic headaches in general (52%) and cluster headache in particular (38%) are the most frequent diagnosis, but, if we include cervicogenic headaches, secondary headaches are diagnosed in one out of five cases. Age can be of important help in their presumptive diagnosis. Supported by the PI11/00889 FISSS grant (ISCIII).

P42
The borderline between cluster headache and migraine: does cluster-migraine exist?
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The Journal of Headache and Pain 2013, 14(Suppl 1):P42

Introduction: Cluster headache (CH) is a well defined disorder. When the attacks fulfill all but one of the criteria for CH, probable CH should be diagnosed, requiring one of the following conditions: 1) attacks lasting >180 minutes, 2) attacks without autonomic signs or restlessness, 3) sporadic (less than one every other day) attacks. Background in the past “cluster-migraine” was considered an atypical variant of CH, but this entity was never categorized.

Methods: Since 1996 we have observed 251 patients with CH. Out of these cases, 33 (19 males and 14 females) could not fulfill all criteria for CH and have been followed-up for at least 5 years.

Results: We could distinguish 4 different subgroups. For 3 subgroups the unfulfilled criteria were: 1) pain duration >3 hours, ranging 4-8 hours (6 cases), 2) absence of autonomic signs or restlessness (5 cases), 3) sporadic attacks, with no cluster periodicity (10 cases). We could also identify a fourth subgroup of 12 patients without cluster pattern and attack duration lasting 3-5 hours, borderline between CH and migraine without aura (MO). Moreover, the coexistence of MO and CH was noted in 8 cases. The first subgroup overlaps with probable MO. Criteria are not fully met and patients are labelled as probable MO or probable CH, either of which could have features of the other. The second and third subgroups meet criteria for probable CH. The fourth subgroup does not fulfill criteria either for probable CH or probable MO, therefore the old definition of cluster-migraine may be still appropriate, even if this term might be considered a regression to the time when CH was considered a variant of migraine [1]. Interestingly, 3 patients in the third subgroup evolved over time into a typical CH.

Conclusion: Patients sometimes present with clinical scenarios having characteristics of both MO and CH, but either do not fully meet criteria for either disorder or have no sufficient symptoms to allow both diagnoses to be present. These occasions may account for the controversial form of cluster-migraine.

Reference

P43
Clinical profile of probable cluster headache without ipsilateral autonomous symptoms
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The Journal of Headache and Pain 2013, 14(Suppl 1):P43

Introduction: Cluster headaches (CH), characterized by strictly unilateral pain localized in or around the eye and accompanied by ipsilateral autonomic features, are the most painful form of primary headache. Probable cluster headache (PCH) is a subtype of CH fulfilling all but one diagnostic criteria for it: for example, with no ipsilateral autonomic features. CH is associated with severe pain and has a considerable impact on social functioning and quality of life. Like CH, PCH without ipsilateral autonomic features (PCHWOAIF) may be associated with severe pain and considerable impact, but PCHWOAIF has not been studied. The present study aimed to clarify the clinical profile of PCHWOAIF.

Methods: Seven patients who had been diagnosed with PCHWOAIF according to the 2nd edition of the International Classification of Headache Disorders were compared with 86 patients with CH. We collected data on laterality and location of headache, pain intensity, impact, additional features (sense of restlessness during the attacks, nausea, vomiting, photophobia and phonophobia), duration of attacks, and time of onset of attacks.

Results: Pain occurred in the forehead, occipital regions, and vertex significantly more often in patients with PCHWOAIF than in patients with CH. There were no significant differences between patients with PCHWOAIF and CH in the mean age at first consultation, mean age of onset, the ratio of males to females, laterality of headache, pain intensity, impact, additional features, duration of attacks, and time of onset of attacks.

Conclusion: The impact of PCHWOAIF is similar to that of CH. Patients with PCHWOAIF should receive the same level of treatment as patients with cluster headaches.

Reference

P44
Efficacy and reproducibility of response of greater occipital nerve blocks in chronic cluster headache: a large-sample prospective analysis
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Introduction: Greater occipital nerve block (GONB) has been shown to be an effective treatment, mainly in episodic cluster headache (CH), with much data available on chronic CH (CCH). In addition very little is known about the reproducibility of response to GONBs.

Objective: To prospectively assess the efficacy and reproducibility of response of GONBs in a large cohort of CCH patients.

Methods: CCH patients referred to our outpatient clinic between 2007 and 2010, and had a unilateral GONB, using a mixture of methylprednisolone 80 mg and 2 ml lidocaine 2%, were prospectively studied. Data on headache characteristics (frequency, severity and duration) were collected using headache diaries before and after the procedure. The outcomes of three subsequent GONBs performed in responders to the first, three-month apart, were also analysed.

Results: Eighty-three CCH patients were studied. A positive response was observed in 59 (71%) patients; 42 (51%) were rendered pain free, whilst 17 (21%) had a partial benefit, lasting a median of 18 days (range: 1-504 days). There was a transient worsening of CH in 6% of patients and mild adverse effects were reported by 34%. The overall rate and average duration of response rate remained similar after the second (n = 43, 35 responders: 81%; median duration: 18 days), third (n = 28, 20 responders: 71%; median duration: 25 days), and fourth (n = 14, 10 responders: 71%; median duration: 23 days) injections.

Conclusion: GONB is an efficacious and reproducible treatment in CCH patients. Given the good tolerability profile when performed every 3 months, GONBs can play a useful role in the management of CCH, allowing frequent periods of relief from an otherwise highly disabling disorder.

P45
Fast and slow titration of verapamil in cluster headache: comparison of electrocardiographic abnormalities
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The Journal of Headache and Pain 2013, 14(Suppl 1):P45

Introduction: Verapamil is an off-label first-line drug in prevention of cluster headache (CH) but little is known about the optimal rate of dose escalation. The safety profile of slow dose increment in 80mg intervals has been previously documented. It is possible to achieve the effective dosage earlier with fast escalation, although the safety and tolerability are of concern.

Objective: To compare the electrocardiographic abnormalities and other adverse events between fast (escalation of verapamil by 120mg
every two weeks) and slow titration (by 80mg of verapamil in CH treatment.

Methods: Electrocardiograms (ECGs) at baseline and every two weeks in parallel with the increment of the drug were performed in patients attending our clinic. Medical records and ECGs performed in CH patients between 2007 and 2011 were retrospectively reviewed.

Results: Of 169 patients, 80 followed the fast and 89 the slow regimen. The slow regimen group differed from the fast regimen group in terms of: higher proportion of chronic CH (84% vs 64%, p=0.002), duration of verapamil use (median 35 vs 10 months, p<0.001) and maximum dosage of verapamil achieved (mean 71±1mg vs 272±61mg±257, p=0.021). Eighty-three (49%) patients showed ECG changes: bradycardia in 60 (36%), first-degree atrioventricular block (AVB) in 22 (13%), second-degree AVB in 11(1%), third-degree AVB in 2 (1%), junctional rhythm in 7 (4%) and bundle branch block in 3 (2%) patients. The rate of arrhythmias did not differ between two groups. Verapamil was stopped only in second- and third-degree AVB. The rate of drug discontinuation due to arrhythmias or non-ECG adverse events did not differ between groups.

Conclusion: The occurrence of verapamil-related serious cardiac arrhythmias was rare in patients adopting fast titration regimen. Our data support the safety and tolerability of rapid escalation of verapamil in patients with CH. Regular ECG assessment is essential throughout the therapy.

P46

Post-traumatic cluster headache: a clinical phenotype study of 16 patients

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The Journal of Headache and Pain 2013, 14(Suppl 1):P46

Introduction: Cluster headache (CH) due to head trauma seems to be an extremely rare entity. To date only two cases of new onset CH that fulfill the criteria for post-traumatic headache have been described.

Aims: Describe the phenotype and response to treatments of a series of post-traumatic CH patients.

Methods: Sixteen cases fulfilling the International Headache Society (IHS) criteria for post-traumatic headache with the CH phenotype were identified out of a cohort of 302 CH patients (chronic: 64%) seen between 2007 and 2011. Details on the head injuries, along with clinical information on CH were collected.

Results: Five percent of our sample of patients had CH secondary to head trauma. All patients developed a chronic form of post-traumatic headache. Fourteen patients had chronic CH and 2 episodic CH (M:F=2:1). The median age of onset of CH was 31 years (range: 10-54). Eighty patients (50%) reported a correspondence between the trauma site and the CH side. The most frequent circumstances of head traumas included: brawls in 5 patients (31%) and sport accidents in 4 (25%). No atypical clinical features were noticed. Remarkably, 3 patients (19%) had familial CH. Sumatriptan mg injection was effective in 15 patient; high dose and flow rate oxygen was effective in 5 patients. Verapamil was effective in 7 patients.

Conclusion: This is the largest series of post-traumatic CH. This condition does not differ from the idiopathic form in terms of phenotype and response to treatment. The frequent occurrence of head injuries during brawls, may suggest a risk-taking trait in some CH patients. The high proportion of familial CH in this series might suggest that exogenous factors, such as a head injury, may alter the homeostasis of the trigeminovascular system giving rise to CH particularly in genetically susceptible individuals.

P47

Effectiveness of antidepressants for treatment of idiopathic orofacial pain

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The Journal of Headache and Pain 2013, 14(Suppl 1):P47

Aims: To determine the efficacy of antidepressants for treating idiopathic orofacial pain fulfilling the International Classification of Headache Disorders 2nd edition (ICHD-II) criteria of persistent idiopathic facial pain (13.18.4; IFP) or burning mouth syndrome (13.18.5; BMS).

Materials and methods: Participants comprised 195 outpatients who attended our orofacial pain liaison clinic between January 1, 2009 and December 31, 2011 and were diagnosed with IFP or BMS. IFP was diagnosed in 124 patients (17 men, 107 women; atypical facial pain, n=16; atypical odontalgia, n=108), with a mean age of 54.8 ±14.4 years and a mean duration of illness of 30.7±22.8 months. BMS was diagnosed in 71 patients (8 men, 63 women; so-called BMS, n=28; glossodynia (pain limited to tongue), n=43), with a mean age of 67.2 ± 10.8 years and a mean duration of illness of 23.1±27.3 months. Patients with mental disorders, including major depressive disorders, who were currently taking antipsychotic agents were excluded. All patients were treated with antidepressants; with first-line therapy comprising amitriptyline or another tricyclic antidepressant (TCA). If a TCA alone proved insufficient for pain control, one of the following agents was added to the TCA for combination therapy, in this order: risperidone; sodium valproate; or lithium. These other antidepressants were also used if the patient could not use TCAs due to underlying disease. Outcomes were assessed as: -effective, pain disappeared or no pain was experienced for 90% of each week; -moderately effective, pain improved, but did not disappear; -no effect, no change; and dropped out, including referral due to difficulty making visits because of the distance.

Results: For IFP, treatment was effective for 91 patients (73.4%), moderately effective, 3.2%, no effect, 0%, dropped out, 23.4%. For BMS, treatment was effective for 56 patients (78.9%), moderately effective, 4.2%, no effect, 1.4%, dropped out, 15.5%.

Discussion: Use of antidepressants can be helpful in the treatment of idiopathic orofacial pain such as IFP or BMS.

Reference

P48

Tension type headache is dead; long live chronic migraine!

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Chronic Migraine (CM) was first defined in 2004. The definition was revised in 2006(1). The definition allows occurrence of both migraine and tension-type headache (TTH). This study analyses the introduction of the new diagnosis of CM in one neurologist’s practice. A patient database for all patients seen in consultation has been maintained since 1994. Total patient numbers are currently over 22,000. Data are collected and recorded at the time of first consultation and updated when the patient is reviewed. All relevant diagnoses are recorded; patients often have more than one diagnosis. Before the definition of CM, patients with other primary headache, and medication overuse headache (MOH), were diagnosed with both the primary headache, and MOH, when appropriate. This practice continued when coding for CM, despite the IHS definition excluding CM in MOH patients. A steady rise in CM since 2004 has peaked at about 150 cases a year. This is mirrored by a fall in diagnosis of TTH to single figures annually. It is likely that patients with chronic headache, formerly diagnosed as both TTH and migraine, can now receive a single diagnosis of CM. CM has proved common in this practice and has largely superseded the diagnosis of TTH.

Conflict of interest: The author has worked with most of not all of the pharmaceutical industry, including Allergan for whom he was a triallist in the PREEMPT study, and member of advisory boards.

Reference
Introduction: The upper cervical nerve roots (C1-3) are increasingly viewed as an important target for therapeutic intervention in headache, but their specific roles in the pathophysiology of head pain remain uncertain. An increased understanding of the role of C1-3 in primary and secondary headache disorders is important for progress with diagnostic and therapeutic interventions involving these structures.

Objectives: The Objectives of this study are to characterize the distribution of pain provoked by stimulation at the C1-3 levels, and to investigate the potential efficacy of a novel, brief low temperature radiofrequency rhizolysis (BLT-RF) as a therapy for patients with occipital neuralgia.

Methods: This study is a retrospective review of data from 9 patients with occipital neuralgia (5 of whom also had migraine) who underwent fluoroscopically guided multi-modal provocation at the C1, C2, and C3 levels followed by nerve root block with anesthetic and steroid. 7 patients underwent subsequent BLT-RF of the C1 spinal nerve and C2 and C3 dorsal root ganglia.

Results: Patients with migraine all reported retro-orbital or periorbital pain with C1 stimulation. By contrast, patients without migraine reported occipital or cervical pain with stimulation at the C1 level. C2 and C3 stimulation evoked pain in occipital and cervical distributions similar to those previously reported. BLT-RF produced sustained pain relief in patients who had only transient relief with nerve block.

Conclusions: The orbital/periorbital pain evoked by stimulation at the C1 level indicates that the C1 nerve root may play an important role in conditions in which pain occurs in this distribution, including migraine and cluster headache. The C1 nerve root may therefore be an important target for therapy for these conditions. The BLT-RF technique appears to be a safe and effective therapeutic approach to occipital neuralgia, with a longer duration of action than nerve blockade with anesthetics and steroids.

References

PSO
Paroxysmal hemicrania-tic syndrome: a new case report
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The Journal of Headache and Pain 2013, 14(Suppl 1):PS0

Introduction: An association of Paroxysmal Hemicrania (PH) with Trigeminal Neuralgia (TN) was described in eight patients [12] and has been called the PH-tic syndrome [3]. Case report. A 52-year-old man presented with a 5-year history of excruciating and burning pain, involving the left ophthalmic trigeminal branch, lasting 30 to 60 seconds, occurred 2 to 5 times a day, without any autonomic sign. Triggering factors included touching, washing face or brushing the teeth. Carbamazepine (600 mg/day) produced marked improvement. Any attempt to reduce the dose resulted in pain recurrence. While the previous pain was in remission by carbamazepine, he complained of a second type of pain that lasted 15 to 30 minutes and occurred up to 8 times per day. The strictly unilateral pain occurred in the left orbit, forehead, temple, nose and was described as severe and sharp with autonomic signs. There were no triggers. Indomethacin (150 mg/day) completely resolved attacks. His past medical history was significant for atrial fibrillation, hypertension and glaucoma; neurological examination and blood analysis were normal. Brain magnetic resonance showed silent lacunar infarcts, while magnetic cerebral angiography was normal. Trigeminal reflexes were also normal. In order to assess the possible involvement of the small myelinated and unmyelinated trigeminal fibers, we recorded, using a Nd:YAP laser stimulator, laser evoked potentials (LEPs) after supraorbital stimulation that showed a normality of A-delta and C fibers activation of the affected compared to the normal side. At the time of LEPs the patient was TN and PH off-indomethacin pain-free.

Conclusion: LEPs study supported the diagnosis of TN idiopathic. It is still debated if the rare association of TN and PH is a new entity or two distinct disease. Further investigations by neuroimaging might be useful to clarify this issue and to better understand the pathophysiology of these entities [4].

References

PS51
Cluster headache—a study of 387 cases
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The Journal of Headache and Pain 2013, 14(Suppl 1):PS51

Background: Cluster headache (CH) is a rare disorder with peculiar clinical characteristics. The most recent epidemiological study on suggested that CH is more common than previously thought and highlighted the long amount of time which elapses from onset of symptoms to diagnosis.

Objectives: To conduct a nationwide study in order to describe the phenotype of CH in Brazil. We ultimately aimed to gather clinical data to support and refine the current diagnostic criteria.

Methods: This study was conducted from January of 2009 to December of 2010. Patients with CH completed an online questionnaire (n=658, and 387 of them were interviewed by phone. We obtained demographic information, initial assigned diagnosis, frequency, schedule, location, lateralization, history of smoking and alcohol consumption.

Results: CH was more common in men (73.1%) than in women at a ratio of 2.7/1. Mean age at the time of assessment was 39.3 years. Most were white (82.7%). Only 28.7% of them. Most had episodic CH (66.9%) from the beginning, and 56.1% used alcohol more than twice per week.

Conclusions: As expected, most sufferers were men, but with a male/ female ratio smaller than previously reported. The proportion of chronic CH was higher than previously described. Some patients did not have strictly unilateral pain, and this possibility has recently been recognized, although not to the frequency found in our study. Delayed diagnosis was the norm, suggesting that continuous medical education on cluster headaches is necessary in order to relieve the incredible burden of these sufferers.

References

PS52
Does tension-type headache patients have a reduced shoulder muscle strength compared to healthy controls?
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The Journal of Headache and Pain 2013, 14(Suppl 1):PS52

Conclusion: LEPs study supported the diagnosis of TN idiopathic. It is still debated if the rare association of TN and PH is a new entity or two distinct disease. Further investigations by neuroimaging might be useful to clarify this issue and to better understand the pathophysiology of these entities [4].

References
Introduction: Tension-type headache (TTH) is the most prevalent headache in the general population. Neck muscles are tense and tender and pain in shoulder muscles is a pronounced complaint. Several studies have found that the trapezius play a major role in TTH and decreased strength capacity and lowered activity of the painful trapezius muscle by office workers with trapezius myalgia are reported.

Objectives: To investigate if TTH patients have a reduced torque during shoulder abduction compared to age- and sexmatched matched healthy controls.

Methods: 60 TTH patients from a multidisciplinary headache center fulfilled the ICHD-2 criteria for frequent episodic or chronic TTH and 30 healthy matched controls were studied. The participants were lying supine on the floor on a thin mattress, with the dominant arm in 90 degree shoulder abduction and the wrist positioned on a force transducer. The participants were instructed to abduct the arm with maximal force as quickly as possible, 3 attempts were made with 60 sec in between tests. The data was registered on a connected computer, and the torque value was calculated as force times moment arm.

Results: 60 TTH patients (19 males, 41 females) with a mean age 34 years and TTH > 8 days/mth, 30 sex and age matched healthy controls completed. There was a numerical but not significant difference in torque between TTH patients (38,66 N × m) and healthy controls (44,32 N × m) during shoulder abduction (p=0.143).

Discussion: We had hypothesized that TTH patients would have a significant reduced torque compared to healthy controls. The results indicate that the influence from the trapezius muscle in TTH headache patients will not result in a reduced torque in shoulder abduction. This also implies that TTH patients are not limited in the use of the shoulder due to pain in trapezius and other mechanisms must be investigated.

P54
Can cigarette smoking worsen the clinical course of cluster headache
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Introduction: Up to 90% of cluster headache (CH) patients have a prolonged history of cigarette smoking prior to the headache onset. It has been suggested a genetic link between CH and nicotine addiction and, also, that toxic agents found in cigarette smoke have a direct effect on the hypothalamus, a pivotal area for the pathogenesis of CH [1-3].

Purpose: To explore the relationship between cigarette smoking and the clinical course of cluster headache.

Methods: All outpatients with cluster headache, diagnosed according to the criteria of ICHD-II, who were, consecutively, seen from October 2010 to April 2012 at the Headache Centre, were subjected to a phone interview by means a specific standardized questionnaire (29 items), administered, always, by the same trained postgraduate medical doctor.

Results: A total of 200 patients were surveyed (172 male, 28 female; mean age ± SD: 48.4 ± 12.7; male/female ratio: 6:1:1). One hundred and twenty patients were current smokers, 42 former smokers and 38 non-smokers. The age of onset of CH was 29.8 ±13.6 years. Among all smokers and former smokers those who started smoking before 18 years had an onset of cluster headache earlier than those who started smoking after age of 18 years (P < .01, Student’s t test). All patients with chronic cluster headache were currently smokers. The episodic form (89%) was more frequent than the chronic one (11%). Chronic CH patients smoked more cigarettes per day (P < .01, Student’s t test) and started smoking before (P < .01, Student’s t test) than patients with episodic CH (P = .001, Student’s t test). The length of the active phase of CH was tripled compared to non-smokers (weeks ± SD: 15.1 ± 17.6 vs. 5.7 ± 4.7). P < .001, Student’s t test).

Conclusion: Our data showed that cigarette smoking is an aggravating factor for cluster headache, in particular for the lasting of the active phase.

Conflict of interest: None.

References:

P55
Accessibility of headache centers for patients suffering for cluster headache in Italy: too far from the patients’ needs
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Background: Due to the extraordinary severity of pain, cluster headache (CH) warrants rapid diagnosis and appropriate treatment. The diagnosis of CH is simple, and rapid and effective treatments exist (injective sumatriptan and oxygen). In spite of this, clinical data have documented that CH is largely under-diagnosed and under-treated and it is common opinion that CH should be managed in a specialist setting. A fast access to headache services for CH patients is required to avoid delays to proper care. Aim of the study. To investigate the accessibility of the headache centers listed on the official websites of the two existing Italian societys involved into the study of CH was tripled compared to non-smokers (weeks ± SD: 15.1 ± 17.6 vs. 5.7 ± 4.7). P < .001, Student’s t test.

Conclusion: Our data showed that cigarette smoking is an aggravating factor for cluster headache, in particular for the lasting of the active phase.

Conflict of interest: None.

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Background: Due to the extraordinary severity of pain, cluster headache (CH) warrants rapid diagnosis and appropriate treatment. The diagnosis of CH is simple, and rapid and effective treatments exist (injective sumatriptan and oxygen). In spite of this, clinical data have documented that CH is largely under-diagnosed and under-treated and it is common opinion that CH should be managed in a specialist setting. A fast access to headache services for CH patients is required to avoid delays to proper care. Aim of the study. To investigate the accessibility of the headache centers listed on the official websites of the two existing Italian societys involved into the study of CH was tripled compared to non-smokers (weeks ± SD: 15.1 ± 17.6 vs. 5.7 ± 4.7). P < .001, Student’s t test.

Conclusion: Our data showed that cigarette smoking is an aggravating factor for cluster headache, in particular for the lasting of the active phase.

Conflict of interest: None.

References:
with the physicians and b) a service measure of call-center efficiency (number of calls necessary to be answered). The study was conducted on April 2012.

Results: 151 headache centers were contacted in the study period. Fast access to a visit was allowed by 41 centres (31.7%, 33 covered by the national health system and 15 in private practice; in 16 cases a special referral of the GP certifying the urgency was requested). Only 9 centres (5.9%) gave to the patients the possibility to talk with the physician. 60 centres (39.7%) did not answer to the call (at least 3 call per day at different times for 5 five days).

Discussion: The accessibility of headache centers for CH patients is inadequate and far from the patients' needs for an irrational organization and a bad use of the technical and human resources. An unacceptable disparity emerges between different geographical areas.

Reference

PS6
Effect of homeopathy on chronic tension-type headache: A pragmatic, randomised controlled single blind trial
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The Journal of Headache and Pain 2013, 14(Suppl 1):56

Introduction: Homeopathy is increasingly used by headache patients in general practice but scientific evidence is lacking. We therefore designed a clinical trial in a way that would not change the practice pattern of homeopathic physicians.

Purpose/background/objectives: The purpose of the study was to explore individualised homeopathic treatment used in general practice for chronic tension type headache (CTTH).

Methods: The study was multicentre, pragmatic, randomised controlled trial with blinded assessment. One hundred twenty seven participants with CTTH were randomly assigned to homeopathy or to usual care. Number of headache attacks, duration of pain, pain intensity on visual analog scale, use of medication and resources were recorded through headache diary at 4 weeks run-in period (baseline), at week 17 post interventions, and end of follow up at week 29. An observer blind to the patients' treatment allocation carried out assessments.

Results: headache frequency and intensity was lower in the homeopathy group than in controls after intervention (P<0.05) and at follow up (P=0.001). The pain duration was shortened slightly after the intervention period reached to significance level at follow up. In homeopathy group headache parameters decreased at post intervention compared with baseline and continued to decrease slightly in follow up period. The overall evaluation of the 2 treatments indicated improvements in both the treatment but later only homeopathy group showed consistent change. Compared with usual care, patients randomised to homeopathy used 35% less medication (P = 0.001) and had 45% fewer visits to general practitioners (P = 0.0001).

Conclusion: The results indicate that homeopathy could have clinically relevant benefits for patients with chronic tension type headache.

References

PS7
Pathway ch-1 study: sphenopalatine ganglion (SPG) stimulation for acute treatment of chronic cluster headache (CCH)
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The Journal of Headache and Pain 2013, 14(Suppl 1):57

Introduction: The pain and autonomic symptoms of cluster headache result from activation of the trigeminal parasympathetic reflex, mediated through the SPG [12]. We aimed to investigate the safety and efficacy of SPG stimulation for the acute treatment of CCH.

Methods: A multi-center, dose range finding, multiple headache attack (HA), acute treatment study with random insertion of placebo was initiated. All subjects met the ICHD-2 criteria for CCH with a minimum of 4 HA/week. Subjects were implanted with a miniaturized neurostimulator which, along with a controller, provides on-demand SPG stimulation. During the blinded experimental period (EXP), each HA was randomly treated with 1 of 3 therapies: full, sub-perception or placebo stimulation. Pain relief at15 minutes (decrease from ‘moderate’ or ‘severe’ to ‘none’ or ‘mild’ on the 5-point scale) and HA frequency reduction were analyzed.

Results: Thirty-two subjects were enrolled, 27 completed the EXP. One subject remains in EXP, 1 skipped EXP, 2 were explanted due to early lead migration, and 1 did not complete the implant due to difficult anatomy. Pain relief was achieved in 67% of HA (n=190) treated with full compared to 8% (n=183) with sub-perception and 8% (n=189) with placebo stimulation. A clinically significant improvement occurred in 19 of 27 (70%) subjects: 7 (26%) achieved acute pain relief in ≥50% of treated HAs, 10 (37%) a ≥50% reduction in HA frequency compared to baseline and 2 (7%) experienced both. Of the 12 frequency responders, HA frequency was reduced to ≤2 HA/week in 9 subjects. Eight (29%) of the 27 did not respond or did not provide sufficient data for evaluation. Most subjects (47%) experienced transient, mild to moderate numbness within the second division of the trigeminal nerve post implant with 62% resolving within the first three months.

Conclusions: Results suggest that acute, on-demand SPG stimulation using the AT1 Neurostimulation System has acute and preventive effects and is an effective novel therapy for CCH. In this study, 70% of subjects responded to the therapy.

References

PS8
Pericranial muscle tenderness in a population based sample of chronic tension-type headache. The Akershus study of chronic headache
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The Journal of Headache and Pain 2013, 14(Suppl 1):58

Objective: The aims of the study were to quantify the pericranial muscle tenderness in a large population based sample of persons with chronic tension-type headache (CTTH). We also wanted to compare pericranial muscle tenderness in CTTH with the general population.

Background: The pathophysiological mechanisms involved in CTTH are not fully understood. Several studies have shown that the tenderness of pericranial myofascial tissues are increased in patients with tension-type headache. However, little is known about CTTH characteristics in the general population.

Methods: This is a cross-sectional population-based study. An age- and sex-stratified sample of 30,000 persons, aged 30–44 years, residing in eastern Akershus County was in 2005 drawn from the National Personal Registry. The study population received a posted questionnaire. Those with self-reported chronic headache were invited to Akershus University Hospital. All headaches were classified according to the explicit diagnostic criteria of the ICHD-II. The response rate to the questionnaire was 71%, and the rate of participation in the interview was 74%. A total tenderness score (TTS) was used to investigate pericranial tissue tenderness. 8 pairs of muscles and tendon insertions were palpated. The 4-point (0-3) scale at each location and values from left and right sides were summed to a total
score. For comparison, cross-sectional data from the Danish general population using the same instruments were used.

**Results:** Those with CTTH had a high TTS compared with the general population. In males, the TTS decreased significantly with age. In women, a significant relationship between headache intensity and TTS was found. Parameters like headache frequency, duration, co-occurrence of medication overuse and migraine had no significant influence on the TTS.

**Conclusions:** Persons with CTTH have an increased pericranial muscle tenderness. The pathophysiological mechanisms involved in CTTH are complex and further research is needed to define the role of pericranial tissues and other factors in the genesis of CTTH.

**References:**

**PS9**

**New recipes for old ingredients: high doses of methylprednisolone and verapamil in cluster headache**

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Corticosteroids (C) rapidly suppress Cluster Headache (CH) attacks during the time required for the preventative agent verapamil (V), to have effects [1]. However, both drugs are often unsatisfactory. We present the case of a woman, affected by Chronic Cluster Headache (CCH), successfully treated with high doses of C and V. Moreover, we treated similarly 20 Episodic Cluster Headache (ECH) patients with satisfactory results. A 62-year old housewife, in 2000 had an isolated cluster (ICHD-II) of 40 days duration, unresponsive to NSAIDs. In 2008, she had a second cluster, responsive to 6 mg sc sumatriptan; oxygen inhalation was ineffective. Patient was successfully treated with V 240 mg and prednisone (P) 50 mg/day per os for 7 days, tapered in a month. In January 2009, she had a new cluster, that became chronic with 2-8 attacks/24 hours, not responsive to P 50 mg/day, V 320 mg/day, lithium (750 mg/day), valproate (1000 mg/day). When we saw her, in August 2011, she had 5 attacks/24 h, despite taking V per os 320 mg/day. Patient was administered methylprednisolone (MP) 500 mg iv/day for 2 days, then 250 mg for 3 days, followed by P 25 mg per os for 2 days, tapered in 8 days. V was increased gradually to 600 mg/day. In the following month there were no attacks. In September, she presented 1-3 attacks/24h nocturnal and mild, lasting 15 min. V was increased to 680 mg/day with disappearance of attacks. In November, V was slowly reduced to 320 with no recurrence. To the best of our knowledge this is the first report about high doses of IV MP associated with high doses of V per os being effective in CCH. Data are being elaborated on a group of 20 ECH patients treated similarly with good results. If confirmed, our findings warrant the reevaluation of the doses and timing of these drugs in CH with appropriate clinical trials.

**Reference:**

**P60**

**Efficacy and safety of occipital nerve blocks in cluster headache: a prospective observational study**

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**Background:** Cluster headache (CH) is characterized by severe trigemino-autonomic cephalalgias. Treatment of CH consists of acute attack aborting and prophylactic strategies. However, a substantial number of patients do not have sufficient control of CH attacks despite oxygen inhalation, triptans, oral steroids and verapamil. To date only two small randomized trial and retrospective case series have investigated the efficacy and safety of occipital nerve blocks in CH.

**Methods:** The effect of a single infiltration of the ipsilateral greater and lesser occipital nerve using a long-acting corticosteroid (10 mg triamcinolone) and anaesthetic (Bupivacaine 0.5%) was prospectively investigated in 101 CH patients (61 episodic CH, 40 chronic CH) who did not have sufficient control of CH attacks in a tertiary headache center during July 2010 and November 2011. Attack frequency, pain intensity and side effects were recorded by repetitive standardized interviews at days 3 and 7 after infiltration and thereafter weekly until reoccurrence of attacks.

**Results:** The mean attack frequency was 2.9±2.5 (eCH) and 3.3±2.9 (cCH) at baseline. This was reduced to 2.2±1.7 (eCH) respective 2.5±2.3 (cCH) after 7 days. 67.2% (eCH) and 50% (cCH) became attack free. 10.9% of the patients reported at least one side effect. Most frequent side effects were: nausea (0.9%), pressure (0.9%) or pain (1.8%) at the injection site, tension type headache (4.6%) and retroorbital pain (1.8%). 83% of patients would repeat nerve block treatment.

**Conclusion:** Occipital nerve block is an easy, safe and effective treatment option for exacerbation of eCH and cCH which can suppress attacks temporarily in a high number of patients with eCH and cCH and results in a complete response in a substantial number of patients with eCH.

**Reference:**

**P61**

**Knowledge, attitudes and clinical practice regarding behavioral treatments and psychological issues in migraine: a survey of AHS members**

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**Background and objectives:** We aimed to gather data regarding knowledge, attitudes, and clinical practices related to behavioral treatments for migraine and psychological issues among healthcare professionals (HCPs), an area about which little is currently known.

**Methods:** 784 American Headache Society (AHS) members were asked to complete a web-based survey. Data on sociodemographics, clinical practice patterns, attitudes, and knowledge were collected. Analyses contrasted HCPs’ (physicians [MD], psychologists/mental health professionals [PSY], and nurse practitioners/physician’s assistants [NP/PA]) knowledge of empirical evidence for efficacy of behavioral treatments, assessment/referral practices, and related beliefs.

**Results:** The 134 respondents were comprised of MDs (74%), PSYS (12%), and NPs/PA (14%). Knowledge that certain behavioral treatments have “Grade A” evidence for migraine prevention was highest among PSYS for biofeedback [p<0.01], cognitive behavioral therapy (p<0.001), and relaxation training (p<0.001). The majority of respondents reported that they routinely assess headache patients for depression (82.9%) and anxiety (69.2%). 30.8% routinely assessed abuse/PTSD. The overall referral rate for non-pharmacologic treatment was below 20%, with stress management, relaxation training, and psychotherapy being the most common referrals. The probability of referring a patient to treatment for headache is correlated with knowledge regarding US Headache Consortium guidelines and availability of behavioral treatment in the respondent’s geographic region.

**Conclusions:** Other than psychologists, the majority of respondents were unaware that behavioral treatments possess “Grade A” evidence for migraine prevention according to US Headache Consortium guidelines.
Low rates of referrals for behavioral treatments may result from a combination of knowledge and beliefs and a lack of available services. A need exists for education regarding the empirical evidence supporting the efficacy of certain behavioral treatments in migraine management.

P62
Clinical characteristics and pharmacological treatment of new daily persistent headache (NDPH)
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Introduction: Despite the fact that NDPH has been considered one of the most refractory headaches, there are limited data available regarding the clinical characteristics, pharmacological treatment and prognosis of NDPH.

Purpose: To discuss cases which were identified as NDPH by the International Headache Society diagnostic criteria.

Methods: Our NDPH patients consisted of 8 females and 3 males, with an onset age ranging from 15 to 72 years old. The duration of the headaches, location, intensity and nature of the pain, precipitating factors and treatments were investigated.

Results: The duration of the headaches ranged from 9 months to 24 years. Pain was diffuse in 3 patients, occipital-neck area in 4, frontal in 1 and left-sided in 1. Pain intensity was mild in 1 case, mild to moderate in 2, moderate in 7 and moderate to severe in 1. The nature of the pain was more similar to a chronic tension-type headache (73%) than a migraine-type, although 4 cases were found to be throbbing in nature. Headaches were related to stressful life events in 2 patients and exercise in 1 case. While two of the patients had received stellate ganglion blocks, all patients had received several kinds of drugs including analgesics, muscle relaxants, tricyclic antidepressants, selective serotonin reuptake inhibitors, anti-anxiety agents and anti-epileptic drugs. Nine patients were refractory to the pharmacological treatments.

Conclusions: Despite the general tendency that the pain of NDPH is dull, patients occasionally suffer from bouts of throbbing pain. NDPH is the refractory headache and requires optimal pharmacological regimens on an individual basis.

Conflict of interest: None

References

P63
Methyprednisolone i.v. alters levels of CGRP and melatonin in cluster headache patients
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Introduction: Treatment with steroids for short term cluster headache (CH) prophylaxis is a widely accepted therapy. However, the mechanism of action of steroids in CH prophylaxis is unknown. Various studies could show that the trigeminovascular system and the hypothalamus play a key role in CH pathophysiology. The neuropeptide calcitonin gene related peptide (CGRP) is released in an acute attack indicating activation of the trigeminovascular system.[1] The hypothalamus regulates the circadian secretion of melatonin which is reduced in CH patients during a bout.[2]

Objective: The aim of this study was to assess if treatment with high dose methyprednisolone (MP) i.v. inhibits release of CGRP and influences secretion of melatonin in CH.

Methods: 10 patients with episodic Cluster headache and 5 control patients with an acute episode of multiple sclerosis (MS) who should receive MP i.v. were included in the study. Patients were treated at the beginning of an episode (CH or MS) with a course of once daily 1g MP i.v. for three days followed by oral tapering. CGRP was assessed in plasma of the external jugular vein and the metabolite of melatonin in urine - 6-sulfatoxymelatonin – was collected separately during the day and night.

Measurements were done before as well as one day, one and two weeks after start of treatment. Patients recorded the number and severity of headache attacks each day.

Results: Treatment with MP led to a transient and significant decline of headache frequency. Simultaneously, CGRP plasma levels were reduced up to one week after end of treatment. Secretion of melatonin increased one and two weeks after treatment significantly. No significant changes could be observed in the control group.

Conclusion: The results could point to a possible mechanism of action of steroids in cluster headache prophylaxis. The altered secretion pattern could be explained through a direct effect of MP on the trigeminovascular system and the hypothalamus but could also be a consequence of the reduced frequency of attacks.

References

P64
Side locked headaches
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The Journal of Headache and Pain 2013; 14(Suppl 1):P64

Methods: Data were prospectively collected from 975 eligible patients (554 females; 583 Caucasians; age range = 4.5-18.1 years) with headaches. Patients were included only if they were > 4 years old and had suffered headache course for > 6 months and or 5 separate headache attacks. We have adopted previous descriptions of terms for anatomical sites for location [1]. Side locked unilateral headache (SLUH) is defined as a headache that is for all time fixed unilaterally and never changed side. Headache diagnosis was made on the basis of ICHD – II, 2004 [2]. Headache diagnosis included migraine (n=585); tension type headaches (n=234); other headache types (n=91) and remained unclassified in 65 (7%) patients.

Results: 119/975 (12%) of patients experienced recurrent SLUH during a mean headache course of 2.3 years. It was more for unilateral SLUH to localise to the right than the left (60% vs 40%). Topographically, temporal headache was the most frequent, followed by frontal and then parietal. Headaches were SLUH in 11.5% of patients with migraine; 8% with TTH and 23% patients with headache that not yet specified. Brain imaging was normal or showed no significant abnormalities in all scanned patients.

Discussion: Sinister aetiologies of SLUH were excluded among our patients. Primary headache was the most common headache category among patients with SLUH. Although, migraine constituted 60% of our study series, frequency of SLUH among migraineurs and those with non-migraine headaches did not reach statistical significance (11.5% vs 13%).

Conclusion: Before one could reach a conclusion of sinister aetiologies when faced with a patient with SLUH, primary headaches such as migraine and TTH should be considered.

References

P65
Greater occipital nerve block in management of chronic migraine; exploring clinical effectiveness and patient experience
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Greater Occipital Nerve (GON) Block is a recognized treatment modality in the management of chronic migraine. Our study aimed to assess the patient experience and clinical effect of this procedure in 20 patients undergoing this intervention. 20 patients with a diagnosis of chronic migraine were admitted from the outpatient department for GON block procedure. Patients were asked to complete a pre-procedure questionnaire.
This questionnaire focused on four domains: 1. Duration of symptoms, 2. Pre procedure ‘Headache Impact Test’ (HIT-6) score, 3. An objective pain score of current pain at time of procedure, 4. Subjective description of current pain character at the time of procedure, 20 minutes following the procedure patients were asked to repeat the objective and subjective assessment of current pain. At a one-month interval patients completed a repeat HIT-6 score.

Summary of key findings: Only 40% of patients reported a reduction in pain score 20 minutes post procedure. 2. A majority of patients (85%) reported a change in the subjective nature of the pain 20 minutes post procedure. 3. A majority of patients (80%) scored a lower HIT-6 score one month following procedure then prior to procedure. Average score difference was 5.4. There was no clear correlation between symptom duration and reported improvement in immediate and one month assessment of headache. We hope to present full details of patient demographics, breakdown of pre and post procedure HIT-6 scores as well as patient feedback of their experience of undergoing a GON block procedure.

P66
Cortical spreading depression impairs hippocampal long-term potentiation by the alteration of glutamate receptor responses
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The Journal of Headache and Pain 2013, 14(Suppl 1):P66

There is a relationship between migraine aura and amnesic attack. Cortical spreading depression (CSD), a phenomenon underlying migraine attack, may be responsible for hippocampus-related symptoms. However, the precise role of CSD on hippocampal activity has not been investigated. This study aimed to investigate the alteration of hippocampal long-term plasticity and basal synaptic transmission induced by repetitive CSDs. Male Wistar rats were divided into CSD and control groups. Repetitive CSDs were induced in vivo by topical application of solid KCl. Forty-five minutes following the ipsilateral hippocampus was removed, and hippocampal slices were prepared for a series of electrophysiological studies. After CSD induction, SDs also appeared in the hippocampus. Repetitive CSDs led to a decrease in the magnitude of long-term potentiation (LTP) in the hippocampus. CSD also reduced hippocampal synaptic efficacy, as shown by a reduction of post synaptic a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor responses. In contrast, post synaptic N-methyl-D-aspartate (NMDA) receptor responses remained unchanged. In addition, there were no changes in paired-pulse profiles between the groups, indicating that CSD did not induce any presynaptic alterations. Despite of unaltered NMDA receptor responses, CSD elevated the ratio of GluN2A to GluN2B subunit of AMPA receptor activity. These findings suggest that a reduction of post synaptic AMPA receptor responses and an increase of GluN2A/2B ratio may be the mechanism responsible for the impaired hippocampal LTP that was induced by CSD.

References

P67
GABA receptors in the nucleus raphe magnus modulate firing of neurons in the trigeminocervical complex
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Background: Nocticeptive transmission in the spinal cord is modulated by descending projections from the nucleus raphe magus (NRM) receiving tonic inhibitory inputs from GABAergic neurons. The NRM modulates transmission of craniovascular nociception, which is related to head pain, in the trigeminocervical complex.

Objectives: To determine whether descending modulation of transmission of craniovascular nociception in the trigeminocervical complex involves GABA receptors in the NRM. If so, to characterize those GABA receptors.

Methods: We used a model of trigeminovascular nociception in Sprague Dawley rats that measures transmission of craniovascular nociception in the trigeminocervical complex (TCC) by the firing of TCC neurons evoked in response to electrical stimulation of afferents from the middle meningeal artery, its branches, and periarterial meninges (MMA). To determine whether GABA receptors in the NRM modulate this nociceptive transmission, and to characterize the modulation, we microinjected GABA, and GABA-A- and GABA-B receptor agonists and antagonists into the NRM.

Results: Microinjection of GABA into the NRM increased firing of TCC neurons evoked by stimulation of MMA afferents (p < 0.05). Moreover, microinjection of the GABA receptor agonist, muscimol, into the NRM also increased evoked firing of TCC neurons. Whereas the GABA receptor antagonist, bicuculline, decreased evoked firing of TCC neurons when microinjected into the NRM (p < 0.05). In contrast, microinjection of neither the GABAB receptor agonist, baclofen, or its antagonist, 2-hydroxyaclofen, into the NRM had no significant effect on the evoked firing of TCC neurons.

Conclusion: This study shows that inhibition of NRM neurons by GABA receptor activation facilitates transmission of craniovascular nociception in the trigeminocervical complex. Our results suggest that GABA receptors in the NRM play a role in the pathophysiology of migraine and other primary headache disorders.

P68
Effects of URB937 on an animal model of migraine pain
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Several studies have suggested the existence of interactions between the endocannabinoids and migraine. URB937, a FAAH inhibitor specific to peripheral tissues, causes analgesia in animal models of pain [1]. In this study, we evaluated whether the URB937 administration may alter nociceptive responses in an animal model of migraine based on nitroglycerin (NTG)-induced hyperalgesia [2]. Rats received systemic NTG and URB937 before being evaluated at the Tail flick test or at the Formalin test. The findings show that URB937 did inhibit NTG-induced hyperalgesia at the Formalin test with only a minimal influence on the hyperalgesia at the Tail flick. The data suggest that availability of anandamide probably at the meningeal level is effective in the migraine pain.

References
Methods: Adult male Sprague-Dawley rats were anesthetized with pentobarbitone sodium (60 mgkg⁻¹). The parietal bone was removed over the MMA for placement of a bipolar stimulating electrode. For recording neuronal activity, a tungsten electrode was inserted into the TCC. CGRP was induced by placing solid KCl (3 mg) on the parietal cortex. This inhibitory response was reversed by intravenous administration of the 5-HT1B/1D receptor antagonist, GR127935 (3mg/kg), and a mu-opioid receptor antagonist, naloxone (1.5 mg/kg), five minutes after injection (p < 0.05).

Conclusion: The present findings show that repetitive CSDs inhibit a subpopulation of dural nociceptive trigeminal neurons, an effect mediated by serotonin and opioids receptors. Understanding how the cerebral cortex modulates trigeminovascular nociception will improve our understanding of the pathophysiology of migraine.

**P70**
Role for TRPA1 receptor channels in trigeminal afferent activation and neuropeptide release from rat cranial dura mater
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The Journal of Headache and Pain 2013, 14(Suppl 1):P70

**Introduction:** TRPA1 receptor channels are activated by environmental irritants and by endogenous mediators released during inflammatory conditions (McMahon & Wood 2006). Activation of TRPA1 receptors causes CGRP release from trigeminal ganglion neurons and increases meningeal blood flow upon nasal stimulation (Kunkler et al. 2011), providing evidence that TRPA1 receptors may be involved in the generation of headaches.

**Objective:** To further examine the role of TRPA1 receptor activation in processes presumably associated with headache generation, we investigated the effects of the TRPA1 agonist acrolein on functions involved in meningeal nociception using four different rat models.

**Methods:** The discharge activity of single meningeal afferents innervating the dura mater was recorded in a hemisected cranial preparation. 2. The activity of second order neurons in the spinal trigeminal nucleus with meningeal afferent input was recorded in anaesthetised animals. 3. In the hemisected cranial preparation the dura mater was superfused with synthetic interstitial fluid, and stimulated calcitonin gene-related peptide (CGRP) release was measured using an ELISA. 4. Meningeal blood flow was monitored in the exposed dura mater of anaesthetised animals using laser Doppler flowmetry. In all preparations the dura mater was stimulated with the TRPA1 agonist acrolein (10⁻⁴ M).

**Results:** Acrolein did not elicit discharges in meningeal Aδ- or C-fibres in the hemisected cranial preparation and did not change the discharge activity of second order neurons with meningeal receptive fields in anaesthetized animals. In contrast, acrolein significantly stimulated CGRP release from the dura mater within 5 min and increased meningeal blood flow. Both responses were suppressed by the TRPA1 inhibitor HC030031.

**Conclusion:** TRPA1 channel activation causes neuropeptide release from meningeal afferents but does not generate propagated afferent information. Therefore an important role for peripheral TRPA1 receptors in headache generation appears unlikely.

**References**

**P71**
Magnesium and memantine do not inhibit nociceptive neuronal activity in the trigeminocervical complex of the rat
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The Journal of Headache and Pain 2013, 14(Suppl 1):P71

**Introduction:** Experimental studies with NMDA receptor antagonists, such as magnesium and memantine, have demonstrated the ability of these substances to inhibit nociceptive trigeminal neurotransmission in electrophysiological studies. Despite these promising experimental results clinical trials results have been less than clear. To investigate further this contrast using the open channel blockers, magnesium and memantine, we studied their effects in a model of nociceptive trigeminovascular activation.

**Methods:** Sprague-Dawley rats were anesthetized with pentobarbitonal (60 mgkg⁻¹) and cannulated for physiological monitoring, maintenance of further anesthesia and drug administration. Anesthesia was maintained with intravenous propofol (20-25 mgkg⁻¹h⁻¹). A cranial window was prepared over the middle meningeal artery (MMA) and a bipolar electrode was placed on the dura mater above the MMA for electrical stimulation. For recording of neuronal activity a tungsten electrode was introduced in the trigeminocervical complex (TCC). Experimental groups received either intravenously administered memantine (10 mgkg⁻¹), magnesium (100 mgkg⁻¹) or vehicle.

**Results:** Magnesium and memantine did not have a significant inhibitory effect on neuronal activity in the TCC. However, blood pressure was significantly reduced after memantine (31 ± 5%, p < 0.05) or magnesium (49 ± 11%, p < 0.05) administration when compared to baseline.

**Conclusion:** The results indicate that the known inhibitory effect of magnesium and memantine after microinjection or in vivo treatment could not be reproduced with intravenous administration. This might be a result of the low drug concentration that can be achieved with this route of administration at the relevant site of action. A further increase in dosage is not feasible since the used dosage already led to significant reductions in arterial blood pressure. The results support the clinical observations and provide a possible explanation for the lack of consistent efficacy of these drugs for the treatment of migraine.

**References**
Reference

P73 Dynamic balance decreased in postdromal migraineurs compared to non-migraine controls
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The Journal of Headache and Pain 2013, 14(Suppl 1):P73

Introduction: Balance is a complex process involving visual, vestibular and neuromuscular control. Migraineurs often report vertigo and dizziness symptoms during and post migraine. The Biodex Balance System SD 1 is a reliable method to measure dynamic balance. Little research 2 has examined dynamic balance in migraineurs compared to individuals who do not have migraines.

Purpose: The purpose of this research is to examine the differences between migraineurs and controls dynamic balance at two testing intervals: baseline (migraine free 7 days) and post migraine (within 48 hours of migraine onset).

Methods: 20 controls (C) (age 25.70±10.77) and 17 Migraineurs (M) (age 25.24±9.55) completed dual limb support testing on the Biodex Balance System SD. Limits of Stability (LOS) testing at moderate skill level (75%) involved center of gravity control within their base of support. The clinical test of sensory integration and balance tested stability and sway indexes within four conditions (eyes open/closed on firm vs foam surface) for 30 second intervals.

Results: A repeated measures ANOVA revealed significant differences [mean diff (post-pre) C=7.06±5.57, M=68.67±4.5, p=.029] between migraineurs and non-migraineurs in overall LOS post migraine. Significant decreases were found between shift of balance to the right [mean diff (post-pre) C=147.1±71.69, M=-2.18±16.97, p=.034] and balance to the left [mean diff (post-pre) C=9.88±15.77, M=-3.75±22.1, p=.019] post migraine. No significant differences were found between groups for stability or sway indexes for all conditions on the clinical test of sensory integration.

Conclusions: Migraineurs exhibit difficulty with center of gravity shifts to the right and left and overall dynamic LOS post migraine. Once LOS is exceeded a fall, stumble or step will ensue. This suggests decreases in lower extremity strength, proprioception and vestibular deficiencies.

References

P74 Neurocognitive function declines are reversible following migraine headache in college students
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The Journal of Headache and Pain 2013, 14(Suppl 1):P74

Introduction: Computerized testing of neurocognitive function yields an accurate and reliable assessment [1]. There is little research on short-term effects of migraine headaches on neurocognitive function or their cognitive recovery patterns [2].

Purpose/background/objective: The purpose of this study was to investigate neurocognitive function and recovery patterns in college students who incur migraine headaches compared to college students who do not.

Methods: Volunteers (ages 18-29) completed computerized neurocognitive baseline (B) testing. Forty-four migraineurs incurring a migraine (M) were matched to 44 non-migraine (NM) controls for sex, age and education level. Verbal and visual memory, processing speed and reaction time were measured at 24 hours, 48 hours and 7 days post migraine.

Results: Repeated measures ANOVAs revealed declines in neurocognitive function of migraineurs in verbal memory [mean diff(md)(24hr-B) M=-1.59±7.82, NM=1.19±6.79, p=.045], visual memory [md(24hr-B)M=-4.70±15.61, NM=3.05±10.94, p=.041], and reaction time [md(24hr-B)M=-0.02±0.9, NM=-0.01±0.4].

References

P75 Sustained pain relief with dihydroergotamine in migraine is potentially due to persistent binding to 5-HT1B and 5-HT1D receptors
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Several studies show that dihydroergotamine (DHE) produces sustained migraine pain relief, measured up to 48 hours, although its serum half-life is only 10-13 hours. The extended duration of action has been attributed to an active metabolite (‘OH-DHE) with a much longer half-life than the parent compound. However, recent pharmacokinetic studies demonstrate that DHE metabolites measured in humans are too low to have substantial clinical effect and probably do not contribute to sustained efficacy. We hypothesized that the long-lasting effect of DHE is most likely due to prolonged binding to receptors, rather than serum half-life. Therefore, to investigate the mechanism of sustained migraine pain relief observed with DHE, we compared its duration of binding to serotonin receptors vs. sumatriptan.

Duration of receptor binding is expressed as the dissociation constant (koff) of the receptor-ligand complex, measured using a competitive radioligand assay. DHE and sumatriptan were tested with human 5-HT1B and 5-HT1D receptors in this study. The dissociation half-life of DHE on 5-HT1B and 5-HT1D receptors is approximately 10 times longer than that of sumatriptan (5-HT1B: 1.38 h for DHE vs. 0.17 h for sumatriptan; 5-HT1D: 1.28 h for DHE vs. 0.09 h for sumatriptan). DHE binds to 5-HT1B and 5-HT1D receptors up to 8-14 times longer than does sumatriptan. These receptors play a key role in the acute treatment of migraine and, therefore, prolonged binding to these receptors may be a mechanism for the sustained pain relief seen with DHE during the acute treatment of migraine.

Study supported by MAP Pharmaceuticals, Inc. and was conducted by EuroScreen S.A. (Belgium).

References

P76 Modulation of trigeminovascular activity by leptin: a novel antinociceptive mechanism?
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The Journal of Headache and Pain 2013, 14(Suppl 1):P76

Introduction: Fasting is a recognized trigger of headache in susceptible individuals. Leptin is a peptide hormone encoded by the mouse obese gene (ob) [1] and is mainly secreted by white adipocytes. Plasma levels of leptin are regulated to reflect body energy stores: levels of leptin fall in response to fasting and are increased in several models of murine obesity [2]. Leptin signaling decreases feeding and increases energy expenditure by activating the longform of its receptor (LepRb) in areas of the brain [3] including the brainstem, midbrain, hypothalamus, thalamus and cortex [4].

Reference
P77
Investigation of 5-HT2B receptor induced dural plasma protein extravasation in a mouse migraine model
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Migraine attacks originate in the meninges which are densely innervated by trigeminal nerve fibers. Stimulated endothelial cells of dural blood vessels secrete nitric oxide, where neuromediators are released from trigeminal nerve fibers. This, in turn, leads to meningeal Plasma Protein Extravasation (PPE), serving as an established indicator for migraine attacks in animal models. In our mouse migraine model, we sensitized mice against the 5-HT2B receptor agonist meta-chlorophenylpiperazine (mCPP). Mice kept under hypoxic conditions for four weeks displayed significantly elevated PPEs in the dura mater upon mCPP injection. Tissue accumulation of the tracer Evans Blue was measured to quantify the extent of the PPE. In this study, several histological tracers were employed to identify the part of the vasculature where PPE occurs and the cellular mechanism associated with it. Injections of BSA-FITC (FITC-linked bovine serum albumin) verified the mCPP induced extravasation of Evans Blue to the dura mater. After leaving the blood vessels, the tracer was incorporated into perivascular, CD68-positive macrophages. With electron microscopic studies using the tracer HRP (horseradish peroxidase) we demonstrated that the PPE is associated with increased transcytotic transport. After 5-HT2B receptor activation, HRP escapes from capillaries and venules of hypoxic mice via an increased transcytotic transport in arterioles, which may be indicative of a proinflammatory state of the endothelium. HRP was also detectable in intercellular clefs, but was always retained at tight junctions. In summary, we demonstrated that in mice hypoxic treatment induces dural PPE via increased transcytosis at arterioles and that this is elevated to capillaries and venules after mCPP-injection.

P78
Activation of 5-HT2B-receptors leads to increased vasodilatation in mouse dura mater blood vessels
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Neurogenic inflammation occurring in migraine may be associated with plasma protein extravasation (PPE) and vasodilatation of dural blood vessels. 5-HT2B receptors may be involved in the onset of migraine attacks, in which receptor activation may induce increased synthesis of nitric oxide and, subsequently, the release of vasoactive CGRP from trigeminal nerve fibres. We found that the activation of 5-HT2B receptors in mice that were kept under hypoxic conditions for several weeks triggered an increased PPE in the dura mater. In addition to the PPE we now asked whether the activation of the 5-HT2B receptors also results in the vasodilation of dural blood vessels. For this purpose we combined intravital microscopy with the hypoxic mouse model. We removed a part of the skull in anesthetized mice and exposed the dura mater. Changes in blood vessel diameter have been observed via intravital microscopy after a topical application of substances directly onto the dura mater. Application of a 5-HT2B receptor agonist led to increased vasodilatation of dural blood vessels. The effect could be completely blocked by specific receptor antagonists. The results confirm the involvement of 5-HT2B receptors in the onset of migraine attacks. While the topical application of CGRP alone was not sufficient to induce similar vasodilatation in the mouse dura mater, the effect occurred when CGRP was applied after a preconstriction of the blood vessels by endothelin 1 (ET-1). Thus, we showed that the activation of 5-HT2B receptors not only induces PPE, but also dilates blood vessels in the dura mater. Whether and to which extent the vasodilatation induced by 5-HT2B receptor activation is associated with the subsequent release of CGRP is subject to further studies.

P79
Monitoring cortical neuronal activity and spreading depression in freely behaving familial hemiplegic migraine Cacna1a R192Q knockin mice
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The Journal of Headache and Pain 2013, Volume 14 Suppl 1

Introduction: Experimental findings from transgenic migraine mouse models that carry a human FHM1 gain-of-function mutation in CaV2.1 (P/Q-type) calcium channels underscore the role of neuronal hyperexcitability in migraine [12]. However, functional data that link the excitability changes to neuronal network activity and the enhanced propensity to cortical spreading depression (CSD), the likely mechanism underlying migraine aura, are largely lacking.

Purpose/background/objectives: Here, we aimed to set up an electrophysiology platform to study changes in cortical neuronal network activity in relation to CSD in freely behaving transgenic migraine mice.

Methods: We developed an electrophysiology system for long-term recordings of DC-EEG and multi-unit-activity from the cortex of freely behaving mice. The system combines a counterbalanced 7 channel swivel with custom-built differential DC-EEG, AC-EEG and unit activity amplifiers. Stable DC-EEG recordings are obtained using Ag/AgCl epidural electrodes, while intracortical platinum electrodes are used for simultaneous recording of multi-unit-activity and AC-EEG. For CSD induction intracortical microdialysis was used for infusion of high KCl solution.

Results: Simultaneous recordings of multi-unit activity, DC- and AC-EEG were made from the sensorimotor and occipital cortex of wild-type and FHM1 migraine mice for up to 3 weeks. Apart from spontaneous cortical activity, visual evoked cortical responses were induced using 1 ms blue light pulses. Microdialysis with KCl solution resulted in successful induction of CSD events in the awake mice.

Conclusion: We established a novel platform for performing longitudinal recordings of cortical neuronal activity and spreading depression in freely behaving mice carrying migraine mutations. Using this platform, we aim to characterize how cortical activity is altered by modulatory factors that predispose for migraine attacks.

References
The objectives of this study are to develop and characterize a Botulinum toxin type A (BTX-A) has been used for pro-
of the vagus nerve through the skin
he progression of migraine
14(Suppl 1):
rsensitivity was
Is chronic migraine a never-ending migraine attack?
edes and in habituation slopes for
Following the 10 infusions of the IS, the rats were allodynic. All
14(Suppl 1):
Cephalalgia
In a rat model of recurrent headache, both behavioral and
ally cortical activation level and VEP
to study the mechanism of action of nVNS on behavioral and
physiological correlates of trigeminal pain.
Methods: One week after the last infusion, electrodes were positioned on
the neck over the vagus nerve and the animal was stimulated for 1min. The
nVNS signal consisted of 1ms bursts of a 5kHz sine wave repeated at
25Hz. The peak voltage applied was 22V. The control for nVNS was
electrode placement, without stimulation. Another group of rats were
were used for microdialysis studies to determine the mechanism of action of
nVNS effect on trigeminal pain. Rats were anesthetized and placed in a
stereotaxic frame. Using a small microdialysis probe, extracellular amino
acids were sampled for up to 3.5hr after GTN (0.1mg/kg) treatment with
and without nVNS stimulation.
Results: Following the 10 infusions of the IS, the rats were allodynic. All
of the rats responded to nVNS stimulation with an increase in their
periorbital pain threshold within 5min. This effect was maintained for at
least 3.5hr after the stimulator was turned off. GTN treatment elicited a
>7 fold increase in extracellular glutamate, which peaked at ~2hr after
this increase in glutamate was completely blocked by 2min of
nVNS stimulation.
Conclusion: In a rat model of recurrent headache, both behavioral and
physiological measures of trigeminal pain and allodynia are suppressed by
1-2min of nVNS. Funding: NIH R01-NS061571, ElectroCore LLC. COI:
Bruce Simon is an employee of ElectroCore LLC.
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P81 Characterization of a novel model for chronic migraine
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The Journal of Headache and Pain 2013, 14(Suppl 1):P81

Introduction: The mechanisms underlying the progression of migraine from
an episodic to a chronic process are poorly understood, and the
development of new therapies for chronic migraine has been slow, in
part due to the lack of clinically relevant animal models.
Objectives: The objectives of this study are to develop and characterize a
new mouse model for chronic migraine, based on repetitive intermittent
exposure to the human migraine trigger nitroglycerin (12). A goal of this
model is to test the effect of known and potential acute and preventive
migraine therapies, in order to gain understanding regarding mechanisms of
action and to develop preclinical evidence to support use of new
therapies in patients with chronic migraine.
Methods: Nitroglycerin was administered IP to mice every second day for 9
days. Basal and nitroglycerin-evoked mechanical hypersensitivity was
evaluated using manual von Frey hair stimulation of the hindpaw.

Results: Acute nitroglycerin administration evoked mechanical hyperalgesia
in a dose dependent manner. Chronic intermittent treatment with
nitroglycerin induced a progressive and sustained basal (T2) after rTMS. We
measured changes in 1st block amplitudes and in habituation slopes for
N1P1 and P1N2 components as outcome measures. Results in the TBE
group (n=13), 1st block P1N2 amplitude and habituation of N1P1 increased
after the stimulation, with partial recovery at 3 hours. Interestingly,
habituation of P1N2 increased with time after the stimulation and was more
pronounced at 3 hours compared to baseline or immediately after rTMS. In
the QPI group (n=11), we found a post-stimulation reduction of 1st block
amplitude, which also increased with time and was greater at 3 hours than
immediately after the stimulation. No significant effect was found for the TBI
and QPE protocols.

Conclusion: Excitatory theta burst and inhibitory quadrupulse rTMS are thus
able to modify durably and differentially cortical activation level and VEP
habituation. The former could be potentially useful in the preventive
treatment of episodic migraine while the latter could have a beneficial effect
in chronic migraine.

References
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P82 The effects of botulinum toxin type A on the trigeminal TRPV1
containing neurons innervating the dura mater of rat
T Shimizu1, M Shibata1, H Toriumi1, T Iwashita2, M Funakubo2, H Sato2,
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The Journal of Headache and Pain 2013, 14(Suppl 1):P82

Background: Botulinum toxin type A (BTX-A) has been used for pro-
phylactic treatment in chronic migraine. However, the precise mechanism of
its action is obscure. We previously reported that the injection of BTX-A into
the facial ophthalmic nerve region reduced the number of the TRPV1-
immunoreactive (IR) neurons in the trigeminal ganglion (TG). The dura mater,
known as an important site of headache generation, is densely innervated by
trigeminal nociceptors. We have recently demonstrated the existence of
TRPV1-IR nerve fibers in the dura mater that originate in TG. In this study,
we explored the effect of BTX-A on the number of the TRPV1-IR TG neurons
innervating the dura mater.
Methods: Six Sprague-Dawley rats were used. The retrograde tracer, true
blue (TB), was applied to the dura mater. Seven days after the tracer
application, 0.5 ng/kg BTX-A was injected into the left side of the face in
three animals, and three control animals were injected with saline at the
same location. After 7 days, TGs were dissected out and immunostained with
an anti-TRPV1 antibody. For analysis, we calculated the ratio of the
TRPV1-IR cells in TB accumulated neurons. Results In the control animals, the
proportion of TRPV1-IR-containing neurons that were also TB-positive was
27 % (n = 372 neurons from 3 animals). In the BTX-A treated animals, tracer
accumulation and TRPV1-IR were also observed. However, the number of
TRPV1-IR neurons retrogradely labeled with true blue was reduced. The
proportion of TRPV1-IR cells in the BTX-A treated animals was 11 % (n = 504
neurons from 3 animals), and this was significantly decreased compared to
the control group (Student’s t-test, p < 0.0001).

Conclusion: Our results indicated the possibility that BTX-A may reduce the
expression of the TRPV1 receptor in neurons of the TG innervating the dura
mater, which may account for its alleviating action against headache
disorders.

P83 Differential cellular localization of antioxidant enzymes in the
trigeminal ganglion
M Shibata1, H Sat01, T Shimizu2, S Shibata2, H Toriumi1, T Kuroi1, T Ebine1,
T Iwashita1, M Funakubo2, C Akazawa1, K Wajima1, T Nakagawa3, H Okamo1,
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Potential vanilloid subfamily member 1
Enhanced excitatory transmission at cortical synapses as
Because of its high oxygen demands, neural tissue is
We used 14 adult transgenic mice expressing the
mismatch model proposed
Corticosterone (20 mg/kg) or vehicle was injected sub-cutaneously
Corticosterone injection increased CSD frequency in FHM1 mice
2009, SD susceptibility in FHM1 R192Q
et al
2011, the production of reactive oxygen
Exp Neurol
9(2)
Four groups of adult female rats (n = 16) were ovariectomized
2012, Epub 2012/05/17.
et al
61
Migraine is sexually dimorphic and associated in 20% of
ency to the level of vehicle-injected
A Cacna1a knockin migraine mouse
Kynurenine metabolites and migraine: experimental studies and therapeutic perspectives. Current
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P85 Corticosterone enhances CSD susceptibility via glucocorticoid receptor activation in familial hemiplegic migraine 1 Cacna1a knock-in mice
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The Journal of Headache and Pain 2013, 14(Suppl 1):P85
Introduction: FH1M mutant mice carrying the R192Q gain-of-function mutation in CaV2.1 (P/Q-type) calcium channels display enhanced glutamate receptor transmission and increased propensity for cortical spreading depression (CSD[1,2]). Corticosteroids released after stress also enhance glutamate receptor transmission but the relationship between stress and migraine is not well understood.
Objectives: We aimed to investigate the acute effects of corticosterone and the role of GR activation on CSD susceptibility in FH1M R192Q knock-in mice.
Methods: Corticosterone (20 mg/kg) or vehicle was injected sub-cutaneously 4 hours before CSD frequency recordings were carried out in FH1M R192Q mice. A subgroup of mice was injected with the glucocorticoid receptor antagonist mifepristone 50 minutes before corticosterone/vehicle injection.
Results: Corticosterone injection increased CSD frequency in FH1M mice compared to vehicle-injected controls but not in wild-types. Pretreatment with mifepristone reduced CSD frequency to the level of vehicle-injected controls. Baseline corticosterone plasma levels were similar in WT and FH1M mice, while 3 hours after corticosterone administration corticosterone plasma levels were strongly elevated to comparable levels in both WT and FH1M mice.
Conclusion: These data suggest that combined effects of glucocorticoid receptor activation and the FH1M R192Q CaV2.1 gain-of-function mutation on excitatory neurotransmission may play a role in proposed effects of stress on migraine attacks.
References
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P86 Repeated methylene blue administration produces analgesia in experimental pain
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The Journal of Headache and Pain 2013, 14(Suppl 1):P86
Introduction: Methylene blue (MB), a widely used inhibitor of NO activity/production, is also a reduction-oxidation agent that can act both as a
powerful antioxidant and as an enhancer of the electron transport chain. Furthermore, it prevents formation of mitochondrial oxygen free radicals and promotes oxygen consumption (Atamna et al. 2010, Rojas et al. 2012).

**Purpose:** The aim of the study was to investigate the effects of chronic (14 days) MB administration on experimental pain in mice.

**Methods:** Sixteen Swiss male mice were divided into 2 groups: control group (n=8) and MB group (n=8); both groups received daily injections, for 14 days, either with saline 20 l/l i.p. (control group) or with MB 5 mg/kg b.w. i.p (MB group). Nociceptive tests (tail flick and hot plate) as well as mechanical and thermal withdrawal thresholds were measured every two days before MB/ saline administration. Before and two hours after the last dose was administered (day 14), each group was evaluated for the nociceptive tests and heat/mechanical hyperalgesia; results were compared with paired Student’s t test. After nociceptive tests, the mice received 20 l/l of 5% formalin into the upper right lip and the intensity of the orofacial pain was assessed. The results were compared with those from saline group using unpaired Student’s t test.

**Results:** Chronic administration of MB increased tail flick and hot plate latencies (p=0.03, p<0.02). We also noted an increase in the reaction time for thermal hyperalgesia assessed by Hargreaves method (p=0.04). As for the formalin-induced orofacial pain, MB produced a significant analgesic effect on both phases (p=0.03).

**Conclusion:** Our study demonstrates that chronic administration of MB has analgesic effects on acute nociception as well as on the orofacial inflammatory pain; further studies must be conducted in order to elucidate the mechanism by which the methylene blue exerts its antinociceptive effect.

**Acknowledgements:** Support provided by Executive Agency for Higher Education and Research Funding (UEFISCSU) Romania project PN-II-ID-PCE-2011-3-0875.

**References**


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**P88**

**Involvement of TRPA1 receptors in meningeal blood flow induced by formation of nitroxyl (NO-/HNO)**

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**Purpose:** We examined the role of TRPA1 receptors of meningeal afferents in the regulation of meningeal blood flow.

**Methods:** In isoflurane anaesthetised rats, meningeal blood flow was recorded by laser Doppler flowmetry. Sodium-alpha-oxypyronitrite (Angel’s salt, AS, 300 μM), which mainly produces NO-/HNO, was topically applied to the cranial dura mater. The distribution of TRPA1 immunoreactive neurons in the trigeminal ganglion was determined by indirect immunohistochemistry.

**Results:** Application of AS causes increases in meningeal blood flow lasting several minutes. Topical pre-administration of 50 μM HC-030031, which may activate TRPA1 receptors of meningeal afferents, considering this possibility we examined the role of NO-/HNO in a rat model of meningeal blood flow.

**Conclusions:** The release of CGRP provoked by NO donors may be indirectly involved in the formation of nitroso (NO-HNO), a reduced congener of NO, partly mediated by the release of CGRP from meningeal afferents (Strecker et al. 2002).

**References:**


P89
Dissertation of nerve fibers storing CGRP and CGRP receptors in the peripheral trigeminovascular system
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The Journal of Headache and Pain 2013, 14(Suppl 1):P89

Background: The dura mater with the meningeal artery has since long been hypothesized to play an important role in migraine. It has been suggested that neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P can activate dura mast cells leading to secretion of vasoactive, pro-inflammatory and neurosensitizing mediators, thereby contributing to migraine pathogenesis. Method: Immunofluorescence was used to study the detailed distribution of and its receptor components-calcitonin receptor-like receptor (CLR) and receptor activity modifying protein 1 (RAMP1)-in whole-mount rat dura mater, using a set of newly characterized antibodies. Their relation to each other, to mast cells, myelin, substance P, neuronal nitric oxide synthase (nNOS), pituitary adenylate cyclase-activating polypeptide (PACAP) and vasoactive intestinal peptide (VIP) were studied. In addition, we examined expression of CGRP and its receptor components in freshly isolated human dura vessels.

Results: CGRP expression was found in thin fibers, while CLR and RAMP1 were expressed in thicker fibers. Double-staining of CGRP and the receptor components showed no co-localization. CLR and RAMP1 expression were found in cells, co-localized with mast cell tryptase. Double-staining with CGRP and MBP showed no co-localization. CLR and RAMP1 immunoreactive fibers co-localized with MBP and NF160/200. Substance P fibers co-expressed CGRP, nNOS and VIP expression was very limited and these fibers were distinct from the CGRP positive fibers. Few PACAP immunoreactive fibers co-localized with CGRP. No expression of functional CGRP receptor was observed in human mast cells.

Conclusions: CGRP is expressed in un-myelinated fibers C-fibers. CLR and RAMP1 are instead expressed in myelinated fibers A-fibers. This supports the view that activation of C-fibers may locally cause release of CGRP, which could act on A-fibers, mast cells and vascular smooth muscle cells. Interestingly, CLR and RAMP1 expression was found in rat dura mast cells, however, human mast cells lack expression of functional CGRP receptor.

P90
Glyceryl trinitrate has opposite effects on different experimental models of pain
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Introduction: The actions of glyceryl trinitrate (GTN) are the result of its bioconversion into NO; NO increases the intracellular concentration of cyclic guanosine monophosphate (cGMP), which produces pain modulation in the central and peripheral nervous system (Griesberger et al. 2011). In addition, GTN administration is considered a reliable experimental model of migraine, based on the neuronal effects on the integrative-nociceptive structures (de Tommaso et al. 2004).

Purpose: to investigate the effects of GTN 4 hours after its administration on different experimental pain models in mice.

Methods: sixteen Swiss male mice were divided into 2 groups: control group (n=8) and GTN group (n=8, 10 mg/kg b.w. i.p.). Assessment of locomotor activity (activity cage) and nociceptive tests (tail flick-TF and hot plate-HP) were performed before GTN administration and considered as baseline. Four hours after GTN injection, locomotor activity assessment and nociceptive tests were re-evaluated; afterwards, 20 h of 5% formalin were administrated into the upper right lip in order to assess formalin-induced orofacial pain. The results were compared with paired and unpaired Student’s t test.

Results: GTN administration significantly increased HP latencies (p=0.0002) and showed a tendency towards increasing TF (p=0.056). A decrease in the locomotor activity was noted for both vertical movement activity (-78% p =0.001) as well as horizontal movement activity (-87% p=0.0001). GTN had no significant effect in influencing formalin-induced orofacial pain response.

Conclusion: In our study GTN administration in mice exerted analgesic effects on acute nociception but had no effect on orofacial formalin pain. In addition, GTN decreased locomotor activity. Taken together, our results demonstrate that trigeminal pain is differently modulated by GTN as compared to nociception in TF and HP.

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References

P91
CGRP and CGRP receptors in human and rhesus monkey cerebellum
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Background: The cerebellum is classically considered mainly involved in motor processing, but recent studies have suggested several other functions, including pain processing. PET studies of acute migraine attacks have revealed activation of the cerebellum. In human pain imaging studies activation of the cerebellum is almost always observed, suggesting a role in nociception. Calcitonin gene-related peptide (CGRP) has been shown to be one of the most important neuropeptides involved in migraine pathology, where there is elevated release of CGRP during migraine attacks and CGRP receptor antagonists have antimigraine efficacy.

Methods: In vitro autoradiography mapping studies were performed on human and rhesus monkey. Slices of cerebellum were incubated with [3H] MK-3207 (a CGRP receptor antagonist) or [125I]CGRP to define the binding sites. Immunofluorescence was used to study the detailed distribution of CGRP and its receptor components- calcitonin receptor-like receptor (CLR) and receptor activity modifying protein 1 (RAMP1)- in human and rhesus monkey cerebellum, using a set of newly characterized antibodies. In addition, expression of procalcitonin was studied.

Results: High [3H]MK-3207 binding densities were observed in the molecular layer of rhesus cerebellum, however due to the limit of resolution of the autoradiographic image the exact cellular localization could not be determined. Similarly, [125I]CGRP binding was observed in the molecular layer of human cerebellum. Immunofluorescence revealed expression of CGRP, CLR and RAMP1 in the Purkinje cells and cells in the molecular layer. Procalcitonin was also found in Purkinje cells and cells in the molecular layer.

Conclusions: The study demonstrated CGRP receptor binding sites and expression of CGRP and its receptor in primate cerebellum, which points toward a functional role of CGRP in cerebellum. It is also suggests that cerebellum may be a site of action of CGRP receptor antagonists.

P92
Measurements of 17β-estradiol levels in mice for migraine research
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The Journal of Headache and Pain 2013, 14(Suppl 1):P92

Introduction: Since migraine prevalence is 2-3 times higher in women than in men, especially during the reproductive years, fluctuations in...
female sex hormone levels seem to be one of the key factors involved in the pathogenesis of migraine. During the last decade, lots of animal research in migraine has been performed on mice, since this species is well suited to create transgenic animal models. To investigate the effect of female sex hormones in a murine model, it is important to analyse the hormone levels and/or to determine the hormone cycle in mice. Although no reliable assay has been available to measure murine plasma estrogen, recently 17β-estradiol assays have been suggested to be able to quantify these hormone levels.

**Purpose:** We set up a pilot study to test 3 different ELISA kits described in the literature.

**Methods:** Plasma samples and vaginal smears of female mice (10-11 weeks) were collected at two different time points: 3 days before and 2 weeks after ovariecotomy (OVX), when the animals were sacrificed. Weights of uterus were also collected. Blood samples were tested in 3 different ELISA kits obtained from Cayman Chemical (Ann Arbor, MI, USA), GenWay Biotech (San Diego, CA, USA) and Calbiotech (Spring Valley, CA, USA), respectively.

**Results:** All the tested ELISA assays did not show any differences in 17β-estradiol levels before and after OVX. Likewise, no differences in 17β-estradiol levels between sham-operated and OVX animals were observed using these assays. Data from vaginal smears and uterus weights (sham: 42.7±9.8 mg, OVX: 16.2±2.0 mg), however, confirmed that OVX was successfully performed.

**Conclusion:** We conclude that the tested ELISA assays are not capable of precisely determining 17β-estradiol levels in mice. Since vaginal smears, uterus weights and ovary staining are indicative of the phase of the cycle, in future studies these parameters may be used to analyze the hormonal status in mice.

**Reference**

**P94**
**Mechanisms of individual differences in heterotopic noxious analgesia (DNIC), an fMRI study**
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**Introduction:** Pain responses can be suppressed by heterotopic continuous noxious conditioning, e.g. continuous noxious cold stimulation.

**Objective:** The aim was to investigate individual differences in heterotopic analgesia (DNIC) using fMRI. We hypothesize that this individual variation might be linked to the different functional connectivity in the sensory and prefrontal cortex.

**Methods:** Using the same protocol, we performed a multi-center fMRI study in 12 healthy subjects from four different institutions. The sample consisted of 3 males and 9 females, with an average age of 25±4 years. The study protocol was approved by the institutional review board (IRB) of each participating center. All subjects gave written informed consent. The primary outcome parameter in this study was the degree of inhibition of laser-induced pain during heterotopic cold stimulation analyzed.

**Results:** Our results show that cold-induced BOLD response in anterior cingulate, orbitofrontal and lateral prefrontal cortices predict cold-induced heterotopic analgesia and attenuation of cerebral BOLD responses to laser stimulation. Prefrontal responses to the onset of cold stimulation were strongly related to the subsequent DNIC effect.

**Conclusion:** We conclude that early responses to noxious conditioning are important for prediction of the analogic DNIC effect. We hypothesize that this predictive effect of frontal cortices may be abnormal in chronic migraine.

**References**

**P95**
**Endothelin-converting-enzyme 1 inhibition and CGRP receptor recycling in human coronary and middle meningeal arteries**
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The Journal of Headache and Pain 2013, 14(Suppl 1):P95

Although best known for its role in the conversion of big endothelin to endothelin-1, endothelin-converting enzyme 1 (ECE-1) also regulates the resensitization of certain neuropeptide receptors, including the receptor for calcitonin gene-related peptide (CGRP) (Padilla et al., 2007). We investigated the role of ECE-1 in the resensitization of responses to CGRP in human coronary (HCA) and middle meningeal (HMA) arteries using the potent and selective ECE-1 inhibitor, SM-19712. Segments of HCA (Ø 0.5–1 mm) and HMA (Ø 0.5–1 mm) were mounted in organ baths and concentration response curves (CRCs) to CGRP were constructed in the absence and presence of the ECE-1 inhibitor SM-19712. After the first CRC to CGRP the segments were washed and after 30-45 minutes a second CRC was constructed in the absence or presence of SM-19712 to investigate ECE-1-dependent CGRP resensitization. Furthermore, CRCs to big endothelin were constructed in the presence or absence of SM-19712. In both HCA and HMA, no differences were seen between the initial responses to CGRP in the absence or presence of SM-19712 (HCA E_max=SM19712 94±8%; E_max=SM19712 92±5%; pEC50=SM19712 9.1±0.2, pEC50=SM19712 9.2±0.1; HMA E_max=SM19712 72±7%, E_max=SM19712 59±7%).
pEC50-SM19712 7.5±0.4, pEC50-SM19712 8.1±0.8), as well as between the second CRs to CGRP in the absence or presence of SM-19712 (HCA E\text{max}=\text{SM19712} 110±13%, E\text{max}=\text{SM19712} 78±22%, pEC50-SM19712 7.5±0.5, pEC50-SM19712 7.9±0.01; HMA E\text{max}=\text{SM19712} 38±13%, E\text{max}=\text{SM19712} 44±1%; pEC50-SM19712 7.6±0.5, pEC50-SM19712 7.8±0.9). Furthermore, contractions to big endothelin were not different in the absence or presence of SM-19712 in either HCA (E\text{max}=\text{SM19712} 118±14%, E\text{max}=\text{SM19712} 115±32%; pEC50-SM19712 6.0±0.5, pEC50-SM19712 6.9±0.2) or HMA (E\text{max}=\text{SM19712} 121±1%, E\text{max}=\text{SM19712} 147±19%; pEC50-SM19712 7.4±0.4, pEC50-SM19712 7.0±0.8). Our results indicate that ECE-1 does not regulate the reseption of CRGPs responses in HCA and HMA.

Reference

P97
The HURT (Headache Under-Response to Treatment) questionnaire: utility in a specialist care center in Denmark
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The Journal of Headache and Pain 2013, 14(Suppl 1):P97

Background: The HURT Questionnaire was developed by Lifting The Burden. A non-governmental organization working in official relations with the World Health Organization as a tool to aid in the management of headache. It has eight questions which the patient answers as a measure of effectiveness of intervention, by indicating when outcome is less than optimal, and by suggesting what changes in management might lead to improvement.

Objective: The objectives of the study were a) to assess test-retest reliability of HURT and b) to show responsiveness to treatment-induced change.

Methods: The questionnaire was administered on three occasions in a specialist headache center: pre-visit, at first visit, and when the specialist judged that the best possible outcome had been achieved.

Results: Of 143 patients, 114 completed all questionnaires and records of 110 were available for analysis. They were mostly female (2:1), with mean age 44.4 years and headache duration of 15.6 years. Internal consistency reliability was α=0.79 to 0.90. Test-retest reliability varied widely: highest for the question on number of days of headache per month (r=0.84, kappa=0.68) and lowest on delaying medication because of side effects (r=0.33, kappa=0.27). Responses post-intervention compared with baseline indicated a favourable outcome overall (80% of patients), reflecting specialist assessment that the best possible outcome had been achieved. There was no improvement in concerns about side-effects of medication (p=0.28). There was a significant association between improvement in HURT total score and migraine diagnosis (p=0.04). Patients with migraine showed the biggest changes in total scores. Records of non-responders were reviewed and there were no significant differences in terms of age (p=0.28) and gender (p=0.13), although 12 patients who were discharged after the study period were followed-up for a significantly longer time (p<0.001).

Conclusions: The questionnaire can help patients describe headache symptoms, disability, medication use, self-efficacy, and knowledge about headache. It has utility in a specialist care setting but must be tested in primary care, for which it was originally designed.

Acknowledgements: The authors acknowledge the work of clinicians and researchers of Lifting The Burden in conceptualizing this paper and developing the HURT questionnaire.

References

P98
Brain perfusion perturbations during migraine attacks without aura
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Introduction: Migraine attacks are caused by a CNS dysfunction, that activates trigemino-vascular system and is subsequently followed by neurogenic inflammation, dilatation of the cerebral blood vessels, and headache. In patients with migraine without aura it has been demonstrated that vascular dilatation at the height of a migraine attack is accompanied by cerebral hyperperfusion According to the majority of studies, cerebral hemodynamic changes are homolateral to the unilateral headache side, and may be confined either to the frontal temporal parietal region.

Objective: The main goal of our study was to gain knowledge on blood supply changes during an attack in patients with migraine without aura using contrast-enhanced perfusion-weighted MRI (PWI). Design Standard MRI, and PWI were performed twice: during an attack (in all three cases) and in between attacks (in two cases). Three females suffering from migraine without aura, as per the ICHD-2 diagnostic criteria, underwent brain MRI during a headache attack. Interventions Contrast medium (Magnevist 20 mL) was administered intravenously.

Results: MRI was performed on a 3.0T Sigma HDx Scanner (GE). The study included standard MRI protocol (DC1, DC2, and FLAIR) for assessment of the brain structures, as well as perfusion-weighted MRI (PWI). Cerebral blood volume (CBV), mean transit time of the contrast bolus (MTT), and cerebral blood flow (CBF) were calculated using Functool package. All three cases produced similar local MR perfusion changes that included reduced CBV and decreased CBF without any change in MTT. As the application software did not allow assessment of absolute perfusion values, all obtained results were compared with those for the symmetrical region of the contralateral hemisphere.

Conclusions: Cerebral blood supply decrease observed during migraine attack is reversible and absent during headache-free interval. Transient perfusion abnormalities occurring during recurrent attacks and confirmed by PWI may serve as one of the mechanisms causing the small subcortical white matter lesions.

References

P99
Headache symptoms of the PREEMPT population
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Introduction: CM is a complex neurological disorder affecting approximately 2% of the general adult population. CM sufferers experience a broad range of debilitating symptoms.

Objective: To assess the daily headache symptoms of chronic migraine (CM) patients over a 4-week period.

Design/methods: PREEMPT (two phase 3 studies: 24-week, double-blind, placebo-controlled, parallel-group phase, followed by 32-week, open-label phase) evaluated onabotulinumtoxinA for prophylaxis of headaches in CM

References
4. Tfelt-Hansen P, et al: Cerebral perfusion abnormalities during recurrent attacks and confirmed by PWI may serve as one of the mechanisms causing the small subcortical white matter lesions.

References
P100
Evaluation of vestibular evoked myogenic potentials in migraine and migrainous vertigo patients
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Objective: Studying subclinical vestibular exposure in migraine patients with and without headache, pathophysiology of vertigo in migrainous vertigo patients, electrophysiological similarity and difference between these patients by applying VEMP test to migraine and migrainous vertigo patients.

Method: 26 migrainous vertigo and 22 migraine patients, and 27 healthy controls were enrolled in the study. VEMP test was applied on ICS-CHARTER auditory potential audiometry. To induce headache by visual stimulation (VS) was used a computer simulation system. VEMP responses were recorded separately before and after VS. Findings: VEMP were obtained from all the cases in the control group while they could not be obtained from 9 ears in migraine and 5 ears from migrainous vertigo group. There are no significant differences for latent periods of VEMP between migrainous vertigo and control group. The lower VEMP's amplitudes, higher amplitude ratio and higher threshold of stimulus intensity were found in migrainous vertigo than the controls. The lower interpeak amplitudes and the longer latencies for VEMP were found in migraine compared to controls. The interpeak amplitude value and latency periods were found to be shorter in the migraine compared to the controls. In migrainous vertigo interpeak amplitude value was higher, and the p13 and n23 latency periods were longer than these in migraine. No statistically significant difference was observed between pre- and post-headache stimulation VEMP records of migraine.

Conclusion: The findings of migrainous vertigo were considered in favor of asymmetric peripheral vestibular exposure. The results have also suggested that migraine have subclinical central or mixed type vestibular disorder. On the other hand unchanged VEMP findings before and during headache induced by VS led to thinking that vestibular symptoms and headache have different pathogenesis in migraine and migrainous vertigo. In addition shorter latency potentials in migraine have suggested that they may be from results of cortical hyperexcitability in migraine.

References

P101
Retrospective trial of influence of atrial septal defect closure on manifestation and prognosis of migraine attacks in pediatric patients
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Introduction: Previous studies found a presence of atrial septal defect (ASD) in some cases of patients with migraine and respective efficacy of ASD closure as a treatment of migraine.

Purpose: To study an influence of atrial septal defect (ASD) closure on clinical course of migraine in children.

Methods: Interviewing was conducted in 75 pediatric patients (age 10 to 18 years) operated for ASD (surgical or occluder implantation) in Children’s National Cardiology Center «RNPC Cardiology» (n = 75, male 31, female 44, mean age = 15.2 ± 3.4 years) to identify their migraine attacks, migraine specific clinical pictures (evaluation of intensity, location of pain, aura), differentiate migraine pain from other types of headache.

Results: Before ASD closure migraine was presented in 8 patients (10.6%): 2 males (25%), 6 females (75%). Complete disappearance of migraine attacks after operation was remarked in 2 patients (25%). Reduction of migraine symptoms was found in other 6 patients (75%). Reduction/disappearance of migraine within 1-7 days after ASD closure was observed in 7 patients (87.5%) and within 7 to 14 days in 1 patient (12.5%). Noteworthy, in 6 patients (66.7%) migraine debut was observed in the early postoperative period (after ASD closure). In all 3 patients migraine starts early in postoperative period (1 to 3 days). Migraine was transient in all 5 patients (100%) persisting for 7-14 days to 3.5 years.

Conclusions: The study indicate that closure of ASD in children effectively reduced migraine in most patients (77.8%), and completely eliminated migraine attacks in other 22.2% of cases, most often in early postoperative period (88.9%). Most often migraine decreased / disappeared in the period 1-14 days after ASD closure. Probability of migraine reduction/disappearance > 14 days after ASD closure is minimal. In some patients (6.8%) debut of migraine was observed early (within first 3 days) in postoperative period but migraine symptom were transient in all patients (100%).

References

P102
Headache, migraine, brain lesion and MRI study
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Introduction: Many people have primary and often disabling headaches. The common forms are migraine and tension headache. Headache in general and migraine in particular have been increased risk if comorbidities. The migraine with aura is a marker for increased risk of cerebrovascular disease, specifically stroke. Migraine has been associated with a variety of structural brain lesion, including silent infarct, like lesion in the posterior circulation territory and with white matter hyperintensities.

Methods: Of the 120 participants with brain scans, we compared the means frequencies of various headache features and associated symptoms were computed.

Results: Of 38,752 total days, patients reported 27,483 (70.9%) days with >4 hours of headache. Patients classified their pain as moderate/severe on 90.9% of their headache-days. The most common associated symptoms patients described experiencing on headache-days were photophobia (81.2%), phonophobia (80.2%), exacerbation with physical activity (80.0%), pulsating quality (70.8%), unilateral pain (63.6%), and nausea (59.8%). Vomiting (13.8%) was reported infrequently.

Conclusion/relevance: These CM patients experienced severe headache symptoms throughout the 28-day baseline period. The overwhelming majority of headaches were characterized as moderate/severe pain intensity, which were often accompanied with sensitivity to both light and sound and aggravated by routine physical activity. The majority of patients also reported pulsating pain quality, unilateral headache, and nausea. The heavy burden of illness suffered by CM patients emphasizes the necessity of prophylactic treatment for their headaches.

Support: Allergan, Inc.
on both T1 and T2 weighted sequences, and these were discriminated from dilated vascular space (Virchow-Robin space) according to their shapes and locations. We applied this definition to all lesion irrespective of location. We distinguished the infarcts in the cerebellum, brain stem and in other locations.

Discussion: In this population we found that any lifetime history of severe headaches was associated with an increased risk of higher volumes of total, deep, and periventricular white matter hyperintensity-for migraine and non migraine headache. Participants who had migraine with aura in general was associated with brain infarcts.

References

P103
Determination of anxiety, mood disorders and disability in cluster and migraine headache

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Introduction: Headache is the most frequent pathology in neurology. Migraine is very frequent in the population and it is a disease of young people, with repercussion in their social life and in their job and with important expenses. In cluster headache the pain is very severe and disabling. The patients have difficulties in having a normal life and are often absent in their jobs – some of them even lose their employment – and very frequently use symptomatic and very expensive treatments. All of the above mentioned causes severe anxiety, mood disorders and disabilities to these patients.

Method and objectives: In order to quantify those effects and to determine quantitative measures of depression, anxiety and disability we applied the “Hamilton Depression rating Scale” test and the “Hamilton Anxiety Rating Scale”, a generic instrument for determining quality of life “SF36-2” and a headache specific instrument of disability “MIDAS test”. We study 54 patients with cluster (17 chronic cluster and 37 episodic cluster) and 80 with migraine (40 chronic migraine and 40 episodic migraine).

Result: Anxiety and depression are more important in chronic migraine and cluster than in episodic forms. MIDAS test results are more affected in chronic forms due to the higher frequency of headache episodes. In the SF36, we can see that these patients have disability in multiple fields, more important in chronic forms. We compare every field in two different kind of headache.

Conclusion: Cluster and migraine are diseases very disabling and with repercussion in the patients life, specially in chronic forms. They lose jobs and money, with very important consequences for their families. It is important to recognize these symptoms to offer better therapies and multidisciplinary management to our patients.

References

P104
Increased levels of CGRP in peripheral blood in women with chronic migraine: A reliable biological marker

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Introduction: The biology of chronic migraine (CM) as a true entity or as a consequence of analgesic overuse is controversial. There are no available biological markers for CM, while CGRP, a marker of trigemino-vascular activation, has been shown to be increased during acute migraine attacks in episodic migraine [1].

Objectives: To determine CGRP levels in peripheral blood in a series of patients with CM as compared with matched subjects without a headache history.

Patients and methods: This series comprises 61 women meeting CM diagnostic criteria (IHC-II 2006) revised with a mean age of 44 years (range 16-63) and 19 women (41 years, 22-55) without any headache history. CGRP levels were determined in blood samples obtained from right cubital vein between 9-12 am with an ELISA kit from USCN following manufacturer’s instructions. Acute medication had not been taken the day before.

Results: CGRP levels were increased in women with CM (77.94 ng/ml, range 27.69-157.72) as compared to controls (40.39 ng/ml, range 20.08-70.75) (+93%; p<0.10-8).

Conclusions: CGRP levels are clearly increased in patients with CM, which is compatible with a permanent activation of trigemino-vascular system in this entity. CGRP determination may constitute the first reliable biological marker for CM.

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Reference

P105
High prevalence of right to left shunt in women with chronic migraine

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Introduction: Prevalence of right to left shunt is estimated as 25% of the general population [1]. The prevalence of shunt has been shown to be increased in migraine with aura and one study has found a high prevalence of shunt in chronic migraine (CM) [2].

Objectives: To study the prevalence of right to left shunt in a series of women with CM.

Methods: This series includes 51 women (age 44 years, range 16-63) meeting diagnostic criteria (IHC-II revised 2006)for CM. There were only 5 women with migraine with aura attacks. We carried out a transcranial doppler study (AploXG, model SSA-790A, Toshiba) following the CODICA study protocol [3].

Results: Thirty patients (58.8%) showed some degree of right to left shunt. Three (60%) out of the 5 patients with migraine with aura had shunt. Seventeen patients (43%, 25 of total series) had hits during normal breathing and 17 (58%, 33% of the total series) during Valsalva maneuver. Shunt was massive in 10 patients (23%, 20% of the total series); in 9 of them shunt became massive only during the Valsalva maneuver.

Conclusions: Prevalence of right to left shunt in women with CM is higher than expected for the general population 1. The clinical implications of our findings need to be determined, though they suggest a relationship between the presence of shunt with an increased frequency of migraine attacks.

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References

P106
Clinical and imaging approach to headache in patients with multiple sclerosis

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Background and aims: Headache has a high frequency in patients (P) with multiple sclerosis (MS), but its underlying mechanism is still unclear. The study aimed to diagnose headache types in P with MS and ascertaining a correlation with neuroimaging changes in these P.
**Materials and methods:** 38 P diagnosed with MS were screened for headache. Headache diagnosis was established in compliance with the International Headache Society diagnostic criteria ed. II 2004. Pain intensity was subjectively assessed by patients on a visual analogical scale (1-10 points). Patient disability assessment was conducted according to the EDDS scale. All P were investigated with brain MRI (1,2T).

**Results:** Of the 38 P: 31 (81,57%) had headache (3 men and 28 women, average age 30.5 and 29.7 years respectively). P were repartized in 3 groups: group I- 18 P (58,06%) with MS and tension-type headache, group II- 9 P (29,03%) with MS and migraine, group III- 4 P (12,90%) with MS and mixed headache: tension-type and migraine. The brain MRI 1,5T detected supratentorial demyelinating lesions located in the frontal lobes and white matter of all 9 P with migraine. Foci of demyelination in the brainstem, red nucleus, substantia nigra and periaqueudal gray matter were found in 8 P (88,88%) with migraine. And only 4 of P (22,22%) with tension-type headache had demyelinating lesions in the brainstem. There wasn’t found an association between EDDS value and headache severity.

**Conclusion:** The results highlight the prevalence of primary headache: 81,57% in P with MS. There has been noted a significant correlation between headache severity and the presence of demyelinating lesions in the brainstem, substantia nigra, red nucleus and periaqueudal gray. These lesions were more common in P with migraine and this fact could explain its comorbidity in these P.

**Reference**

**P109**
Associations between cerebral and systemic endothelial function in migraine patients

**Purpose:** To investigate the role of endothelial function in migraine patients.

**Methods:** We carried out a prospective study in the out-patient department of the neurology service of Fann teaching hospital, in Dakar.

**Results:** One hundred patients were collected, aged from 9 to 64 years with sex-ratio 5.25. It was migraine without aura in 83% of patients and with aura in 17%. Trigeminal factors were mainly psychical, climatic, hormonal, food, fatigue, physical effort, sensorial. The pain was hemicranial in 73%, throbbing in 82%, tightening or itching in 18%. Headache duration varied from 4 to 72 hours in 75%, less than 4 hours in 10%, more than 72 hours in 15%. Pain intensity was mild for 2%, moderate for 49% and severe for 49%. It occurred once a day to less than once a month. Photophobia was found in 78%, nausea in 48%, vomiting in 33%. Aura was visual, psychical or sensorial. All patients benefited from treatment of acute pain, while 83% underwent permanent treatment in addition. Fifty eight per cent of women who had already been pregnant reported improvement during pregnancy. Of the whole sample, 59% had never seen a doctor for their migraine, using self-treatment or not pain-killer at all. Fifty three per cent of patients experienced a good outcome, while it was satiorial for 31%, 17% being lost sight.

**Conclusion:** Even if it is less studied in Africa, and is supposed to be less frequent in black people [1], migraine keeps its classical features. It considerably alter quality of life [23] but yet tend to be neglected by patients who do not care enough about it [3].

**Reference**

**P107**
Migraine in neurological department of fann teaching hospital in Dakar

**Introduction:** Migraine is the most frequent primary headache, one of the main complaint of our neurological out-patients department, but it has not been studied enough in our structure.

**Purpose:** To assess clinical features of migraine in a sub-saharan teaching hospital.

**Methods:** We carried out a prospective study in the out-patient department of the neurological service of Fann teaching hospital, in Dakar.

**Results:** One hundred patients were collected, aged from 9 to 64 years with sex-ratio 5.25. It was migraine without aura in 83% of patients and with aura in 17%. Trigeminal factors were mainly psychical, climatic, hormonal, food, fatigue, physical effort, sensorial. The pain was hemicranial in 73%, throbbing in 82%, tightening or itching in 18%. Headache duration varied from 4 to 72 hours in 75%, less than 4 hours in 10%, more than 72 hours in 15%. Pain intensity was mild for 2%, moderate for 49% and severe for 49%. It occurred once a day to less than once a month. Photophobia was found in 78%, nausea in 48%, vomiting in 33%. Aura was visual, psychical or sensorial. All patients benefited from treatment of acute pain, while 83% underwent permanent treatment in addition. Fifty eight per cent of women who had already been pregnant reported improvement during pregnancy. Of the whole sample, 59% had never seen a doctor for their migraine, using self-treatment or not pain-killer at all. Fifty three per cent of patients experienced a good outcome, while it was satiorial for 31%, 17% being lost sight.

**Conclusion:** Even if it is less studied in Africa, and is supposed to be less frequent in black people [1], migraine keeps its classical features. It considerably alter quality of life [23] but yet tend to be neglected by patients who do not care enough about it [3].

**Reference**

**P110**
Provocation of migraine with aura using natural trigger factors

**Objective:** To evaluate the role of migraine attacks following photo stimulation.

**Methods:** We recruited 27 MA patients who reported that bright or flickering light and/or strenuous exercise would trigger their migraine attacks. The patients were experimentally provoked by either different types of photo stimulation, strenuous exercise or a combination of these two factors. During and following provocation the patients would report any aura symptoms or other migraine related symptoms.

**Results:** Of 27 provoked MA patients 3 (11%) reported attacks of MA following provocation. An additional 3 patients reported MO attacks. Following exercise, 4 out of 12 patients reported migraine, while no patients developed attacks following photo stimulation.

**Conclusion:** Experimental provocation using self-reported natural trigger factors causes MA only in a small subgroup of MA patients. Prospective confirmation is important for future studies of migraine trigger factors and in the clinical management of migraine patients.
P111

Overreactions to noxious vascular stimuli in migraine and effect of NMDA receptor blockade

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In ‘94 we enlighten vascular hyperalgia/allodynia in migraine (M) sufferers [1]. Central pain is defined as “spontaneous pain and painful overreaction to stimulation”. Delayed painful sensation was also described in so-called hyperpathia following partial lesions in the CNS. The aim was to stress possible overreaction and its NMDA antagonists blockade after non-noxious stimulation of vein walls induced as elsewhere described. Procedure: a sharp stretch of vein walls, insensitive in controls, was induced in M sufferers. Delayed overreaction might be reported and scored on a 0-10 VAS in 189 M sufferers (101 females, 88 males, mean age 32.5 +3.8 SD) reporting 6-10 attacks A3/month. It was planned to administer ketamine, specific non-competitive antagonist at NMDA receptor sites, to M sufferers to observe possible overreaction. Tested M sufferers reported delayed overreaction ranging from 3 to 8 on a 0-10 VAS (mean 4.5 + 1.5 SD). Delayed overreaction lasted from 5 min to 4320 min, mean 210.22 min + 623. SD. The majority of sufferers reported overreaction till 25 min after application of the stimulus revealing their visceral/vascular hyperalgia/ allodynia, 5 reported overreaction lasting 4320 min and 6 were ailed by overreaction for 5 mins. The duration of overreaction was directly related to the severity/frequency of headache attacks, ANOVA failed in evidencing sex or M duration relationship, whereas a modest significance (p=0.02) was related to high scores in Wang and Zung tests (cut off = 40). Ten days later the same stimulus was applied after 0.1 mg/Kg/ i.m. administration of ketamine, after a 3 days wash-out period. Patients reported neither allodynia/hyperalgia or overreaction. The experience indicated the occurrence of overreaction in M. The partial deafferentation condition was inhibited by using a sub-anesthetic dose of ketamine. Thus, the drug likely acted by altering process of neural deafferentation-like related discharge.

Reference


P112

Imaging the premonitory phase of migraine - new insights into generation of the migraine attack

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Background and introduction: When questioned closely the majority of migraineurs report premonitory symptoms before headache that represent the earliest clinical manifestations of the attack [1]. The premonitory phase has not been hitherto imaged and offers an opportunity to understand fundamental aspects of the disorder.

Objective: To image brain areas involved in the premonitory phase of migraine.

Methods: We included patients with episodic migraine without aura, not taking preventive medications that experienced premonitory symptoms before headache. Patients were triggered with intravenous nitroglycerin on a first occasion to select those who responded with habitual premonitory symptoms and delayed headache which resembled their migraine [2]. On a second occasion, the triggering was repeated and PET scans were performed with H215O during baseline, premonitory phase(no pain) and delayed headache. The main outcome was comparing the first premonitory scans of all patients versus the baseline scans of all patients (n=8) using statistical parametric mapping [3].

Results: Tiredness, neck stiffness and increased thirst were the three most common premonitory symptoms during the scanning session. All patients had either right-sided or bilateral with predominantly right-sided delayed headache. Comparing the first premonitory scans of all patients versus baseline scans of all patients, we found activations in the postero-lateral hypothalamic region, adjacent midbrain ventral tegmental area in the region of substantia nigra, peri-aqueductal grey and dorsal pons in the region of locus coeruleus. We also found activations in bilateral occipital cortex, right temporal cortex and bilateral but predominantly right-sided prefrontal cortex.

Conclusion: Hypothalamic and brainstem structures are activated early in migraine - during the premonitory phase, before the appearance of headache. Hypothalamic involvement can explain many of the premonitory symptoms and also the reason why change in homeostasis triggers migraine. This study was funded by a grant from the Sandler Family Trust.

References


P113

Prostaglandin E2 induces immediate migraine-like attack in migraine patients without aura

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Background: Prostaglandin E2 (PGE2) has been suggested to play an important role in the pathogenesis of migraine [1]. In the present experiment we investigated if an intravenous infusion of PGE2 would induce migraine-like attacks in patients with migraine.

Methods: Twelve patients with migraine without aura were randomly allocated to receive 0.4 μg/kg/min PGE2 (Prostin®E2, dinoprostone) or placebo over 25 min in a two-way, cross-over study. Headache intensity was recorded on a verbal rating scale, middle cerebral artery blood flow velocity (VMCA) was measured by Transcranial Doppler (TCD) and diameter of superficial temporal artery (STA) was obtained by c-series scan (Dermascan C).

Results: In total 9 migraine patients (75%) experienced migraine-like attacks after PGE2 compared to none after placebo (P = 0.004). Seven out of 9 (78 %) patients reported the migraine-like attacks during the immediate phase (0-90 min) (P = 0.016). Only two patients experienced the delayed migraine-like attacks several hours after the PGE2 infusion stop (P = 0.500). The VMCA decreased during the PGE2 infusion (P = 0.005) but there was no significant dilatation of the STA (P = 0.850).

Conclusion: The migraine-like attacks during, and immediately after, the PGE2 infusion contrast with those found in the previous provocation studies, where the other pharmacological compounds triggered the delayed migraine-like attacks several hours after the infusion. We suggest that PGE2 may be one of the important final products involved in the generation of migraine attacks.

Reference


P114

Prostaglandins and prostaglandin receptor antagonism in migraine

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Human models of headache may contribute to understanding of prostaglandins’ role in migraine pathogenesis. The current thesis investigated the migraine triggering effect of prostaglandin E2 (PGE2) in
Traditional and non-conventional therapy can be obtained with a low cost, group, integrated yoga in a community based nonclinical setting.

### References


### P115

**Other cortical dysfunctions during visual and sensitive migraine aura**

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Migraine aura is the cortical phenomenon for which spreading depression is suggested to be the underlying pathophysiological process. The most common form of migraine aura is visual, followed by the combination of visual and sensitive aura. The majority of these patients also report the presence of the transient disturbances related to other cortical functions (CF) during aura. The aim of this study was to identify disturbances of CF during visual and/or sensitive aura in our group of patients. From the database of patients treated in our Headache Center from 2005 to 2011, 89 patients with migraine with visual and/or sensitive aura were indentified and 60 of them accepted to participate in this study. The questionnaire was filled in by the patient in the presence of the doctor (LP). The questionnaire consisted of 17 questions related to color and face recognition; agnosia, memory and speech disturbances, spatial disorientation, apraxia and hallucinations during aura. The demographic data, frequency and duration of aura, as well as the type and number of the CF disturbances were compared between patients with and without CF disturbances. CF disorders were reported by 39 (63.1%) patients. The aura duration was longer in the patients with CF disturbances than without it (28.5±16.4 vs. 19.8±11.2; minutes, p<0.05). The most frequently reported were motor dysphasia (82.1%), dysnomia (30.7%), and impaired recalling. The patients with visual and sensitive aura had longer duration of aura than the patients with only visual aura. The results suggest that during the visual and sensitive aura in patients with migraine disorders of other CF are frequent and related to the duration of the aura.

### References

obtained on the basis of interviews with 500 patients (F:M=400:100), aged between 18 and 40. 12% of the patients have experienced MA, whereas 88% of the patients have suffered from M. The number of patients for each subject of research has been also displayed in the form of percentages.

**Results:** 280 (70%) females and 55 (55%) male patients suffer from one or several postdromal symptoms. 480 (88%) patients of either sex experience postdromes lasting up to 24 hours, whereas 60 (12%) of patients experience postdromes lasting over 24 hours. The fatigue symptom is present in 360 (72%), diffuse headache in 165 (33%), a cognitive disturbance in 60 (12%), the loss of appetite in 35 (7%), hunger in 1 (0.2%), depression in 20 (4%), euphoria in 10 (2%), hangover in 55 (11%) and general weakness in 30 (6%).

**Conclusion:** A large number of patients of either sex suffering from M or MA have postdromal symptoms lasting as much as 48 hours, which additionally aggravates their quality of life. It is therefore necessary to consider potential therapeutic protocols aimed at treating these complaints. Key concepts of migraine postdrome: qualitative study to develop a post-migraine questionnaire.

**Reference:**

**P118**
Phase I single and multiple dose study to evaluate the safety, tolerability, and pharmacokinetics of BMS-927711 in healthy subjects

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The Journal of Headache and Pain 2013, 14(Suppl 1):P118

**Introduction:** Calcitonin gene–related peptide (CGRP) may play a causal role in migraine. Blocking the CGRP receptor may be an effective approach to migraine relief without avoiding the vasoconstrictive effects associated with triptans. BMS-927711 is a potent, selective, CGRP receptor antagonist. The obiective of this Phase I study was to assess the safety, tolerability, and pharmacokinetics of single (SAD) and multiple ascending (MAD) oral doses of BMS-927711 in healthy subjects.

**Methods:** For SAD, 8 healthy subjects received a single dose (25,75,150,300,600,900, or 1500 mg) of BMS-927711 or placebo. For MAD, 8 healthy subjects received a daily dose (75,150,300,450, and 600 mg) or 300 mg daily of BMS-927711 or placebo for 14 days.

**Results:** BMS-927711 was well tolerated at single doses up to 1500 mg and at multiple doses up to 600 mg for 14 days. There were no serious adverse events (AEs). The maximum tolerated dose was not reached. The most common AEs among BMS-927711 groups during MAD were nausea (n=7 BMS; n=0 placebo, and dizziness (n=5 BMS; n=0 placebo), and constipation (n=8 BMS; n=3 placebo) and headache (n=8 BMS; n=2 placebo) during MAD. All AEs were mild in nature. 2 subjects discontinued the MAD due to skin rash, and 1 discontinued due to elevated creatinine. BMS-927711 antagonizes CGRP-induced increases in marmoset facial blood flow (a surrogate marker for intracranial artery dilation) with 75% inhibition at ~700 nM, a surrogate for efficacious exposure. Following single doses, the plasma exposures exhibited biphasic disposition with a terminal T1/2 of ~700 nM at 2 hrs post dose, and famotidine coadministration reduced bioavailability (Cmax ~26%, AUC ~42%).

**Conclusions:** BMS-927711 appeared to be safe and well tolerated over a range of doses in this healthy population. After single oral doses ≥25 mg, clinical exposures are above the efficacious margin of 700 nM at 2 hrs post dose, supporting further clinical development in acute migraine.

**P119**
Postural sway in migraine patients and controls, results from a population based camera-2 study

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**Background:** Impairment of balance and oculomotor function have been found in several small clinic based studies investigating migraineurs inter-icically. Whether these functional abnormalities are due to migraine specific brainlesions or the migraine phenotype, has never been investigated.

**Purpose:** To investigate trunk stability during everyday stance and gait tasks in migraineurs and controls in a population based study and to correlate findings with presence of cerebellar infarcts and infratentorial hypertensive lesions (IHLs) on MRI.

**Methods:** Trunk sway in the medio-lateral (roll) and anterior-posterior (pitch) plane was measured using two digital angular velocity transducers attached to the lower back. Subjects completed three different trials. All tests were done interictically and investigators were blinded for all participant characteristics. Outcomes are given as trunk sway angles and angular velocity in both the roll and pitch plane.

**Results:** A total of 190 subjects participated; 71 migraineurs with aura (MA, 72% women, mean age 58 yr), 53 migraineurs without aura (MO, 72% women, 58 yr) and 53 controls (62% women, 55 yr). As an additional positive control group we also investigated trunk sway in 13 patients with Familial Hemiplegic Migraine with a CACNA1A mutation (FHM1, 69% women, 42 yr). Migraineurs (MA and MO) and controls performed equally in all three trials. Trunk sway angles and angular velocities of both the roll and pitch plane were significantly higher in FHM patients, compared to MA, MO, and controls, for the simple trial (p<0.001). The difficult trial was completed by none of the FHM patients. Subjects with a cerebellar infarct (n=3) had higher pitch velocity (M=46.8 SD 7.6) while completing the difficult trial compared to the non-infarct group (n=72, M=35.2 SD 9.4), p=0.04. The presence of IHLs did not influence trunk sway measurements in any trial.

**Conclusion:** FHM1 patients, but not ordinary migraineurs with or without aura, have diminished postural control inter-ictally. IHLs do not affect trunk sway.

**P120**
The effect of the cold pressor test on a visually evoked cerebral blood flow velocity response in patients with migraine

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**Introduction:** Our previous study has shown that visually evoked cerebral blood flow velocity response (VEFVR) is increased during cold pressor test (CPT) in healthy human subjects [1]. Our results supported the assumption that the activity of neurovascular coupling (NVC) increases during tonic pain stimulus due to the modulatory influence of activated subcortical structures [1].

**Purpose:** In the present study, we investigated the hypothesis that the effect of tonic pain stimulus on NVC is altered in patients with migraine.

**Methods:** 23 healthy subjects (10 males, mean age 36 ± 10 y; 13 females, mean age 38 ± 15 y) and 29 patients with migraine (8 males, mean age 39 ± 13 y; 21 females, mean age 36 ± 11 y) participated in the study. Arterial blood pressure, heart rate, end-tidal carbon dioxide partial pressure and blood flow velocities in the right posterior and the left middle cerebral artery were continuously measured. VEFR was calculated as relative increase in blood flow velocity in the posterior cerebral artery from average values during last 5 seconds of stimulus OFF period to average values during last 10 seconds of following stimulus ON period. Three consecutive experimental phases were compared: basal, CPT and recovery.

**Results:** In healthy subjects, during CPT, end-diastolic VEFR increased from 20.2 to 23.6% (p<0.05) and subsequently decreased to 17.7% in recovery phase (p<0.05). In patients with migraine, no statistically significant change in end-diastolic VEFR was observed between phases (p>0.05). Additionally, the differences in end-diastolic VEFR between the basal phase and the CPT phase and between the CPT phase and the recovery phase were statistically significantly higher in healthy subjects than in patients with migraine (p<0.05).

**References:**
Conclusion: Our results are consistent with the assumption that there is a lack of effect of tonic pain on the activity of NVC due to dysfunction of modulatory subcortical pain structures in patients with migraine.

Reference

P121
Altered thalamic microstructure in migraine without aura patients: a diffusion tensor magnetic resonance imaging study
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Background and objectives: Studies of spontaneous EEG and visual or somatosensory evoked high frequency oscillations indicate that the abnormal fluctuations of cortical responsivity over time in relation to the migraine attack could be due to abnormal thalamic control. Here we searched for possible structural changes in the thalamus of migraineurs by means of acquiring diffusion tensor magnetic resonance imaging (DTI). This DTI technique provides quantitative data on water molecular motion, as a marker of tissue structure. Materials & Method – Seventeen untreated migraine without aura (MO) patients underwent MRI scan (3-Tesla Siemens Gyrospec) during (n=7) and between attacks (n=10) and were compared to a group of 14 healthy volunteers (HV). We examined fractional anisotropy (FA) and mean diffusivity (MD) in the thalamus. Results: Between attacks MO patients had a significantly higher FA and lower MD values in the bilateral thalamus when compared to HV (p<0.05). During attacks, all MRI quantitative measurements in migraineurs were similar to those found in HV. In MO patients, FA of the right thalamus was positively correlated with the number of days since the last migraine attack (r=0.588, p=0.034).

Conclusion: The higher thalamic FA values noted between attacks in MO patients may be related to a decrease in regional branching and crossing of fibers, which normalizes during an attack. Whether these changes could be considered as the anatomical counterpart of the cyclic functional fluctuations previously observed with the neurophysiology in migraine remains to be determined.

P122
Multimodal evoked potentials in chronic migraine
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Background and objectives: Chronic migraine (CM) is a disabling health condition. The exact pathophysiologic mechanisms are not completely clarified, but a crucial role was attributed to central sensitization. When still episodic, migraine is characterized by a deficient habituation to any kind of sensory stimulations between attacks, and by an icctal EPs normalization. Less is known about how central sensitization alter this electrocortical profile in CM. Materials & Method – Fifteen episodic and 14 chronic migraine patients underwent median-nerve somatosensory (SSEPs) (right stimulation, 500 sweeps, 4.4 repetition rate, 1.2 motor threshold) and visual (VEPs) evoked potentials (right eye stimulation, 600 sweeps, 3.1 repetition rate, 15 min of arc check) randomly during the same recording session. Patients groups were compared to a group of 22 healthy volunteers (HV) of comparable age and gender distribution. Habituation was calculated as the slope of the linear regression between block 1 to 3 for SSEPs or between block 1 to 6 for VEPs.

Results: In episodic migraineurs recorded between attacks, 1st amplitude blocks of VEPs and SSEPs were respectively reduced (p=0.05) or tended to be reduced (p=0.07), but thereafter both failed to habituate along subsequent blocks of responses. In CM patients initial VEP and SSEP amplitudes were in the same range of activation of HV (p>0.05), then habituated normally during stimulus repetitions. When data of MO and CM patients were combined, the SSEP 1st amplitude block was positively (r=0.411, p=0.04) and the slope negatively (r=-0.624, p=0.001) correlated with the monthly number of days with headache.

Conclusion: Our results show in CM abnormalities that are also reported during attacks in episodic migraineurs, namely response habituation, which contrasts to its lacking detected between attacks. This suggests that from an electrophysiological point of view, CM looks like a never ending migraine attack.

P123
Influence of varying estrogen levels on trigeminal CGRP release in healthy women
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Migraine is 2-3 times more prevalent in women than in men, with frequent perimenstrual attacks. TRPV1 receptors on sensory nerve endings of the trigeminal track are important in mediating migraine attacks by releasing the vasodilator calcitonin gene-related peptide (CGRP). Variation in estrogen levels during the menstrual cycle may have an influence on the sensitivity of the TRPV1 receptor or on the amount of CGRP in perivascular nerve terminals and hence on CGRP release. Capsaicin, the active ingredient of hot chilli peppers, stimulates the TRPV1 receptor and causes CGRP-dependent vasodilatation [1]. We set up a model to study trigeminal CGRP release in humans. We compared the vasodilator effects of capsaicin application and electrical stimulation on the forehead skin. Healthy women, not using hormonal contraceptives (age: 18-45, n=14), were studied with a Laser Doppler Imager on day 19-21 of their menstrual cycle and on day 1-2 of their menstruation. A 0.2 mM and a 20 mM capsaicin solution were applied to the skin. In addition, iontophoresis of saline was performed as a TRPV1-independent stimulus. Increases in dermal blood-flow (DBF) were measured. Blood samples were collected to measure estrogen levels. We measured higher DBF responses to application of 0.2 mM capsaicain (Max:226±34 a.u.) and 20 mM capsaicin (Max: 507±39 a.u.) during day 1-2 (low estrogen levels: 15±2 pg/ml) of the menstruation, than during day 19-21 (high estrogen levels: 67±9 pg/ml) of the menstrual cycle (Max: 176±34 a.u. and 432±33 a.u. for 0.2 mM and 20 mM, respectively, P<0.05). There was no difference in DBF responses to electrical stimulation of the forehead skin, suggesting that the observed changes are related to the sensitivity of the TRPV1 receptor. Our results indicate an influence of variation in estrogen levels on trigeminal CGRP release, with the highest reactivity observed around the menstruation when estrogen levels are low. This mechanism may, at least partly, explain the high incidence of migraine attacks during the perimenstrual period.

Reference

P124
Capsaicin-induced CGRP-mediated vasodilatation of the human skin: influence of gender, female hormones and migraine
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Migraine is much more common in women than in men. It is associated with changes in female sex hormone levels with peaks of migraine frequency occurring when estrogen levels drop. Calcitonin gene-related
peptide (CGRP) is a potent vasodilating neuropeptide with a pivotal role in migraine headache. Endogenous release of CGRP is induced by capsaicin through activation of the transient receptor potential vanilloid 1 (TRPV1) channel. This study aimed to investigate the influence of gender, hormonal changes and migraine on dermal blood flow (DBF) resulting from capsaicin-induced release of CGRP.

Healthy, non-smoking female volunteers (n=16) not using hormonal contraceptives, were investigated weekly during 2 menstrual cycles. Weekly, two doses of capsaicin (300 and 1000ug) and vehicle were applied topically on the skin of both forearms. DBF was assessed before and at 10, 20, 30 and 40 minutes after capsaicin/vehicle application using laser Doppler imaging. DBF is expressed as percentage increase versus baseline and presented as area-under-the-curve from 0 to 40 minutes (AUC, % min, mean±SEM).

Period differences in capsaicin-induced DBF were observed after both doses of capsaicin (p<0.001, repeated-measures ANOVA). During menstruation, capsaicin-induced DBF, expressed as AUC, was larger after 300ug (1488±178 versus 1228±157 %,min, p=0.019; paired T-test) and 1000ug of capsaicin (1639±150 versus 1394±163 %,min, p=0.014) compared to the second week of the secretory phase of the menstrual cycle. Analyses of gender differences and migraine patients versus healthy subjects are ongoing and will be presented at the meeting.

Conclusions: In healthy women, a hormonal influence on capsaicin-induced CGRP-mediated vasodilatation of the skin is observed. In particular, an increased dermal blood flow response is documented during the menstruation period. This could be the result of increased neuronal sensitivity to capsaicin, increased release of CGRP or increased sensitivity to CGRP. These results support the hypothesis that female hormones are related to the susceptibility to migraine.

References

P126
Changes in glutamatergic neurotransmission within the migraine cycle
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Background: Although some neurophysiological studies have showed cortical excitability changes during different phases of the migraine cycle, the pathophysiological mechanisms underlying attacks recurrence remain unknown. Here we evaluated the response of the migraine motor-cortex to brief trains of 5-Hz repetitive transcranial magnetic stimulation (rTMS) in order to study, indirectly, presynaptic mechanisms of glutamatergic neurotransmission across the different phases of the migraine cycle.

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

Results: As we previously showed [1], in the interictal phase MEPs decreased significantly in size during 5-Hz trains. A significant greater inhibitory response was recorded during the ictal and post-ictal phase. Conversely, in the pre-ictal phase, we observed a facilitatory response to the trains similar to that of normal subjects. No significant differences were recorded between MwA and MwoA patients.

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

Reference

P127
Migraine days and body mass index (BMI) in a series of Japanese migraineurs
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Chronification of migraine headache is one of the most important issues. We analyzed possible association of migraine chronification and obesity in a Japanese series.

Subjects and methods: We have examined 2662 headache sufferers from February 2010 to March 2012 in our Headache Center. We interviewed all patients with structured questionnaires. Height and body weight were recorded. Types of headache were determined in accordance with ICHD-II criteria. 1356 subjects had migraine (Mf=349;1007; 152 with aura, 1204 without aura). Mean age of migraineurs was 37.8 ± 15.0 (SD) years old. 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. The data were analyzed with chi-square test and one-way ANOVA.

Results: 94 out of 231 underweight migraineurs (40.1%), 383 of 945 normal-weight ones (40.6%), 61 of 139 overweight ones (43.9%), 15 of 31 obese ones (48.4%), and 9 of 10 morbid obese ones (90.0%) had more than 15 headache days and 8 migraine days (p<0.05, Pearson’s chi-square test). Mean headache days were 13.9 ± 0.7 (SE), 13.7 ± 0.35, 14.8 ± 0.9, 15.2 ± 2 and 20.5 ± 2.5 days/month in underweight, normal, overweight, obese and morbid obese migraineurs, respectively (N.S., ANOVA). Mean migraine days were 6.4 ± 0.4, 6.5 ± 0.2, 8.2 ± 0.5, 9.5 ± 1.3 and 12.5 ± 1.3, respectively (p<0.0001, ANOVA). BMI was significant risk factor after age adjustment (p<0.001, partial correlation analysis).

Conclusion: Overweight or obese migraineurs tended to have more migraine days than normal or underweight migraineurs in a Japanese series. Although the number of obese migraineurs is not large, obesity is a
P128
Pressure pain thresholds in chronic migraine associated with hypertension
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Introduction: Studies on pain thresholds in migraine populations are contradictory and have not used algometry.

Objectives: To evaluate pressure pain thresholds (PPT) in chronic migraine patients associated with arterial hypertension (Mg+AHT) and without hypertension (Mg-AHT).

Methods: Study consisted of 40 chronic migraine (CM) patients divided in 2 groups: Mg+AH - 18 pts (mean age 46.19 ± 6.77 years), Mg-AHT - 22 pts (mean age 40.77 ± 12.0 years), and 10 healthy controls (mean age 37.56 ± 10.45 years). PPT were obtained bilaterally by mechanical pressure algometry from 15 anatomatic points (ophthalmic nerve, temporalis muscle, median nerve, radial nerve, ulnar nerve, Achilles tendon, thenar eminence, subcostal muscle insertions, trapezius muscle, supraspinatus muscle, second rib, lateral epicondyle, gluteal, greater trochanter, knee) using Somedic algometer (SBMEDIC electronics, Sweden). Pressure algometry was applied three times on the same point and pain threshold was calculated as an average value.

Results: The mean PPT value for all 15 examined points was higher in Mg+AHt vs. Mg-AHT group (447.36 ± 112.32 vs. 377.67 ± 77.71, p<0.05) but didn’t differ from the control group. In Mg-AHT group PPT was lower compared to Mg-AHT control group (377.67 ± 77.71 vs. 437.00 ± 81.86, p<0.05). In the Mg-AHT pts PPT was higher than in Mg-AHT group for eight aplication points (53.3%): radial nerve, ulnar nerve, Achilles tendon, thenar eminence, trapezius muscle, supraspinatus muscle, greater trochanter and gluteal. In Mg-AHT group PPT was lower than healthy controls for seven aplication points (46.6%): radial nerve, Achilles tendon, thenar eminence, greater trochanter, lateral epicondyle, gluteal and knee.

Conclusion: The arterial hypertension is associated with the increase of pain pressure thresholds evaluated by algometry in chronic migraine with hypertension patients and interacts with hyperalgesia and alldynia phenomena induced by chronic migraine through central and peripheral sensitization mechanisms.

Reference

P130
Migraine headache is present in the aura phase—a prospective study
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Objectives: The migraine aura is commonly considered to be a distinct phase of a migraine attack that precedes headache [1]. The objective of the study was to examine a large number of prospectively recorded attacks of migraine with aura and determine the timing of headache and other migraine symptoms relative to aura.

Methods: As part of a clinical trial we collected prospective data on the time course of headache and other symptoms relative to the aura. Patients (n=267) were enrolled from 16 centers, and asked to keep a headache diary for one month (phase I). They were asked to record headache symptoms as soon as possible after aura began and always within 1 h of aura onset. A total of 456 attacks were reported during phase I in 201 patients. These patients were then randomized and included in phase II, during which a total of 405 attacks were reported in 164 patients. In total, we present data from 861 attacks of migraine with aura from 201 patients.

Results: During the aura phase, the majority of attacks (73%) were associated with headache. Other migraine symptoms were also frequently reported during the aura; nausea (51%), photophobia (88%) and photophobia (73%). During the first 15 minutes within the onset of aura, 58% of patients reported headache fulfilling the criteria for migraine.

Conclusion: Our results indicate that headaches as well as associated migraine symptoms are present early, during the aura phase of the migraine attack in the majority of patients. These results show that the phases of a migraine attack may not be as discrete as originally believed. They underscore the fact that migraine is a complex brain disorder in which multiple anatomical and physiological mechanisms may be occurring simultaneously and in parallel. An increased understanding of the timing and interactions between these mechanisms has the potential to identify new approaches to therapy.

P131
Eliptritan provides consistent migraine relief: results of a within-patient multiple-dose study
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Objective: To evaluate the consistency of response to eletriptan in migraine.

Background: Surveys indicate that more than 40% of individuals have an average headache frequency of 2 or more attacks per month. Lack of consistent response has been cited in patient surveys as one of the top 3 reasons for dissatisfaction with migraine treatments.

Methods: Patients first completed an open-label, lead-in period in which they treated 3 migraine attacks with eletriptan 40 mg. Based on response to open-label treatment, patients were treated with either eletriptan 40 mg (E40; N=539) or eletriptan 80 mg (E80; N=432) in a 4-attack per-patient multiple-dose study. Addi- tionally, patients were treated with either placebo (49% vs. 32%; p < 0.001) and E80 vs. placebo (43% vs. 11%; p < 0.001).

Results: During double-blind treatment, within-patient consistency was 77% for E40 and 73% for E80. For patients (N=47) who had responded to 0/3 attacks on E40 in the open-label phase, titration to the E80 dose resulted in headache response in 55%. A repeated measures logistic regression analysis found that sustained headache response at 24 hours, averaged across 3 attacks, was significantly higher on both E40 vs. placebo (49% vs. 32%; p < 0.001) and E80 vs. placebo (43% vs. 11%; p < 0.001). Sustained pain-free at 24 hours, averaged across all 3 attacks, was also significantly higher on both E40 vs. placebo (30% vs. 5%; p < 0.001) and E80 vs. placebo (25% vs. 3%; p < 0.001).

Conclusion: Eliptritan showed consistent and sustained efficacy in the treatment of migraine. Funded by Pfizer Inc.

P132
Clinical characterization of “visual snow” (Positive Persistent Visual Disturbance)
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Background: Visual snow has a major impact on patients’ quality of life. They describe persistent, dynamic, black & white tiny dots in the entire visual field (main criterion). Additional symptoms might be present.
The literature on this condition is scarce [1-3] and there is some confusion with persistent migraine aura or LSD-flashback.

**Objective:** To describe the clinical phenotype of patients with visual snow.

**Methods:** Preliminary additional criteria for visual snow were generated retrospectively based on an internet-survey. By using telephone interviews, we re-tested these criteria prospectively and collected further information.

**Results:** The survey-data of 120 patients with self-reported visual snow was reviewed to generate preliminary criteria. These were re-tested by interviewing 115 patients. The main criterion (black and white visual snow) was met by 57 patients. Additional visual symptoms were excessive floaters (84%), persistent after-images (83%), “hard time seeing at night” (65%), “little cells that travel on a wiggly path” (77%), photophobia (70%), “moving objects leave trails” (56%), “swirls, clouds or waves with eyes closed” (51%), and bright flashes (51%). Requiring at least one or three of these additional criteria reduced the sensitivity by 2% and 7%.

No patient described the visual symptoms consistent with persistent visual aura in migraine. A history of migraine was seen in 54%, with 35% having typical migraine with aura. None of the patients noted intake of illicit drugs prior the onset of visual snow. All ophthalmology tests were non-contributory.

**Conclusions:** (i) Visual snow is a unique clinical syndrome. The main criterion (visual snow) is almost always associated with at least three additional criteria. (ii) The visual symptoms are distinct from migraine aura. (iii) The high prevalence of history of migraine (with aura) points to a susceptibility for visual snow in patients with migraine. (iv) Intake of illicit drugs and ophthalmological diseases may not be of pathophysiological relevance.

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**References:**

**P134**

**EEG and transcranial dopplerography of middle cerebral artery in patients with primary headaches**

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The objective of this study was to evaluate relationships between EEG and TCD changes of middle cerebral artery (MCA) in patients with primary headaches. Seventy seven patients with primary headaches (age=24.2±7.0) and 15 normal subjects were assessed using TCHD-2, neurological evaluation, visual analogue scale (1-10 points), transcranial dopplerography (TCD) and an EEG analysis of absolute and relative band amplitude at rest. Three groups were compared: 30 patients with Tension headaches (TH), 32 patients with migraine (MG), 15 patients with cluster headache (CLH) and the control group. Were used dominant frequency, amplitude, index of waves, correlation analysis of EEG, standardized low resolution brain electromagnetic tomography (sLoreta) and maximum, minimum, average frequency, RI, PI by TCD of middle cerebral artery (MCA). The EEG showed significant differences between the control group and patients with TH, MG and CLH. Oscillation of delta in left frontal lobe (Brodmann area 11) in patients with TH, in the right frontal lobe in MG patients and bilateral in CH patient. The maximal density of theta in the left occipital lobe (Barea 18) in TH patient, in right occipital lobe in MG and bilateral in CLH patients. In occipital lobe in patients with TH, MG and in frontal lobe in the patients with CH was find the maximal density of Alpha 1 waves, as well as the alpha 2 in occipital lobe in all patients. Maximal density of beta 1 was registered in the right occipital lobe in TH, MG patients and in frontal lobe in CLH patients. Gamma waves were registered in frontal lobe in all patients and in control group (F1,56)=18.2, p<0.001. Abnormalities on the EEG were essentially associated with the occurrence of increasing of the frequency and dominate in patients with MG and CH. Were found relationship between dominant frequency of EEG and TCD parameters (Vmax, PI, RI) p<0.01. Were determined that TCD parameters such as RI, PI decreased in MG, CLH patients (p<0.001). This study suggested EEG and TCD of MCA as a possible physiological tool in the assessment of pathogenesis of headaches.

**Medical equipments:** EEG is a product of the company "Mitsar", Russia TCD is a product of company "Spectromed", Russia

**P135**

**Low use of placebo in comparative drug rcts in migraine. Are clinical investigators unaware of basic methodological issues?**

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If feasible placebo should be included in randomized, controlled trials (RCTs) comparing two presumably active drugs. Inclusion of placebo in comparative RCTs was recommended generally by FDA in 1982, by the International Headache Society for migraine in 1991, and by the European Medicines Agency (EMEA) for migraine in 2007.

**Methods:** We searched the world migraine literature from 2002 to 2011 for comparative drug RCTs of acute and prophylactic treatment of migraine. We primarily registered whether placebo was used or not.

**Results:** In 67 acute comparative RCTs placebo was included in 26 RCTs and in 26 prophylactic comparative RCTs placebo was included in only 2 RCTs [sic]. For the acute RCTs without placebo (n=41) the median number of patients was 76 (range: 12-2,436) and for acute RCTs with placebo (n=50) the median number of patients was 505 (range 42-2,113).

**Discussion:** Recommendations by FDA, IHS and EMEA for inclusion of placebo in comparative RCTs are plenty but, seemingly, clinical investigators and the pharmaceutical industry need to be informed more about why these rules should be followed. The most important fact to be aware of is the “effectiveness” of placebo in drug RCTs in migraine. Thus, in acute RCTs with oral triptans the placebo response for headache relief at 2 h varied from 17 to 50% [1]. In prophylactic RCTs the placebo-response is usually in the 20 to 40% range but 50% and even 70% [2] have been reported. So if two "active" drugs both show similar response rates of 45% and 49% in a prophylactic RCT in migraine one cannot speak of
We retrospectively evaluated the clinical characteristics of migraine. The population included 2,232 patients with migraine without aura. Of these, 291 migraine patients (mean age 40 years) and 40 healthy controls (mean age 30 years) completed a baseline questionnaire and occlusal records of 3,727 patients diagnosed with primary headaches referred to our Headache Centre from 2005 to 2011.

**Methods:** After signed informed consent, brain MRIs were obtained in 50 women from our headache clinic meeting chronic migraine according to the International Classification of Headache Disorders, 3rd edition criteria. Six had a history of migraine with aura attacks and 19 meet overuse criteria. Their ages ranged from 16 to 63 years (mean 40.9 years) and the length of chronic migraine range from 6 months to 27 years (mean 7.5 years). At least 11 patients had a minimum of one vascular risk factor and the prevalence of right to left shunt with transcranial Doppler was 58%. Brain MRIs were acquired on a 1.5T unit Signa LX 9.1 (General Electric Systems, USA). Protocol includes whole brain weighted images in sagittal T1 (5 mm slices), axial FLAIR T2 (3 mm) and combined proton density and T2 fast spin echo (3 mm). Two independent neuroradiologists carefully analysed all the cerebellar images.

**Results:** After an in depth review of all posterior fossa slices, we were unable to find even one cerebellar infarct-like lesion, which would have obvious clinical and management implications.

**Objective:** To determine whether chronic migraine patients are at increased risk of cerebellar infarct-like lesions on MRI.

**Method:** After informed consent, brain MRIs were obtained in 50 women from our headache clinic meeting chronic migraine according to 2006 ICH-I revised criteria. Six had a history of migraine with aura attacks and 19 meet overuse criteria. Their ages ranged from 16 to 63 years (mean 40.9 years) and the length of chronic migraine range from 6 months to 27 years (mean 7.5 years). At least 11 patients had a minimum of one vascular risk factor and the prevalence of right to left shunt with transcranial Doppler was 58%. Brain MRIs were acquired on a 1.5T unit Signa LX 9.1 (General Electric Systems, USA). Protocol includes whole brain weighted images in sagittal T1 (5 mm slices), axial FLAIR T2 (3 mm) and combined proton density and T2 fast spin echo (3 mm). Two independent neuroradiologists carefully analysed all the cerebellar images.

**Results:** After an in depth review of all posterior fossa slices, we were unable to find even one cerebellar infarct-like lesion in any of these chronic migraine patients.

**Conclusion:** Following the same MRI methodology of the previous studies, we demonstrate that, at least for migrainous women, there is no relationship between migraine frequency and the presence of cerebellar infarct-like lesions. Therefore, at least for the cerebellum, frequency of migraine attacks itself does not seem to be a factor increasing the risk of vascular brain lesions. These findings call for caution when extrapolating findings from the general population into current clinical practice.

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**References:**

**P138**

**The comorbidity between migraine and hypothyroidism**

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**Introduction:** Comorbidity refers to greater than coincidental association of separate conditions. The International Headache Society classification brought as new entry the headache attributed to hypothyroidism. The diagnostic criteria require the headache to resolve within 2 months after effective treatment of hypothyroidism (HT). This condition seems to be rare in clinical practice, whereas it is more common to see migraine patients also affected by HT.

**Objectives:** To demonstrate the comorbidity between migraine and HT.

**Materials and methods:** We retrospectively evaluated the clinical records of 3,727 patients diagnosed with primary headaches referred to our Headache Centre from 2005 to 2011.

**Results:** The population included 2,232 patients with migraine without aura (MO), 485 with tension-type headache (TTH), 367 with MO + TTH, 228 with migraine with aura (MA), 203 with MO + MA, 143 with cluster headache, and 69 with other primary headaches. Overall, 98 cases (95 females and 3 males) with full-blown HT requiring hormone therapy were noted. Ninety of these cases (2 males) were migraineurs and 8 suffered from TTH. Therefore, the prevalence of HT was 3.0% in migraine and 1.6% in TTH. Interestingly, HT occurred after migraine onset in 87 patients (96.7%), whereas it preceded migraine in 2 MO subjects and in 3 TTH patients. In a population-based study the prevalence of HT resulted to be 0.84% [1]. In our clinic-based survey the prevalence of HT in migraineurs was 3.0%. For 52.0% of patients the headache showed a significant worsening after the onset of HT and hormonal replacement therapy. It is challenging to speculate whether the worsening could be attributable to the hormonal disorder, to levodopa/levodopa treatment or both.

**Conclusion:** We found a high prevalence of HT in migraine, significantly higher than in the general population. HT should be considered as one of the variety of migraine comorbidities, even if possible pathophysiologic relationships remain unclear. This is the first study that reports the comorbidity between the two conditions.
Reference


P139
Cardiovascular activity in migraine patients: Influence of age and headache chronification
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Introduction: Heart rate variability (HRV) is a useful tool to evaluate cardiovascular activity in different pathologies including migraine. Reduced HRV over 24 hours predicts increase in cardiovascular morbidity. Objectives: To evaluate and analyze cardiovascular activity by mean of HRV in migraine patients and elucidate the influence of age and chronification.

Methods: Study group consisted of 65 pts with migraine: 40 pts with chronic (CM) and 25 pts with episodic migraine (EM); mean age 47.7±11.29 (CM) and 47.6±12.6 years (EM). All the patients underwent 24-hour ambulatory ECG monitoring with evaluation of HRV. The analyzed time domain parameters were: VAR, CBBP, avNN, SDNN, RRNN, SDANN, SDNN index, RMSSD and pNN50 % and frequency domain parameters: LF, HF and VLF. All expressed as mean, day time and night time values.

Results: CM patients had increased VAR (94.8±433.4 vs. 785.6±214.4, p<0.05), SDNN index (53.1±17.8 vs. 45.7±6.8, p<0.05) and VLF (2013.05±1151.5 vs. 1567.2±1526.6, p<0.05). In the middle age (40-50 years old) EM patients had increased Heart rate (84.6±8.6 vs. 77.4±7.9, p<0.05) and CM patients increased: avNN (837.6±93.7 vs. 787.0±78.3, p<0.05), SDNN index (60.1±15.0 vs. 45.8±6.3, p<0.05) and VLF (2724.4±1449.1 vs. 1618.2±509.9, p<0.05). In the advanced age (50-59 years old) CM patients had increased HF (30.6±13.1 vs. 19.7±11.9, p<0.05). Compared between groups (EM 40-50 vs. EM 50-59) - EM 50-59 patients had increased pNN50% and CBBP and CM 50-59 patients had reduced pNN50%, SDNN index, VLF, HF but increased HF (%). Conclusions CM patients presented an increased HRV and parasympathetic activity compared with EM in whole study sample and in the 40-50 age group but just parasympathetic hyperactivity in the 50-59 age groups. Older CM patients presented more reduction in total HRV, sympathetic and parasympathetic influence (day time), except HF (%) night time which reflect strong vagal influence probably as a consequence of chronification process.

Reference

P141
Can induced headache be used in the differential diagnosis of primary headaches as a diagnostic tool?
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The Journal of Headache and Pain 2013, 14(Suppl 1):P141

The objectives of this study are to create headache by visual stimulation (VS), to examine the similarities between spontaneous headaches and visually stimulated headaches (if the latter occurs), to determine if VS can be used as a model in headache researches and to evaluate if it can be used as a diagnostic tool for the differential diagnosis of primary headaches.

Methods and materials: In this study, total of 43 migraine patients - 21 with aura and 22 without aura migraine, 21 tension type headache patients and 20 healthy individuals as a control group were included. For VS, a computer simulation was used that was programmed to be 9 Hz frequency color change, 11.2 radius, with the pattern of a yellow-blue dart board and 14 seconds off and 14 seconds on. In order to create headache, stimulation was applied maximum for 45 minutes by using VS. Results: The application of VS triggered headache neither in the TTH patients nor in the healthy control subjects. All of the migraine patients were observed to have developed headache. Yet, none was detected to have developed any form of aura. Only two migraine patients without aura did not develop a headache. These two cases were detected to have undergone migraine treatment one day prior to VS. It was observed that the characteristics (location, pattern, and severity) of headache induced by VS in migraine patients and those of spontaneous migraine attacks were almost the same. However, headache severity and accompanied signs were also found to be 1-2 points lower in the induced headache with respect to visual analog scale (VAS).

Conclusion: It was inferred from our study that experimental headache was observed only in migraine patients and shown that as a differential diagnostic tool the method could be applied in the daily practice. It has also been concluded that the VS can be utilized in migraine researches since it is the most almost-natural method.

References

P142
Usefulness and applicability of web-based headache diagnostic software
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P144
Is ischemic stroke more severe in patients with migraine vs. other headache types?
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Background: Migraine (Mg) is recognized as a cardiovascular risk factor and connection with stroke (S) is well known, especially for Mg with aura.

Objectives: To evaluate the influence of Mg on the severity of S compared to other types of headache and the relationship between Mg and S (according to Welsh criteria).

Material and methods: The study included 134 pts with S and headache. After statistical adjustment for age, gender and affected vascular brain system, 2 groups were formed: I - 15 pts with S and Mg, II- 16 pts with S and other types of headache. All patients had confirmation of S on the cerebral CT or MRI 1.5T. Headache was assessed according to ICHD-II (2004), Welch criteria were applied for the relationship between Mg and S. The Rankin score for S disability was preformed.

Results: The I group (8 women and 7 men) mean age 49, 53 ± 11.59 years: 9 pts had Mg with aura (MA) and 6 pts - without aura (MO). The second group (8 women and 8 men) mean age 53.87± 6.8 years, 12 pts - tension type headache, 3 pts - headache attributed to HTA and 1 pts - unclassified.

There were no differences between groups on main vascular risk factors (blood pressure, cholesterol level and ischemic cardiopathy). According to Welch criteria 2 pts (13.3%) had class I category of relationship between Mg and S – “coexisting migraine and stroke” - S occurs in a patient with Mg, but not during an attack, 9 pts (60%) had class IIb “migraine-induced stroke; with risk factors” - MA produces S in the presence of another risk factor and 4 pts (26.6%) had the class IV - “uncertain” history of MO and S during a Mg attack. The Rankin disability scale was significantly worse in S and Mg group (3.0 ± 1.0 vs. 2. 18 ±1.1, p<0.02) compared to S with other headaches types.

Conclusions: A patient with Mg had a high probability to have a more severe S with increased degree of motor deficit on Rankin disability scale than patients with other types of headache. The relationship between Mg and S is complex and difficult to evaluate and future studies are needed.

Reference

P143
Analysis of subjects with menstrually related migraine vs. Non-menstrually related migraine treated with MAP0004
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Menstrually related migraine (MRM) is defined as occurring from days -2 to +3 of menstruation in at least 2 out of 3 menstrual cycles, and additionally at other times of the menstrual cycle. MRM is generally longer lasting, more severe, and more difficult to treat compared to non-MRM attacks. MAP0004 is an investigational orally inhaled dihydroergotamine (DHE) for the acute treatment of migraine. In a large Phase 3 study, MAP0004 was effective and well tolerated in treating an acute migraine attack compared to placebo. This post-hoc analysis compares the efficacy of MAP0004 in treating MRM versus non-MRM, including an analysis of recurrence rates using 4 different, previously published recurrence rate definitions. The efficacy of MAP0004, as measured by pain relief at 2 hours, pain free at 2 hours, sustained pain relief at 2-24 and 2-48 hours, and sustained pain free at 2-24 and 2-48 hours values, was not significantly different between subjects with MRM and non-MRM. Furthermore, the MRM recurrence rates after pain relief were not statistically higher than that of non-MRM treated with MAP0004. There were no significant differences in the frequency of adverse events for MRM vs. non-MRM subjects, and no drug-related serious adverse events were reported. In the study, MAP0004 was effective and well-tolerated for both MRM and non-MRM.

References

P145
Darling, the doctor says I slept well but I still have headache in the morning: an actigraphic study in couples
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Introduction: Morning headache (MH) affects about 5% of the general population [1] and have been related to insomnia symptoms. Snoring and obstructive sleep apnea syndrome (OSAS) are frequent sleep disturbances and may cause also impaired sleep quality in bed partners.

Purpose/background/objectives: To date, prospective data on subjective and objective sleep quality in individuals with MH are lacking. Hence, the objective of this prospective actigraphic study was to compare sleep data of nights preceding days with and without MH in habitual snorers and their bed partners.

Methods: We recruited habitual snorers and their non-snoring bed partners via newspaper articles. The participants completed a semi-structured interview, filled in questionnaires about sleep quality, daytime sleepiness, depression and anxiety. Simultaneous actigraphy and sleep diaries were recorded during a 14-day period in these couples.

Results: Forty five (11 female) snorers and 45 (34 female) bed partners with a mean age of 47±13 and 43±12 years were included in this study. Apnea screening yielded snoring without OSAS, mild OSAS, moderate OSAS and severe OSAS in 27 (60%), 8 (18%), 3 (7%) and 6 (15%) snorers. MH occurred on 63% and 4.9% of the recorded days in snorers and bed partners, respectively. In snorers, snore efficiency (85±9 vs. 84±9, p=0.5) and fragmentation indices (34±16 vs. 36±14, p=0.5) did not differ.
significantly between nights followed by MH and nights not followed by MH. Bed partners showed a significantly higher sleep efficiency (86±8% vs. 89±6%, p=0.04) and lower fragmentation index (33±16 vs. 26±12, p=0.01) during nights, which were followed by MH compared to nights not followed by MH.

Conclusion: In contrast to previous reports our prospective data do not confirm the relationship between insomnia and MH. In fact, bed partners of habitual snorers had even slept more efficiently if they reported MH the following day.

Reference

P146
Can DoloTest predict the efficacy of psychological treatment in patients suffering from severe headache?

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The Journal of Headache and Pain 2013, 14(Supp 1):P146

Objective: To test whether DoloTest [1], a new instrument for measurement of pain and quality of life, also is a valid test for documenting changes related to psychological treatment, in patients suffering from severe headaches.

Method: DoloTest is a validated pain and quality of life assessment tool that has been applied to patients in different pain clinics, but never tested in a headache clinic. It measures 8 different domains: Pain, problems with light physical activities, problems with more strenuous physical activities, problems doing your job, reduced energy and strength, low spirit, reduced social life and sleeping problems. The patient is asked to score an average of the past week on a VAS-scale for each domain. The maximum value of each domain score is 100 and 800 for the total score. The DoloTest provides a graphic picture of a patient’s pain, as well as a numeric score. Headache patients from the Danish Headache Center were referred to weekly psychoeducational group sessions within a cognitive framework including intensive relaxation training over a 9-weeks period, with 8 patients per group. Psychological treatment was given in addition to other multidisciplinary interventions. DoloTest was applied before, under and after the psychological treatment.

Results: Baseline data for 110 patients, 22 males and 88 females, with an average age of 36.1 years (range 18 – 69) are collected. Most of the patients suffer from more than one type of headache: primarily migraine with or without aura n=66, frequent or chronic episodic tension-type headache n=70, others n=45. At baseline the average frequency of headache is 24 days/month, and the average total DoloTest score was 358 (range 32 – 675).

Conclusion: The DoloTest may be a valuable tool to measure the effect of psychological treatment, and further evaluation is ongoing.

Reference

P147
Catastrophizing and pain impact in migraineurs

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Introduction: One of the important determinants of the chronic pain experience is pain catastrophizing [12]. In migraine, a handful of works has studied the relationship between catastrophizing and pain, i.e. its role in the development and/or maintenance of migraine episodes, and its interactions with other psychological variables (coping strategies, anxiety, depression and personality traits). The aims of this study were (1) to examine whether there are differences among migraineurs and nonmigraineurs in catastrophizing, as well as on the psychological variables, (2) to explore the relationship between these variables and catastrophizing in the migraine group, and (3) to put into relation the headache impact with the other studied variables. METHOD: 81 subjects participated in this study (43 migraineurs). 81.5% were women, mean age was 30.2 (SD=10.93) and 67% were students. Personality, depression, anxiety, coping strategies, catastrophizing and headache pain impact were measured.

Results: Catastrophizing was positively related to depression (r=0.40, p<0.01), anxiety (r=0.44, p<0.01), and aggression-hostility (r=0.39, p<0.05), and negatively to distraction (r= -0.37, p<0.05). Regression analyses revealed anxiety as a unique predictor of catastrophizing (R2=0.19, p<0.05) and headache impact (R2= 0.32, p<0.01). Migraineurs reported higher scores on catastrophizing, anxiety, and personality dimensions: activity, neuroticism-anxiety and aggression-hostility compared to nonmigraineurs. Nonmigraineurs used more passive coping strategies, specifically catharsis. Migraine characteristics (pain intensity, frequency and duration) were not associated with catastrophizing.

Conclusions: Results show that migraineurs present distinctive psychological characteristics from nonmigraineurs. Catastrophizing was one of them, which was predicted by anxiety that also predicted the impact of headaches. Additional research is needed to explore the link between anxiety, catastrophizing and migraine. The role of these psychological factors should be specially considered when treating migraine.

References

P148
No increase in headache after previous intracranial infections: a historical cohort study (The Nord-Trøndelag Health Survey)

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Introduction: Despite the absence of robust scientific evidence, it is today generally accepted that the acute headache typical for intracranial infections can develop into permanent headache complaints.

Objective: The widespread concept of chronic post-infection headache was explored in the first, large, longitudinal, population-based study.

Methods: Data on confirmed exposure to intracranial infections amongst all adult inhabitants in a geographical area during a 20-year period were assembled from hospital records. Surviving individuals were later invited to the third Nord-Trøndelag Health Survey (HUNT 3), where 39,690 (42%) of 94,194 invited inhabitants aged ≥20 years responded to a validated headache questionnaire. Using logistic regression, the 1-year prevalence of headache and its subtypes according to the diagnostic criteria of the International Headache Society was assessed and compared between those with and without previous confirmed intracranial infection. Age and sex were used as covariates.

Results: Overall, 43 participants were identified with earlier intracranial infection, whereof three had more than one infection: bacterial meningitis (n=19), lymphocytic meningitis (n=18), encephalitis (n=9), and brain abscess (n=1). The mean interval from infection to participation in HUNT 3 was 11.2 (range 1.5–19.7) years. There was no significant increase in the prevalence of headache (OR 1.10, 95% CI 0.58-2.07), its subtypes (migraine, or tension-type headache), or chronic daily headache (OR 1.85, 95% CI 0.45-7.68) amongst participants with previous intracranial infection compared with the surrounding population.

Conclusion: This study challenges the existence of chronic post-bacterial meningitis headache and does not indicate the presence of other long-term headaches induced by intracranial infection.

Conflict of interest: None.

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P149

Pain perception is altered in patients with medication-overuse headache but can improve after detoxification

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Objective: To investigate pain perception before and during detoxification in patients with medication overuse headache (MOH).

Background: Previously, central sensitization has been found in chronic primary headaches but pain perception in MOH patients has only scarcely been studied and never in long-term follow-up studies.

Methods: 35 patients with MOH following structured detoxification programmes were tested before and 2, 6 and 12 months after withdrawal and 40 age and sex matched, healthy volunteers were tested for comparison. We measured cephalic and extra cephalic pressure pain thresholds (PPT) and supra-threshold pressure pain (STPP) as well as extra cephalic pain thresholds, supra-threshold pain and wind-up for electrical stimulation.

Results: At baseline, cephalic and extra cephalic PPTs were significantly lower in patients with MOH compared with healthy volunteers. Cephalic STPP was significantly higher in MOH patients compared with healthy volunteers but decreased significantly from baseline to the 6-month and 12-month follow-up. Supra-threshold pain for a single electrical stimulus was significantly higher in MOH patients compared with healthy volunteers. In contrast to healthy volunteers, patients with MOH did not exhibit wind-up before withdrawal. After 2 months, MOH patients had regained ability to wind-up and this persisted at 6-month and 12-month follow-up.

Conclusions: Patients with MOH have altered pain sensation and exhibit both allodynia and hyperalgesia indicating central sensitization. Withdrawal from medication overuse causes significant decrease in central sensitization. The ability to wind-up is altered in MOH patients, probably as a consequence of medication overuse, but it can be regained after withdrawal. These findings emphasize the need for detoxification in MOH.

P150

Detoxification in a structured programme is effective for so-called refractory medication-overuse headache

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Introduction: The strategy regarding whether detoxification for medication overuse headache (MOH) is needed or not has been heavily debated. Patients are often regarded as treatment resistant if they fail one withdrawal attempt. Further, many report a substantial relapse to MOH within the first year after withdrawal.

Objective: To evaluate the long-term efficacy of two different treatment programmes for MOH in so-called treatment-resistant patients.

Methods: MOH patients who had previously been unsuccessfully treated by neurologists were enrolled in one of 2 structured detoxification programmes in a tertiary headache centre: A) a one-week withdrawal with restricted analgesics, rescue medications and prophylactics from Day 1 followed by advice of restricted intake of symptomatic medications or B) a 2-month drug-free period and multidisciplinary education in groups and subsequent initiation of restricted symptomatic medication and prophylactics as required. All patients were closely followed up for a year.

Results: 86 of 98 patients completed the 12-month follow-up. Totally, headache frequency was reduced by 39% (p<0.001), medication use by 63% (p<0.001) and 83% remained cured of MOH. Headache frequency was reduced with more than 50% in 42 patients (49%) and 52 (61%) reverted to episodic headache, and with no difference between the groups. Patients in programme B used significantly less symptomatic medication: 6.5 days/4 weeks compared with 8.7 days/4 weeks in programme A (p=0.02), and the 56% of patients in programme B who needed prophylactic medication was significantly less than the 80% in programme A (p=0.02). Further, programme B required fewer resources from the staff.

Conclusion: Structured detoxification with close follow-up by a multidisciplinary team for one year is highly effective in patients with previously treatment-resistant MOH. We recommend a multidisciplinary educational programme for patients in groups due to cost-effectiveness and limited use of medication.

P151

Occipital neuralgia secondary to CerebroSpinal fluid leak

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Introduction: Spontaneous CSF leakage is now recognized as a secondary chronic daily headache (CDH) and its characteristic feature is a postural (orthostatic) headache. Despite occipital headaches being common, only one published case report exists of occipital neuralgia associated with significant cerebrospinal fluid (CSF) leak. Our case is the first one, occurring without prominent cerebrospinal descent. Potential pathogenic mechanisms are discussed.

Purpose: To report a spontaneous CSF leak as an unusual cause for occipital neuralgia.

Methods: Case report.

Results: A 51-year-old woman with CDH for 3 years presented with bilateral, pressure-like headache aggravated by valsalva and alleviated by lying down. Neurologic exam, brain MRI/MRV/MRA and cervical MRI were all unremarkable. Considering a New Daily Persistent Headache (NDPH), amitriptyline was started but failed. Her headache changed to bilateral occipital, shock-like pains, lasting seconds to minutes superimposed on a "spongy, numb" occipital sensation but without postural component. Occipital nerve block resulted in a dramatic response. Repeat brain MRI showed dural enhancement with subtle "brain sagging". An empiric lumbar epidural blood patch failed. Spinal MRI showed extradural fluid collections in the lower thoracic region. Conventional computed Tomography (CT) myelogram confirmed a mid-thoracic CSF leak. Subsequent dynamic CT myelography confirmed the location of fast CSF leakage at T4-T5 secondary to a disc extrusion. A decompressive laminectomy with repair of the CSF leak completely aborted her headaches.

Conclusions: Occipital neuralgia secondary to CSF leakage may be an under-diagnosed phenomenon. Pressure to the C2-C3 nerve roots during prominent cerebrospinal descent may be the underlying headache cause. In cases without significant cerebral descent such as ours, traction of the C2-C3 nerve roots or the occipital nerve may be a better explanation. Other mechanisms, however, are likely role players as occipital neuralgia is a rare happening in the setting of a spontaneous CSF leak. Further, the occipital nerve block can be useful in some cases.

References

P152

Migraine in the elderly: clinical characteristics in a series of 71 cases

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Introduction: Though headache prevalence drops markedly in the elderly, this causes a significant burden on the quality of life of this population. However, few studies have investigated primary headaches at this age range.
Objectives: We aim to analyze characteristics of patients older than 65 attended due to migraine in an outpatient headache clinic in a tertiary hospital.

Methods: We prospectively considered patients attended from January 2008 to May 2012. Migraine with and without aura was diagnosed accordingly to International Classification of Headache Disorders, II edition (ICHD-II) criteria. For medication overuse headache (MOH) and chronic migraine (CM) we considered ICHD-II revised criteria. We gathered in each patient age, gender, time from onset, complementary tests required, and symptomatic or prophylactic therapies previously used.

Results: 262 patients (189 females, 73 males) out of 1868 (14%) attended in our headache clinic during inclusion period were older than 65 years, and 71 (53 female, 18 male) of them (27.1%) were diagnosed of migraine. Most elderly patients (61, 85.9%) reported that migraine complaints appeared for the first time before 50 years. 26 cases (36.6%) suffered episodic migraine, 18 (25.4%) CM, and 27 (38%) CM with MOH. Only 3 patients (4.2%) were diagnosed of migraine with aura, one of them appearing after 50 years. All patients had received at least one symptomatic treatment, but only 31 (43.6%) had previously used a preventative.

Conclusion: Migraine represents a burdensome group of elderly patients in our headache clinic. In most of them, onset of migraine was reported before the age of 50. Migraine with aura is infrequent in our series. Chronic migraine is a common diagnosis in our population and medication overuse seems to play an important role. Despite the long time from onset, preventatives were not widely used in our elderly patients before referral.

References

P153
Clinical analysis of orthostatic headache in Korean patients
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Introduction: Orthostatic headache is defined as a headache that is significantly worsened in the standing position and relieved with recumbency. The major cause of orthostatic headaches is cerebrospinal fluid (CSF) leak. But orthostatic headache also occurs in variable diseases. Therefore clinical manifestations, MRI findings, and outcomes are seems to be various.

Objectives: We analyzed clinical and radiological differences between favorable and non-favorable groups.

Methods: We reviewed 45 patients with orthostatic headache. All patients were underwent brain MRI, CSF tapping and radioisotope cisternography was performed as occasion demands. All patients were performed conservative therapy. Autologous blood patch was done in patients who did not respond to conservative therapy. We divided patients to two groups, favorable (F), unfavorable (UF) groups. The F group defined as clinical improvement by conservative therapy, or once trial of blood patch. More than 14 days of hospitalization, two more trials of blood patch, or relapse defined as UF group.

Results: 21 of 45 patients were classified as a F group. There were no significant differences in age between two groups. The F group had short hospitalization period (7.5 days vs 16.0 days, p=0.009). The UF group had more abnormal MR findings (5 vs 17, p<0.001). There were 1 platybasia, 1 skull hypoplasia, 1 Chiari I malformation, 1 enhancement of dural and epidural layer of thoracic spine, 3 pituitary enlargement, 3 sagging brain and 4 subdural hemorrhages in UF group. 12 of UF group showed pachymeningeal enlargement in brain MRI (3 patients in F group, p<0.001). 16 of F group and 7 of UF group showed normal MRI. 1 of 16 normal MRI in F group and 5 of 7 normal MRI in UF group had CSF leakage on non-lumbar lesion (p<0.001).

Conclusions: Orthostatic headache presenting unfavorable outcome had more brain MRI abnormalities and CSF leakage on upper spinal level. Due to small in number of cases, further recruit of patients is needed.

References

P154
Trigeminal sensitisation by subdural bleeding may mediate brain swelling in acute traumatic brain injury
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Introduction: Understanding of phenomena such as neurogenic inflammation (NI) and sensitisation of the trigeminovascular system is grounded in migraine research, but may have application in traumatic brain injury (TBI).

Objectives: Catastrophic brain swelling and poor prognosis seen in TBI associated with small volume subdural bleeding (SDH) is currently unexplained; the mass of SDH is insufficient to explain the swelling. Instead we propose that traumatic dural bleeding and inflammation sensitize the trigeminal system, as demonstrated in animal models, and may mediate brain swelling in TBI.

Methods: Human autopsy dura was studied by immunocytochemistry for mast cells and for the trigeminal neuropeptides, SP and CGRP.

Results: Dural bleeding is associated with increased mast cell numbers and altered expression of SP and CGRP. SP expression in dural nerves varies with age and gender.

Conclusion: SDH is associated with increased numbers of mast cells, which can cause prolonged excitation in trigeminal meningeal nociceptors. SDH also leads to altered SP and CGRP expression in the dural nerves, indicating trigeminal activation. This has been shown to cause vasodilatation and increased blood flow in the ipsilateral hemisphere, sparing basal ganglia and hindbrain and closely replicating the specific distribution of brain swelling described beneath thin film SDH, particularly in young people. SP variation with age and gender corresponds to patterns of dural pathology; the high female rate of migraine after puberty and the high rate of dural effusions and sinus thrombosis in male infants. Further, vascular leakiness due to trigeminal excitation may explain post-traumatic dural effusions. The role of the trigeminovascular system in the cascade of brain injury following trauma has not been explored and we believe there is an urgent need for the wealth of information derived from migraine research to be applied to the study of brain trauma. This may point to new treatments that could reduce the morbidity and mortality in acute head trauma associated with SDH.

References

P155
Cognitive, emotional and somatic symptoms among patients with chronic posttraumatic headache. A controlled study
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The Journal of Headache and Pain 2013, 14(Suppl 1):P155

Introduction and aim: Patients with chronic posttraumatic headache (CPTH) after mild traumatic brain injury may develop multiple emotional, cognitive and somatic symptoms but these symptoms are often unspecific and reported among other headache patients, too. The aim is
to investigate whether CPTH patients report more symptoms in general and with a higher severity of these symptoms than other headache patients.

Method: The Rivermead Post Concussion Symptoms Questionnaire (RPQ) by King et al.[1], is a validated instrument, which measures the severity and number of cognitive, emotional and somatic symptoms commonly experienced after head injury. The 16 symptoms are rated on a 5-point Likert scale (0=not experienced at all, 1=slightly more of a problem, 2=a mild problem, 3=a moderate problem, 4=a severe problem). All RPQ items were summed to a total score. The symptoms were divided into the three sub-scales: cognitive, emotional and somatic.

Results: 78 CPTH patients and 45 age- and sex matched patients with other headaches (control group) from the Danish Headache Centre were included. The F/M ratio was 6/4 in both groups, the mean age was 34 and 38 years, resp, and headache frequency 26 vs. 24 days/month resp. The CPTH group, compared to the control group, showed a significantly higher number of symptoms and severity of the symptoms on all the three sub-scales (severity 0-4 scale): cognitive (2.5 vs. 1.5), emotional (1.7 vs. 1.2) and somatic (1.9 vs. 1.5).

Discussion: These results (being part of a larger study) suggest that CPTH patients compared to other headache patients with equally number of headache days are significantly more burdened by cognitive, emotional and somatic symptoms, and present a greater severity and impact on their life compared to other headache patients. This indicates that treatment of CPTH should focus broader than just headache treatment, indicating the need for multidisciplinary treatment.

Reference

P156

Clinical, EEG and neuroimaging features of ictal epileptic headache
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Introduction: Migraine end epilepsy have common pathophysiologic mechanisms and share essential and defining attributes which distinguish them from other common neurological disorders. They are both characterized by paroxysmal symptoms and are, therefore, episodic disorders. Occipital lobe to be the brain structures most responsible for development of migraine and occipital lobe epilepsies Both are characterized by visual symptoms followed by headache and other autonomic symptoms. Recognition of headache as an epileptic manifestation per se still represents a challenge.

Methods: This study included consecutive 89 patients with IEH= ictal epileptic headache, at our hospital and our diagnostic department – MRI and EEG.

Results: EEG recordings high voltage rhythmic 11-12 Hz activity with intermingled spikes over the right TO regions. Other–high voltage theta activity intermingled with sharp waves over occipital region. And third bilateral SWC.Brain MRI showed secondary brain lesion in the right TPO region with restricted diffusion in the right occipital region.

Conclusion: IEH be used to classify the events in wich headache represent the only ictal epileptic feature These rare cases should be classified as autonomic epilepsy.

References
1. European headache school. 2012

P157

Tolosa-Hunt syndrome: focus on MRI findings and diagnostic criteria
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Introduction: Tolosa-Hunt Syndrome (THS) is a rare disorder characterized by periorbital or hemicanal pain, ipsilateral oculomotor paralysis and prompt response to steroids [12].

Purpose/background/objectives: The etiology of THS is still unknown [3]. According to the diagnostic criteria demonstration of the presence of granuloma through MRI imaging and/or biopsy is mandatory for diagnosis. The initial standard MR imaging may not be sufficient for diagnosis.

Methods: According to the criteria revised in 2004 by the International Headache Society, seven cases diagnosed as THS have been assessed from the perspectives of type, age, symptoms and findings, accompanying diseases, MRI techniques used, localization of the determined lesion, response to the treatment and clinical progress. Routine biochemical tests, cranial MRI and CT angiographies were done on each patient, and lumbar punctures were also carried out on four.

Results: Four of seven cases diagnosed are males. Age average of patients is 45.7 + 18.1 (25-69). In three of seven cases, cranial nerve paralysis of the third, in one case the fourth, another in sixth, two with fifth, and one with seventh nerve, and in two cases the third, fourth and/or sixth cranial nerves were determined to be bunched. In all cases a response was obtained within 24-72 hours to the corticosteroid treatment. Four out of seven cases had recurrence.

Conclusion: Dynamic contrast enhanced MRI may be necessary to demonstrate the presence of granuloma. THS is a diagnosis of exclusion requiring careful patient evaluation to rule out vascular causes, tumour, or other forms of inflammation in the region of the cavernous sinus. In some cases, even though MRI is normal, the most logical diagnosis is THS. Patients categorized in this group may be diagnosed as “probable THS” and follow-up at least two years until the necessary MRI methods are clearly defined in the IHS diagnostic criteria.

References
Conclusion: In the small number of cases CCF can be presented by minimal symptoms such as persistent daily headache. This condition must be diagnosed and treated promptly since it has a high risk of clinical progression.

References

P159
Quantitative sensory testing in atypical odontalgia patients after local anesthesia
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The Journal of Headache and Pain 2013, 14(Suppl 1):P159

Introduction: Atypical Odontalgia (AO) is a term applied to a continuous pain in the teeth or in the tooth socket after extraction in the absence of any identifiable dental cause, under the International Classification of Headache Disorders (ICHD) and somatosensory abnormalities are common features in these patients, where Quantitative Sensory Testing (QST) are helpful tools to evaluate these cases.

Objectives: The aim of the pilot study was to determine the effect of topical application of anesthetic cream in quantitative sensory testing (QST) findings of AO patients.

Methods: Ten (7 women and 3 men) consecutive AO patients (60±14,97 years) with mean pain duration of 2.7 years (range 1-10 years) were recruited from Bauru School of Dentistry, University of São Paulo (Brazil). QST was performed in all patients at baseline and 3 minutes after topical application of anesthetic cream (Benzocaine 2% - Benzotop 200mg/g, DFL). QST included tests of mechanical detection threshold (MDT) and mechanical pain threshold (MPT) with von Frey monofilaments, dynamic mechanical allodynia with cotton swab (DMA1) and with toothbrush (DMA2), heat pain thermal detection (HPD), cold pain thermal detection (CPD), temporal summation (WUR) and controlled pain modulation (CPM). The present pain intensity was also recorded with visual analogue scale (VAS). Results were analyzed with non-parametric Wilcoxon test with significance level of 5%.

Results: QST mean values showed no differences after topical application of anesthetic cream, except for DMA2 (p=0.02) and WUR (p=0.02). Moreover mean pain in visual analogue scale relieved from 6.03 to 2.12 (64.84%; p=0.02).

Conclusion: In this pilot study significant changes in intraoral somatosensory function were observed in AO after topical application of anesthetic cream for dynamic mechanical allodynia, associated to a reduction of pain intensity. These results may reflect peripheral and central sensitization of trigeminal pathways.

Conflict of interest: There were no conflicts of interest in the performance of this study.

References

P160
Impact of hypertension on somatic pain sensitivity in chronic headache
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Aim of investigation: Previous studies have shown that chronic headache (migraine and/or tension-type; CH) is characterized by diffuse somatic hyperalgesia, while arterial hypertension (HY) produces somatic hypoalgesia which is only partly attenuated by antihypertensive treatment. The aim of the study was to assess if comorbidity between CH and HY results in an attenuation of the hyperalgesia due to headache.

Methods: Forty-eight patients of both sexes [28-56 years] with moderate essential hypertension plus chronic headache (HY+CH) were examined. Twenty-two received no treatment for hypertension, the remaining 26 were under therapy, with good control of pressure values. All underwent measurement of a) blood pressure at rest; b) pressure and electrical pain thresholds in the trapezius, deltoid and quadriceps muscle of one side. The results in this group were compared with those of 40 healthy control subjects (C), 52 patients with chronic headache without hypertension (CH) and 190 patients with hypertension without headache (82 without and 108 with treatment)(HY) (all age and sex-matched).

Results: Immediately before threshold evaluation, untreated hypertensive patients had higher than normal blood pressure levels, while hypertensive patients under treatment, headache patients without hypertension and control subjects had normal blood pressure values. Pain thresholds at all sites in HY+CH were significantly lower than normal and HY in both treated and untreated patients (p<0.001). They were not significantly different from thresholds recorded in CH.

Conclusion: Comorbidity between chronic headache and arterial hypertension (with or without antihypertensive treatment) does not involve any attenuation of the typical diffuse hyperalgesia that characterizes chronic headache. These results suggest that the sensitization process behind diffuse hyperalgesia in chronic pain forms such as chronic headache prevails on the hypoalgesia-determining mechanisms of hypertension in comorbid patients.

References
Three patients received GAN blocks: all noted dramatic improvement in their pain. One was successfully treated with serial blocks over 2.5 years. The other two transitioned from GAN blocks to GAN stimulators with almost complete resolution of their pain.

**Conclusion:** Great auricular neuralgia should be considered in the differential for paroxysmal stabbing periauricular pain. Like other craniofacial neuralgias, it may be idiopathic or secondary to underlying pathology. More study is needed, but it may be reasonable to consider GAN blocks or stimulators in treatment of these cases.

**References**

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**P162**

Medication overuse headache is a manifestation of opioid induced hyperalgesia: a neuroimmune hypothesis and novel approach to treatment

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The Journal of Headache and Pain 2013, 14(Suppl 1):P162

**Introduction:** Patients with chronic headache who consume large amounts of analgesics are often encountered in clinical practice. Excessive intake of analgesics is now considered to be a cause, rather than simply a consequence of frequent headaches, and as such the diagnosis “medication overuse headache” has been formulated [1]. Despite the prevalence and clinical impact of medication overuse headache the pathophysiology behind this disorder remains unclear and specific mechanism-based treatment options are lacking.

**Methods:** Preclinical and clinical data from the literature were reviewed.

**Results and discussion:** Although most acute headache treatments have been alleged to cause medication overuse headache, here we conclude that opioids are the drug class most strongly associated with worsening headache. Recent evidence indicates that chronic opioid administration may exacerbate pain in the long-term by non-specifically activating Toll-Like Receptor-4 on glial cells, resulting in a pro-inflammatory state that manifests clinically as hyperalgesia [2]. We hypothesise that medication overuse headache is a specific form of opioid-induced hyperalgesia, which derives from a cumulative interaction between central sensitisation, due to repeated activation of nociceptive pathways by recurrent headaches, and pain facilitation due to glial activation.

**Conclusions:** Treatment strategies directed at inhibiting glial activation may be of benefit in the management of medication overuse headache. Potential treatment options could include agents such as ibudilast, minocycline and (+)-naltroxone.

**References**

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**P163**

Syndrome of headache with neurologic deficits and CSF lymphocytosis (HaNDL)

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The Journal of Headache and Pain 2013, 14(Suppl 1):P163

**Objectives:** To describe a case of syndrome of headache with neurologic deficits and CSF lymphocytosis (HaNDL).

**Background:** HaNDL is a rare condition with defined diagnostic criteria as outlined in section 7.8 of the second edition of the International Classification of Headache Disorders (ICHD II).

**Methods:** Case Study.

**Results:** Clinical presentation.

In November 2009 a 21-year-old white female experienced 5 episodes of sudden ascending left side hyposthesia, dysarthria and sensory aphasia followed by a nausea and then by severe throbbing unilateral headache. Headache was accompanying with nausea, vomiting, photo- phono and osmophobia, and was located in the right temporal area. Neurological deficit resolved in one hour, headache aborted in 8 hours. At the moment of admission she had subfebrile temperatures but she had not any focal neurological deficit or meningeal signs. Patient had not any personal history of migraine, but her mother suffered from migraineous headaches. Lumbar puncture revealed lymphocytosis (86/mm3) and slightly elevated total protein (66 mg/dL). All investigations including MRI of the brain, EEG, carotid duplex and serological tests for certain viruses and bacteria were normal. Patient had not any episode of neurological deficit or migraineous headache during 10 months follow-up. This patient fulfilled the ICHD II criteria for HaNDL syndrome. It is supposed that HaNDL syndrome could have viral, autoimmune or vascular origin or to be a rare variant of migraine with aura. There is no any specific treatment for this syndrome.

**Conclusion:** HaNDL syndrome should be considered as a differential diagnosis for patients presenting with headache and neurological deficit.

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**P164**

Use of acute anti-migraine medication and risk of development of chronic headache: a prospective population based study

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The Journal of Headache and Pain 2013, 14(Suppl 1):P164

**Introduction:** Overuse of acute pain medication is a risk factor for developing chronic headache.

**Objectives:** To investigate the association between the use of acute anti-migraine medication as single analgesics (SA), combination analgesics (CA) and triptanes (T) and the risk for chronic headache in patients with episodic migraine.

**Methods:** We used data of the German Headache Consortium (GHC) Study which is a population-based sample of 18,000 participants aged 18 to 65 years. Information about headache features, frequency, use of medication and years of education were collected at baseline (2003-2005) and follow up one (t1) and two (t2) years after baseline using mailed questionnaires. Participants with prophylactic headache or other prophylactic pain medication were excluded (n=209). Primary outcome was defined as incidence of chronic headache (any headache on ≥15 days/month) at t1 or t2 in participants with episodic migraine (≤14 days of migraine/month) at baseline. We estimated odds ratios (OR) and 95%-confidence intervals (95%-CI), adjusting for headache days at baseline (interval scaled), education, age (interval scaled), gender and BMI classes (normal, overweight, obese).

**Results:** Of 18,000 people 9,944 (55.2%) responded at baseline, of those 6,688 (67.3%) resp. 6,975 (70.1%) responded at t1 resp. t2. At baseline 1,601 participants had episodic migraine. The incidence of chronicity was 6.2%. Use of anti-migraine medication had a protective effect compared to no intake (SA: OR=0.39, 95%-CI=0.19-0.78; CA: 0.60, 0.22-1.61; T: 0.34, 0.10-1.15). This effect was stronger for SA than for CA (OR=0.65, 95%-CI=0.28-1.50). Adjusting for age, gender and BMI classes did not notably change these results.

**Conclusion:** Our data indicate that use of acute anti-migraine medication irrespective of the type (SA, CA, T) reduces the risk for developing chronic headache.

**Conflict of interest:** Z. Katsarava received speaker honoraria and/or travel reimbursement from Allergan, Merck Serono, Bayer Schering, Boegen, St Jude Medical and served as consultant to Allergan.

**Reference**

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**P165**

A giant cause of a low pressure headache

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**Objectives:** To describe a case of a giant cause of low pressure headache.

**Methods:** Case Report.

The patient was a 15 year old girl, born preterm with severe cerebral palsy and a history of recurrent meningitis. She presented with a 1 week history of increasing headache. Examination revealed a tense fontanelle and a clinically low CSF pressure. A lumbar puncture was performed which revealed the pressure to be 5 mmHg. A diagnosis of arachnoid cyst was made and treated with an external ventricular drain.

**Conclusion:** Giant arachnoid cyst is a rare cause of low pressure headache and should be considered in the differential diagnosis.
We present an unusual case of low pressure headaches in a patient with Marfan’s Syndrome caused by a giant anterior sacral meningocele. The patient, a lady with Marfan’s Syndrome and previous cardiac and ocular complications, presented initially with recurrent postural headaches, worse on standing, occurring over a 5 year period. During these periods she would develop pulsatile tinnitus on standing and also felt the headaches improved when she breathed in. CT brain scans, MRI scans of head and neck and recurrent lumbar punctures done during this period where normal although opening pressures were not recorded. Since 2007 she has had a chronic daily headache with no associated features. Neurological examinations were normal throughout her presentations. A MRI of her lumbosacral spine was performed in 2011 with showed a massive fluid filled structure in the pelvis and a diagnosis of a giant dural ectasia or anterior sacral meningocele was made. Anterior sacral meningoceles are an uncommon congenital abnormality consisting of a spinal fluid filled sac in the pelvis communicating with the subarachnoid space. They are associated with Currarino’s syndrome (premesal mass, a sacral defect and an anorectal malformation) and Marfan’s syndrome. Patients most often present with abdominal symptoms, symptoms of cauda equina or with headaches (both high and low pressure). Neurological symptoms may respond to surgical treatment of the meningocele.

P166
Diagnostic value of optical coherence tomography for intracranial pressure in idiopathic intracranial hypertension
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The Journal of Headache and Pain 2013, 14(Suppl 1):P166

Introduction: Idiopathic intracranial hypertension (IHH) primarily affects young obese women. It can cause chronic headache and permanent visual loss due to papilloedema and secondary optic atrophy.

Purpose: To evaluate the diagnostic value of optical coherence tomography (OCT) as a marker of cerebrospinal fluid (CSF) opening pressure in patients with IHH.

Methods: We investigated CSF opening pressure, peripapillary retinal nerve fibre layer thickness (RNFLT), total retinal thickness (RT), and headache symptoms in 20 patients newly diagnosed with IHH, 21 patients with long-term IHH, and 20 healthy controls. The diagnostic ability of OCT as a marker of increased ICP (>25 cmH2O) was explored by multiple regression analyses and receiver operating characteristic (ROC) curves. As a new diagnostic tool, we developed an OCT elevation diagram.

Results: OCT elevation diagrams showed that 60% of patients newly diagnosed with IHH and in 10% of patients with long-term IHH, 50% or more of the OCT scans were above normal. The percentage of abnormal OCT scans was significantly associated with increased opening pressure (p<0.00001). By including OCT in the multiple regression model, the estimated areas under the ROC curves increased from 77.1 to 86.9.

Conclusion: OCT elevation diagram accurately predicts opening pressure in IHH patients. OCT is an important early symptom of IHH, which despite treatment, persists and disables the vast majority of patients.

P167
Idiopathic intracranial hypertension is not benign: a prospective long-term follow-up study
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Introduction: Idiopathic Intracranial Hypertension (IIH) primarily affects young obese females, and potentially causes visual loss and severe headache.

Purpose: To examine relapse rate and long-term outcome in patients with IIH.

Methods: A prospective controlled study of 18 patients with newly diagnosed IIH followed for a mean observation period of 21.1 (+8.0) months. Treatment regime included diuretics, dietary recommendations and check-up visits at a dietician. Baseline and follow-up included neurological examination, detailed headache history, and comprehensive neuro-ophthalmological examination, including fundus photography, Humphrey visual fields, and measurement of the retinal thickness (RT) and retinal nerve fibre layers (RNFL) by optical coherence tomography (OCT). Relapse was defined as recurrence of either: 1) papilloedema or 2): symptoms and demonstrated raised intracranial pressure.

Results: Relapse was found in 28%. Visual function improved from baseline to follow-up and was generally favourable. In patients without relapse of papilloedema RT and RNFL were significantly thinner than in healthy controls (p = 0.003 and 0.02), although atrophy was clinically detectable in only one patient. Headache was still present in 67 % of the patients at follow-up. Headache was heterogenic and unrelated to relapse. After an initial weight reduction in both groups, patients in the relapse group gained weight in contrast to patients in the non-relapse group who maintained weight or gained further weight loss (p=0.013).

Conclusion: Headache was persistent, difficult to classify, and equally represented in relapse and non-relapse patients. Headache was thus a poor marker of active disease. Relapse rate was high, and by OCT we discovered clinically undetectable optic disc atrophy in apparently well treated IIH patients.

P169

Coexistence of "headache attributed to airplane travel" and "mountain descending headache"  
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Introduction: Recently, we have published a paper on our study of "Airplane headache" (AH) features in a large series of patients [1]. AH refers to a form of recently described headache disorder, whose attacks are strictly related to airplane travel, mostly to the landing phase.  
Materials and methods: Through a detailed questionnaire we identified, in our population of 85 AH cases, 11 patients suffering from headache attacks also occurring during the rapid descent of mountain by car.  
Results: These patients (5 males, 6 female, mean age 37 years), who have complained of AH attacks during landing in more than 50% of their flights, referred the occasional onset of jabbing, severe, unilateral headaches in the fronto-temporal region when descending a mountain by car. They described the headaches as quite similar, with exactly the same features, as compared with those experienced during landing. No accompanying symptoms were reported. The pain began shortly afterwards the rapid descent by car from a medium altitude of 1,800 metres, the maximum peak of intensity developing in a few minutes. All of them reported the pain subsidence within 20 minutes of the rapid way down. No concomitant airways disturbance was reported during the travel. General and neurological examination, brain MRI, Angio-MRI, and cranial CT-scan for sinuses were normal.  
Conclusions: The coexistence of headache attacks, sharing peculiar features, triggered by these different situations, landing by airplane and descent of high altitude by car, strengthens the hypothesis of a possibly common pathophysiological mechanism, i.e. the change of air pressure, which occurs in both conditions.  
Reference

P170

Synovial cyst of temporomandibular joint, a potential etiology for auriculotemporal neuralgia?  
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The Journal of Headache and Pain 2013, 14(Suppl 1):P170

Introduction: Synovial cysts of the Temporo-Mandibular Joint (TMJ) are rare. To date, eleven case reports exist. Auriculo-Temporal Neuralgia (ATN) is a distinct form of facial pain with no clear etiology. We report a case of synovial cysts of the TMJ with symptoms suggesting ATN.  
Purpose: To explore the relationship between synovial cysts of the TMJ and ATN.  
Method: Case report.  
Results: A 63-year-old female with left facial pain. This began intermittently and progressed to constant, dull, mild aching pain in the left temple and preauricular area with superimposed exacerbations of shooting and pulsatile pain. She described multiple paroxysmal jabbing, stabbing pains lasting 30 seconds each. These occurred in episodes lasting 1-15 minutes, five or six times/day, without clear triggers. Exam revealed tenderness anterior to tragus. Brain MRI/MRA were negative. Concern for temporal arteritis led to a prednisone trial and bilateral temporal artery biopsies, which were negative. She was then treated for presumed trigeminal neuralgia with carbamazepine and gabapentin, but could not tolerate the medications. She was on amitriptyline for fibromyalgia and we suggested she continue that treatment. Over next 18 months, she developed intermittent numbness/paresthesias in the preauricular area and ear canal. MRI of face revealed a 5 mm nonenhancing cyst in TMJ, anterior to left mandibular condylar process. Left arthroscopy and surgical pathology confirmed synovial cyst diagnosis.  
Conclusions: Articular branches of the auriculo-temporal nerve innervate the TMJ joint, especially the lateral capsule. ATN is a distinct form of facial pain. Synovial cyst of the TMJ is a rare condition with varied symptoms based upon the size of the cyst. Our patient’s symptoms were highly suggestive of ATN, which had not been reported in the previous 11 cases. We recommend evaluation of the TMJ area in patients with idiopathic ATN.  
Conflict of interest: None.  
References

P171

Headache as a symptom of Multiple Sclerosis  
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The Journal of Headache and Pain 2013, 14(Suppl 1):P171

Introduction: Our aim was to investigate the prevalence of headache in Multiple Sclerosis (MS). We studied data from our department’s day clinic files of MS patients. The associations between headache characteristics and clinical features of MS were investigated.  
Purpose/background/objectives: Our main goal is to study the comorbidity of headache and MS. We investigated possible correlations between MS clinical course and headache characteristics. Headache is a common complaint between Multiple Sclerosis (MS) patients. It has been found that headache prevalence during MS is above 50% and this is different from the percentage of the general population. There are many studies that show comorbidity of headache and MS (56.2% 2).  
Methods: We retrospectively studied demographics data from MS patients of our department’s day clinic (sex, age, duration of MS, presence of headache, type of headache, number of headache attacks per year).  
Results: From 144 patients, 75 (52%) presented with symptoms of headache. 69.2% were female and 30.8% were male. 25% of the patients had headache before MS diagnosis and migraine was a symptom of 61.5% of the above mentioned patients. No statistical significant associations could be determined between duration of MS disease and the frequency, strength and duration of headache.  
Conclusion: Headache with or without other neurological signs could be coexist with MS in greater frequency than the healthy population. The above outcome could be explained by some common underlining biological mechanisms. Further studies are needed to clear up the mechanisms of headache co-morbidity with MS.  
References

P172

Neuroimaging, neuropsychological and psychopathological findings in Medication Overuse Headache (MOH) before and after detoxification  
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Our hypothesis is that in MOH there are metabolic anomalies in brain areas which are implicated in drug dependence and impulse control. **Objective:** To identify changes in the dopamine D2 receptor in the striatum and, evaluate neuropsychological and psychopathological traits in MOH (before and after detoxification), chronic migraine (CM) and episodic migraine (EM) patients. **Method:** We studied 18 MOH, 14 CM, 18 EM patients and 5 controls using iodine-123-iodobenzamide (IBZM) brain SPECT. MOH patients were studied before and, one and six months after detoxification. Neuropsychological and psychopathological traits were evaluated using standard tests and auto-applied scales. **Results:** SPECT quantification using spatially normalized images to an IBZM template showed the following mean and standard deviations for striatal ratios: 1.77±0.15 (Controls), 1.73±0.25 (EM), 1.61±0.10 (MOH) and 1.53±0.10 (CM). MOH and CM showed a similar downregulation of D2 receptors different to the D2 ratios seen in EM and controls. Statistical differences were found between controls/EM and CM (p<0.05). No differences were found in the serial SPECT’s done to the MOH patients. Significant differences were found between EM and MOH regarding an anxiety disorder and in tests measuring attention, executive function and verbal memory. There were also differences between CM and MOH patients, MOH patients’ quality of life and neuropsychology traits clearly improved after 6 months, with a lower medication intake (67.31 to 8.21 pills/month).

**Conclusion:** There were two different groups regarding the IBZM-SPECT results MOH/CM vs. EM/controls. MOH was different than CM/EM neuropsychologically and psychopathologically. MOH patients clinically improve after detoxification even if their IBZM-SPECT does not. So, maybe CM and MOH patients are clinically different because of their cultural and personal pain-coping strategies; and lower levels than expected of medication intake or a longer history of headpain, could alter D2 receptors of the brain.

**References**

**P174**

The “care” protocol: the role of personality in a three-year follow-up study of medication overuse headache

**P175**

Predictive factors for the relapse medication overuse headache. A prospective study

**P173**

**Introduction:** The prevalence of medication overuse headache (MOH) in population is 1-2 percent, in headache centers is 60-70 percent [12]. The MOH relapse during the 1st year after therapy occurs in 30-45 percent [3]. **Objectives:** Prospective study of predictive factors of MOH relapse after drug withdrawal and prophylactic therapy.

**Methods:** Trial was performed in 45 patients with MOH in age from 18 to 65 years (mean age 55±9.9 years). All patients underwent abuse drug withdrawal and the course of preventive therapy. Prospective analysis of clinical-psychological characteristics at 2, 6 and 12 months was performed.

**Results:** Predictors of treatment effectiveness and return to episodic headache after 1 year are initially low intensity of headache, low dose of an analgesic per month (<30 dose per month), the absence of drug dependence and of high level of depression. Predictors of MOH relapse after 1 year are impossibility of simultaneous withdrawal of the abuse drug, prolonged course of disease, early age of debut, combination of comorbid disorders (depression, anxiety, personal and mood disorders), high level of analytic dependence, analgesics containing barbiturates.

**Conclusion:** The hypothesis of heterogeneity of the MOH was confirmed. The 1st type is MOH without comorbid psychiatric disorders with high level of effectiveness of preventive therapy. The 2nd type is MOH with comorbid psychiatric disorders (depression, anxiety, personal and mood disorders), drug dependence and low efficiency of preventive therapy. The choice of strategy of preventive therapy should be implemented depending on the type of MOH and identified predictors of relapse.

**Conflict of interest:** The authors declare that they have no conflict of interest related to the publication of this manuscript.

**References**

**P174**

The “care” protocol: the role of personality in a three-year follow-up study of medication overuse headache

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**Introduction:** The negative prognostic value of psychiatric disorders in Medication Overuse Headache [1] has been previously outlined, however, to the best of our knowledge, the role of personality factors as potential predictors of MOH evolution has never been studied. Aim of this study was to analyse the role of personality in the prognosis of MOH.

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

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

**Conclusions:** Personality is important not only because they characterise patients with MOH, but also probably for their outcome predicting value. We provide support for the existence of a small sub-group of MOH patients (Group A) with addiction-related personality and behavioural problems that are likely to play a major role in influencing and nurturing drug abuse and chronic headache.

**Reference**

**P175**

The “care” protocol: outcome of medication overuse headache in a three year follow-up study

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**Introduction:** Medication Overuse Headache (MOH) has become one of the major challenges in headache management. The main aim of the present
study was to evaluate the factors associated with a negative outcome in a three-year follow-up of subjects diagnosed with MOH.

Methods: All consecutive patients with MOH entering, for the first time, the centre’s inpatient detoxification program were analyzed in a prospective, non-randomized way. They were enrolled as outpatients and gave their verbal informed consent to undergo the protocol (inpatient detoxification and three follow-up visits in the first year, then six-monthly clinical controls). The diagnosis of MOH was made according to the revised-IHCD-II criteria [1]. All the participants were assessed using an ad hoc patient’s record form. Variables analyzed as possible predictors were: gender, age, socio-demographic characteristics, alcohol/coffee/smoking habits, positive family history for drug abuse and/or headache, past medical history, primary headache type, type, duration and quantification of drug overuse and duration of chronic headache. Categorical variables were analyzed with the Chi-square test. For quantitative variables, statistical differences were analyzed with ANOVA. Odds Ratios (ORs) were calculated for dichotomous outcomes as well.

Findings: One-hundred-fifty patients completed the 3-year follow-up (79.3% females, age 46.40±11.31): 13 patients never stopped overuse (Group A), 38 patients stopped drug overuse, but relapsed at least once (Group B) and 99 patients never relapsed (Group C). Patients in Group A differed from B+C groups because they were more frequently single (OR 0.134; p=0.007) and unemployed (OR 3.273; p=0.04), they took a higher number of acute drugs (p<0.001) and used less frequently coffee (OR 3.273; p=0.04).

Conclusion: The outcome of disease in this group of MOH patients was influenced negatively by the severity of overuse (and possibly of the disease) and by specific socio-economic conditions. Other factors that emerged as possible modifiers of outcome were voluptruous habits.

Reference

P176
Survey of the differences between Migraine and MOH pre-existing migraine
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The Journal of Headache and Pain 2013, 14(Suppl 1):P176

Objective: Most patients with medication-overuse headache (MOH) have a history of migraine. The author evaluated patients with migraine and patients with MOH pre-existing migraine.

Subjects and methods: All patients completed questionnaires and were interviewed by the author. The Headache Impact Test (HIT6), Body Mass Index (BMI), and Zung Self-rating Depression Scale (SDS) were investigated. Headache diagnosis was based on ICHD-2 and Appendix 8.2 Medication Overuse Headache [2].

Results: During 7 years, 3754 patients (901 men and 2853 women, 5-93 years old) visited the clinic. At the first visit, 2034 patients (425 men and 1609 women) were diagnosed with migraine, 295 (43 men and 252 women) with migraine and frequent tension-type headache, 98 (18 men and 80 women) with migraine and chronic tension-type headache and 560 (103 men and 457 women) with MOH. Of 560 patients with MOH, MOH pre-existing migraine in 447 patients (67 men and 380 women). The average BMI was 21.3 for MOH pre-existing migraine in 447 patients (67 men and 380 women). The average BMI was 20.8 for the migraine group and 21.3 for MOH pre-existing migraine. The average SDS was 40.9 for the migraine group and 44.8 for MOH pre-existing migraine. Patients with MOH pre-existing migraine experienced more occipital pain than patients with migraine (56% vs. 52%). There were no differences in associated symptoms such as nausea, vomiting, photo/phonophobia between the two groups. Patients with MOH pre-existing migraine had more neck/shoulder stiffness and/or pain and reported more trigger factors such as neck/shoulder stiffness or pain, crowded places, weather changes, lack of sleep or oversleeping psychological stress than the migraine group. Patients with MOH pre-existing migraine had greater psychological disorder than the migraine group (13% vs 6%).

Conclusions: Neck/shoulder stiffness and/or pain is reported more often in patient with MOH pre-existing migraine.

References

P177
Grey matter changes in medication-overuse headache before and after medication withdrawal
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The Journal of Headache and Pain 2013, 14(Suppl 1):P177

Background: Medication-overuse headache (MOH) is a complication of migraine that causes significant burden and cost. Recent studies have demonstrated metabolic and structural abnormalities in MOH 1,2, including a grey matter increase in the midbrain periaqueductal grey. We hypothesised that structural changes related to MOH should return to normal after medication withdrawal in patients with significant clinical improvement (responders). In contrast, no changes were expected in patients without improvement (non-responders).

Methods: Thirty-one MOH patients and 28 healthy controls were investigated in a longitudinal voxel-based morphometry study, comparing structural MRIs at 2 time points.

Results: In responders, grey matter in the midbrain decreased close to normal values after withdrawal. In contrast, in non-responders no grey matter decrease from scan 1 to scan 2 was observed. At baseline, non-responders had significantly less grey matter in the right and left orbitofrontal cortex, left insula, midbrain, and the thalamus compared to responders. In MOH patients grey matter in the right gyrus rectus at base line correlated positively with treatment response.

Conclusions: Increased grey matter in the midbrain, which is involved in pain modulation, seems to decrease after successful treatment. Poor response to treatment is associated with decreased grey matter in the orbitofrontal cortex, consistent with dysfunction of this region.

References

P178
Temperament and character profiles of patients with chronic migraine and medication-overuse headache
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Background and purpose: The frequency of psychiatric co-morbidity or psychological distress has been reported to be high among patients with chronic migraine (CM) and medication-overuse headache (MOH). However, the personality profile of such patients is unclear. The objective of this study was to assess the personality profile of a sample of Japanese patients with migraine by using the Temperament and Character Inventory (TCI).

Methods: This was a cross-sectional study that included 138 adult patients with migraine. In total, 100 age-, sex-, and educational level-matched healthy subjects were selected as a control group. The patients were divided into 3 groups according to the second edition of the
International Headache Classification: those with episodic migraine (EM; n = 79), those with CM (n = 28), and those with MOH (n = 31). The patients in the 3 migraine groups and individuals in the control group completed psychometric questionnaires, including the TCI and Beck Depression Inventory (BDI).

Results: The mean BDI score and the dimension harm avoidance (HA) score of the patients in the 3 migraine groups were significantly higher than those of individuals in the control group. The mean BDI and HA scores were the highest in the MOH group among the 3 migraine groups.

Conclusion: Our results indicate serotonergic involvement in the physiopathology of migraine. In addition, it might risk factor of the migraine chronicity that BDI and HA score are high.

Competing interests: The authors have no potential conflicts of interest to disclose.

Reference

P179
DNIC in whiplash and ankle-injured controls. 1-year prospective findings
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The Journal of Headache and Pain 2013, 14(Suppl 1):P179

Aim of investigation: The role of central processing of pain in the development of chronic neck pain and headache and work disablement after whiplash injury is not well understood. Studies have supported findings of spread of pain in chronified patients. This study examines development of massester muscle tolerance to pressure pain during cold pressor counter-stimulation in whiplash and ankle-injured controls.

Methods: Consecutively 141 acute WLP and 40 ankle injured recruited from emergency units were examined after 1 week, 1, 3, 6, 12 months obtaining neck/head VAS score, number-of-non-painful complaints, epidemiological, social, psychological data and neurological examination, active neck mobility, and furthermore muscle tenderness and pain response, strength and duration of neck muscles. Pressure pain tolerance threshold of massester muscle was performed before and during the counter-stimulation by “The Cold Pressor Test” after 1, 3, 6 months. Based on initial results within 1-week after injury risk factors derived (reduced CROM, intense neckpain/headache, multiple non-pain complaints were applied in a Risk Assessment Score and divided into 7 risk-strata.

Results: Significant differences was found in strata after 1 month, but not after 3 and 6 months. Furthermore, after 3, 6 months all whiplash patients did not process pressure pain different from ankle injured controls during counter-stimulation.

Conclusions: Change in central processing of pain by means of central inhibitory or facilitatory mechanisms may play a role in delayed recovery or even development of chronic disability after whiplash. But presented data here are only partly supportive of this.

Reference

P180
Treatment and outcome in medication overuse headache patients
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Background: Medication overuse headache (MOH) is a frequent condition in headache centers with elusive management and outcomes. Aim: to present the pharmaceutical treatment and outcome of MOH patients from the outpatient Headache Clinic of the Athens Naval Hospital.

Methods: This is an open, retrospective, single center observational study. The electronic files of patients with MOH of the Athens Naval Hospital Out-Patient Headache Clinic were reviewed to assess the outcome.

Results: One hundred forty six patients (29 males and 117 females) with MOH were evaluated (mean age 38.5±12.7 years; mean body mass index 26.1±4.44). Patients overused triptans (38.9%), analgesics (61.1%), NDAIDs (48.4%), codein plus paracetamol (77.6%), bezdiazepines (23.3%), or ergotamine (17.5%). Scores for Hamilton scale for anxiety and depression were 23.9±5.6 and 18.8±6.5, respectively. Prophylactic treatment consisted of naproxen 1000mg (plus gastroproplylaxis), SNRI (venlafaxine 150-300mg/d, or mirtazapine 45-90mg/d) and one of three agents: propranolol (160-320mg/d), topiremate (100mg) or valproate (500-1500mg/d). In cases of anxiety disorder comorbidity (HAM-A score>18) prazepam was added (10-20mg/d). All patients were advised to withdraw immediately the substance overused. After one to three months treatment 37% and 45.6% of patients reported a greater of 50% or 75% decrease of days with headache per month, respectively. The 17.3% of the patient population did not respond to treatment.

Conclusion: Immediate withdraw of substance overused combined with a strong prophylactic treatment, which included naproxen, SNRIs and preventative antimigraine agents is efficient to decrease headache impact in most patients with MOH.

Reference

P181
Occipital locked headache
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Methods: Clinical data for 1029 patients (588 females; 627 Caucasians; mean age =11.4 years) with headaches were prospectively examined in this hospital based study. Headache diagnosis was made on the basis of ICHD II. 2004, 1. Headache diagnosis included migraine (n=598); tension type headaches (n=158); other headache types (n=91) and remained unclassified (n=182) patients. We have adopted previous descriptions of terms for anatomical sites for headache location. 2. Occipital locked headache (OLH) is defined as headache that is for all time fixed to the occipital region and never changed side.

Results: 48/1029 (4.7%) of patients experienced recurrent OLH during a mean headache course of 2.3 years. It was more for OLH to localise bilaterally (87.5%) as only four (8%) and two (4%) patients had right and left OLH respectively. Headache diagnosis was migraine (n=29); tension type headaches (n=5); and other headache types (n=5). Headache remained unclassified in 10/48 patients. Brain imaging was either normal (n=46) or showed no significant abnormalities (n=2).

Discussion: In this study, sinister aetiologies of OLH were excluded among our patients. Primary headache was found to be the most common headache category among patients with OLH. Frequency of OLH was 5% and 4.4% patients with migraine and those with non-migrainous headaches respectively.

Conclusion: Primary headaches such as migraine and TTH are common causes of OLH, although OLH was infrequently found among patients with migraine and those with other primary headache types.

References

P182
Abstract not submitted

The Journal of Headache and Pain 2013, 14(Suppl 1):P182

P183
In vitro characterization of AA71, a potent and selective human monoclonal antibody against CGRP receptor
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The Journal of Headache and Pain 2013, 14(Suppl 1):P183
Objectives: To characterize the in vitro pharmacological properties of AA71, a human monoclonal antibody against the CGRP receptor.

Introduction: Calcitonin gene-related peptide (CGRP) is a neuropeptide that plays a key role in the pathophysiology of migraine. Clinical studies have demonstrated that CGRP receptor antagonism is an effective approach in treating acute migraine pain. We have previously reported the successful generation of a group of human monoclonal antibodies (MAb) that specifically target the human CGRP receptor (1). In our present study, we detail the characterization of AA71, a potent and selective human monoclonal antibody against the CGRP receptor.

Results: AA71 potently competed with the binding of [125I]-CGRP to the human CGRP receptor with a Ki of 0.03 nM. AA71 fully inhibited CGRP-stimulated cAMP production with an IC50 of 2 nM in cell-based functional assays, with no intrinsic agonist activity up to 10 fM. Functional potency of AA71 at the cyto CGRP receptor was similar to that at the human receptor with an IC50 of 4.5 nM, but potency at dog, rabbit and rat receptors was significantly reduced (>5000-fold). AA71 also demonstrated > 5000-fold selectivity over other closely related receptors in the family. Through a saturation analysis using SK-N-MC membrane preparations, [125I]-AA71 was shown to bind the CGRP receptor in a monophasic and saturable fashion with a Kd of 0.08 nM. The binding of 0.1 nM [125I]-AA71 to the CGRP receptor reached equilibrium at approximately 240 min. A prolonged dissociation of [125I]-AA71 binding from the CGRP receptor was observed with a dissociation t1/2 off of 267 min. In a competition study, CGRP’s capability of displacing [125I]-AA71 binding is significantly less robust, with an observed Ki of 370 nM.

Conclusion: AA71 is a potent and selective antibody against the human CGRP receptor with potential for use in the treatment of migraine pain.

Reference

P184
Prevention of migraine by supraorbital transcutaneous neurostimulation using the Cefaly® device (PREMICE): a multi-centre, randomized, sham-controlled trial
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Introduction: Subjects who have frequent migraine attacks (≥ 2 / month) are in need of a preventive anti-migraine treatment. Available preventive drugs have incomplete efficacy and/or unpleasant side effects.

Purpose: Supraorbital transcutaneous neurostimulation (STNS) has shown encouraging results for migraine prevention in pilot studies and has no side effects [1-3]. We assessed efficacy and safety of STNS in migraine prophylaxis with the Cefaly® device in a multicentre, double-blind, randomized, sham-controlled trial.

Methods: Five Belgian tertiary headache clinics participated in the study. After a 1-month run-in period, patients with ≥ 2 migraine attacks/month were randomized to verum or sham stimulation, and applied the Cefaly® device daily for 20 minutes during 3 months. Primary outcome measures were change in monthly migraine days and 50% responder rate, i.e. the percentage of subjects having a ≥ 50% reduction of monthly migraine days. Patients and enrolling neurologists were blinded from the randomization.

Results: Sixty-seven patients were randomized and included in the intention-to-treat analysis. Between run-in and 3rd month of treatment the mean number of migraine days decreased significantly in the verum (4.88 vs 6.94; p=0.023), but not in the sham group (6.22 vs 6.54; p=0.608). The 50% responder rate was significantly greater (p=0.023) in the verum (38.1%) than in the sham group (12.1%). Monthly migraine attacks (p=0.044), monthly headache days (p=0.041) and monthly acute anti-migraine drug intake (p=0.007) were also significantly reduced in the verum but not in the sham group. There were no adverse events in either group.

Conclusions: STNS with the Cefaly® device is effective as a preventive therapy for migraine. The therapeutic gain (26%) is within the range of those reported for other preventive drug and non-drug anti-migraine treatments [45], and the safety profile is excellent.

Conflicts of interest: LH: Allergan. JS: ATI Redwood California, St Jude Medical USA, Allergan USA, ATI USA, Medtronic USA and Cyberonics USA.

References

P185
An open-label trial of alsuma auto-injector for migraine
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The Journal of Headache and Pain 2013, 14(Suppl 1):P185

Objective: To assess the ability of patients, during an acute migraine attack, to successfully self-inject a single dose of sumatriptan using the Alsuma Auto-Injector; and to evaluate the safety and tolerability of the Auto-Injector.

Background: The Alsuma Auto-Injector is a single-use system for the rapid subcutaneous delivery of 6 mg of sumatriptan succinate in the acute management of migraine pain. The Auto-Injector was developed to address the clinical need for an easy to use and rapid to administer system that did not require any assembly.

Methods: This was an open-label, Phase 3 trial conducted at 10 sites in the US. Male or female adults, ages 18 to 60 years old, were eligible for study entry if they met IHS criteria for migraine with or without aura, with at least 2 attacks per month, and if they reported use of subcutaneous injectable sumatriptan on at least 2 occasions within the previous 2 months. During the onset of a migraine attack of moderate-to-severe intensity, patients were asked to administer a 6 mg subcutaneous dose of sumatriptan using the Auto-Injector. Subjects returned to the study site within 72 hours of the migraine for the post-treatment assessment visit.

Results: A total of 63 patients met entry criteria and received a dose of study medication. All self-administered the Alsuma Auto-Injector successfully. On the patient questionnaire, 100% of patients agreed that the written instructions for the Auto-Injector were clear and easy to follow, and that the Auto-Injector was easy to use (95%). A majority of patients agreed that they preferred the new Auto-Injector to the traditional one that they were using prior to study entry (65.1%). The most frequent AE’s was injection site bruising, reported by 15.9% of patients, and rated in all instance as mild in intensity.

Conclusion: The majority of injection-experienced patients reported the pre-assembled, single-use Alsuma Auto-Injector to be an easy to use, preferred treatment for an acute migraine attack. The study found the Auto-Injector to be safe and well-tolerated.

Acknowledgements: Funded by Pfizer Inc.

P186
Review of 500 migraine cases treated with combination of antidepressant & CBT & specific group of dietary supplement with 6 month follow up
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Migraine is a condition which consumes maximum revenue of a family, state & nation & still the suffering goes on. In the world millions are suffering from Migraine .. & having pain killer medicine & suffering from their side effect like kidney failure etc Migraine sufferers may have depression deep down... but psychiatry being a stigma - very few sufferer
goes for consultation to psychiatrist. History of migraine needs a long time to listen & the ability to listen,... which normally a psychiatrist does not have time to listen the painful past & long details without getting revenue - or fee or financially paid for - so depression goes unnoticed. Depression assessment scale -although available - but very few psychiatrist has a team work in India & most of the countries.

**Purpose:** 1. To see that by treating depression & adding specific group of dietary supplements - is there any effect on frequency severity & relapse? 2. Frequency of pain killer - can it be reduced & patient be saved from kidney failure?

**Methods:** 1. Used exclusion criteria ... where no other cause of migraine found ... all investigation within norm. 2. After assessment treated with antidepressant & CBT & specific group of dietary supplement. In follow up video of their statement regarding frequency was noted & use of pain killer was recorded.

**Result:** 1. 50 patients dropped out of the study. 2. 450 completed the study. 3. 90% of patients reported a 90% reduction in the use of pain killer. 4. 100% reported that CBT helped them. 5. 10% of patients reported a mixed picture of attacks but reported reduced severity.

**Conclusion:** Migraine patient may have depression underlying which if addressed can be a useful method to reduce severity of migraine attacks. If stigma of mental health or depression can be reduced - will benefit migraine patient. NI depressant therapy coupled with CBT & specific group of dietary supplement plays an important role in treatment of migraine.

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**P187**

**Hull prospective analysis of Botulinum Toxin type A (Botox) use in the treatment of chronic migraine**

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*The Journal of Headache and Pain 2013, 14(Suppl 1)*

**Introduction:** Botulinum toxin type A (BOTOX) is licensed for the prophylaxis of headaches in adults with chronic migraine (CM). A prospective study was performed to examine the change in frequency of CM symptoms before and after treatment with BOTOX in the real-life setting.

**Methods:** Adults with CM were offered BOTOX after discussion of treatment options. Patients were injected intramuscularly as per PREEMPT, and maintained a headache diary for 30 days before/after BOTOX treatment. Data were collected for the number of headache, migraine and crystal clear (headache free) days. A responder was defined as 50% reduction in headache or migraine days, or an increment in clear crystal days twice that of the baseline in a 30-day period.

**Results:** Full data were available on 67 patients (16 males (mean age 47.2 years; range 26-76 years); 51 females (mean age 42.4 years, range 19-70 years) who received BOTOX. 57/65 (87%) tried 3 preventive treatments and 36/67 (53.7%) were overusing analgesics. The median number of headache days reduced from 27 before BOTOX to 18 after BOTOX (p<0.001); the median number of migraine days reduced from 12 before to 7 after (p<0.001); the median number of crystal clear days increased from 3 before to 12 after (p<0.001). Of the cohort, 34% reported 50% reduction in headache days, 48% a 50% reduction in migraine days and 54% a 50% reduction in crystal clear days. Triptan days reduced from 8 before BOTOX to 3 after (p<0.001). Data on days off work was available for 17/67 patients; in these, the median number of days off work per month reduced from 6 before to 3 after BOTOX (0.004). 13/67 (19.4%) reported adverse events; 8 with pain at injection sites, 1 with worsening headache, 3 could not frown and 1 fainted during Rx.

**Conclusions:** BOTOX is a valuable addition to preventive treatment options in patients with CM. It significantly reduces the number of headache and migraine days, and significantly increases the number of crystal clear days in a real-life setting.

**Conflict of interest:** None.

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**P188**

**OnabotulinumtoxinA injections for the pain relief and long-term symptom control in a patient with hemiplegic migraine: case study**

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*The Journal of Headache and Pain 2013, 14(Suppl 1)*

**Introduction/background:** Treatment of Hemiplegic Migraine can be challenging. Migraine-specific abortives, the triptans and ergotamines, are currently contraindicated in the treatment of Hemiplegic Migraine because of their vasoconstrictive properties.

**Method:** Case study to report the effects of OnabotulinumtoxinA injections for the pain relief and long-term symptom control in a patient with Hemiplegic Migraine. Case: 54-year-old woman with Hemiplegic Migraine for the past 12 years. Severe migraines with right unilateral retro-orbital pain, with progression to the left side, followed by right facial weakness with complete ptosis on the right side and less prominent left facial weakness, immediately progressing to right hemiparesis and then later to left hemiparesis. Attacks were accompanied with nausea, vomiting, dysarthria and dysphasia. Migraine and paralytic episodes 1/week lasting 3-5 days. Headache frequency 20 days/month. Failed the following therapy: Topamax, Inderal and Memantine. Inconsistently responded to IV Maxeran and Benadryl 2-3 times/month between injections. Also on 100 mg of Amitriptylin all along. Effect of OnabotulinumtoxinA wears off in 3 months. No side effects reported.

**Conclusion:** OnabotulinumtoxinA appears to help in alleviating symptoms and reduce care needs of Hemiplegic Migraine in this case.

**Conflict of interest:** None.

**References**


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**P189**

**Ornithine in chronic migraine therapy and allodynia pattern: comparison with dopaminergic activation**

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*The Journal of Headache and Pain 2013, 14(Suppl 1)*

Glutamate is converted to ornithine. Many enzyme reactions are involved in the inter-conversion of glutamate and ornithine by intestinal mucosa [1]. The modulation of the conversion might be a target in the final modulation of glutamatergic transmission. Since ornithine synthesis depends on glutamate, a larger amount of ornithine can explicate a feedback limiting effect on glutamatergic availability. A possible limited glutamatergic availability is here compared with a dopaminergic activation obtained by means of amantadine. In fact, both limited glutamatergic action and increased dopaminergic activity have been indicated to be crucial in analgesia determined at the level of anterior cingulate cortex (ACC) [2]. Experiences in chronic Migraine (M) therapy: in 107 chronic M sufferers (69 females, 38 males, mean age 33.8 + 4.1 SD) ornithine (500 mg twice a day for 3 months) induced an amelioration paralleling the amantadine induced-relief (100 mg amantadine/day for 3 months). Indeed, both the active compounds induced a decrease of
the attacks of 40% >0.001 versus 30-days wash-out and 30-days run-in periods A 14-days treatment induced a decrease (p>0.0001) of visceral/vascular hyperalgesia/allodynia rating -65% in a 0-10 VAS when comparing baseline values with the ones after both amantadine and orimidine administered in the aforementioned doses. These results suggest: a) that orimidine may act in the interconversion of glutamate in all the tissues. Moreover, large doses of orimidine may induce a negative feedback in the mentioned interconversion. b) Dopaminergic and glutamatergic transmission, having opposite activity in pain processing in the ACC, that, in turn, seems to have a crucial structure in pain dyshomeostasis, seemingly act on the central mechanisms of chronic M. References.


P190
MAP0004 provided consistent migraine pain relief even after repeated administration
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MAP Pharmaceuticals, USA
The Journal of Headache and Pain 2013, 14(Suppl 1):P190

Oral tablets are the predominant route of administration for the acute treatment of migraine. Gastric Stasis (GS) is commonly associated with migraine, and can significantly alter the rate of intestinal absorption of an oral tablet, leading to inconsistent response to the administered drug. The Tmax of a triptan administered as a tablet can vary from 25-120 min. MAP0004, an investigational drug that delivers dihydroergotamine (DHE) systemically via the lungs using the TEMPO® inhaler, bypasses the gastrointestinal tract. Consequently, GS is likely to have no effect on the absorption of drug into the bloodstream. MAP0004 administration consistently achieves a DHE Tmax between 7-12 min. A consistent Tmax, however, does not necessarily represent a consistent clinical response. A retrospective analysis was undertaken to determine whether pain relief rates were consistent across the 1st, 5th, 15th and 25th headache treated with MAP0004. A total of 153 subjects within the open label, long term safety study who had at least 25 qualifying migraines were analyzed. Pain relief at 2 hours was seen on an average of 54.1%, and there was no significant difference when comparing subsequent migraines to the first qualifying migraine or comparing the 1st, 5th, 15th and 25th all together. Similarly, analysis of pain free values at 2 hours (average=24%), sustained pain relief from 2-24 hours (average=38-44%), and sustained pain free values from 2-24 hours (average=67.6%) were not statistically different from the first qualifying migraine or comparing the 1st, 5th, 15th and 25th all together. In this retrospective analysis, MAP0004 provided a consistent and similar response rate in treating an episodic migraine attack, whether it was the 1st, 5th, 15th or the 25th headache treated.

Reference.
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P191
Frovatriptan vs other triptans in the treatment of menstrual migraine: pooled analysis of three double-blind, randomized, cross-over studies
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Objective: To review the efficacy and safety of frovatriptan (F) vs. rizatriptan (R), zolmitriptan (Z) and almotriptan (A), in women with menstrual related migraine (IHS criteria) through a pooled analysis of three individual studies.
Methods: Sedated women with a history of migraine with or without aura were randomized to F 2.5 mg or R 10 mg (study 1), F or Z 2.5 mg (study 2), and F or A 12.5 mg (study 3). The studies had an identical multicenter, randomized, double blind, cross-over design. After treating 3 episodes of migraine in no more than 3 months with the first treatment, patients had to switch to the next treatment for other 3 months.
Results: 346 subjects formed the main study intention-to-treat population; 280 of them were of a female gender (81%) and 236 in the fertile age. A total of 187 out of the 236 eligible women (79%) treated at least one episode of menstrual migraine with both medications and were thus included in the present subgroup analysis. Rate of pain free at 2, 4 and 24h was 23%, 52% and 67% with F and 30%, 61% and 66% with comparators (p=NS). Pain relief episodes at 2, 4 and 24h were 37%, 60% and 66% for F and 43%, 55% and 61% for comparators (p=NS). Rate of recurrence was significantly (p<0.05) lower under F either at 24h (11% vs. 24% comparators) or at 48h (15% vs. 26% comparators). Number of menstrual migraine attacks associated with drug-related adverse events was equally low (p=NS) between F (5%) and comparators (4%).
Conclusions: According to our analysis of individual studies F is as effective as other triptans in the immediate treatment of menstrual migraine attacks, but exhibits a more sustained effect.

Reference

P192
Frovatriptan vs almotriptan for treatment of menstrual migraine: a double-blind, randomized, cross-over, multicenter Italian study
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The Journal of Headache and Pain 2013, 14(Suppl 1):P192

Objective: To compare the efficacy and safety of frovatriptan and almotriptan in women with menstrually related migraine (IHS Classification of Headache disorders) enrolled in a multicenter, randomized, double blind, cross-over study.
Methods: Patients received frovatriptan 2.5 mg or almotriptan 12.5 mg in a randomized sequence: after treating 3 episodes of migraine in no more than 3 months with the first treatment, the patient switched to the other treatment for other 3 months.
Results: 67 of the 96 female patients of the intention-to-treat population of the main study had regular menstrual cycles and were thus included in this subgroup analysis. 77 migraine attacks classified as related to menses were treated with frovatriptan and 78 with almotriptan. Rate of pain relief at 2- and 4-hrs was 36% and 53% for frovatriptan and 41% and 50% for almotriptan (p=NS between treatments). Rate of pain free at 2- and 4-hrs was 19% and 47% with frovatriptan and 29% and 54% for almotriptan (p=NS). At 24-hrs, 62% of frovatriptan- and 67% of almotriptan-treated patients had pain relief, while 60% vs. 67% were pain free (p=NS). Recurrence at 24-hrs was significantly (p<0.05) lower with frovatriptan (8% vs. 21% almotriptan). This was the case also at 48-hrs (9% vs. 24%, p<0.05).
Conclusions: Frovatriptan was as effective as almotriptan in the immediate treatment of menstrually related migraine attacks. However, it showed a more favorable sustained effect, as shown by a lower rate of migraine recurrence.

Reference

P193
Occipital Nerve Stimulation (ONS) for the treatment of chronic headache syndromes
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The Journal of Headache and Pain 2013, 14(Suppl 1):P193

Introduction: Migraine is highly prevalent along with the high percentage of treatment-refractory cases. ONS may provide pain relief for patients with otherwise refractory primary headache disorders. It is more generally applicable than other invasive therapies.

Objectives: We therefore investigated ONS in a series of patients to determine efficacy, complications and outcome.

Methods: We included a case series of 20 patients who had chronic headaches for a duration of 5.3 y who underwent ONS lead implantation (SJIM, Octrode). Prior to surgery patients had received conservative and surgical therapies including antidepressants, occipital nerve blocks, opioids, cervical posterior fusion (one patient), without success. 9 patients suffered from chronic migraine, 1 had a history of thalamic infarction, 1 patient suffered from cluster headache, 4 patients complained tension headache and 5 patients with recurrent cervicocerephalgia after spine surgery. Using a midline approach two octrodes were placed subcutaneously and positioned across the level of C1 using fluoroscopy. Leads were placed under general anesthesia and externalized for three days.

Results: Device dislocation was found in 3 cases. 16 patients mentioned significant relief of pain, so that they all underwent insertion of the generator (eon MINI, SJIM). In 3 patients 30% pain reduction was achieved, one patient did not benefit. Decreases in pain led to an improvement in functional capacity during the 3 months follow-up after implantation. The mean VAS score changed from 8.2 ± 1.5 to 3.5 ± 1.3 at the 6 months follow-up. No complications occurred.

Discussion: The exact mechanism of neuromodulation in the treatment of different headache syndromes remains unclear. ONS is safe and efficacious in the treatment of medically intractable headache conditions. Further investigations are required to evaluate predictor for patient selection and stimulation setting among this crucial pain conditions.

Conflict of interest: SS and JV received consultant fees, GB received a fellowship stipendium from St. Jude Medical.

References

P194
Anodal transcranial direct current stimulation of the visual cortex for migraine prevention: a proof-of-concept study
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The Journal of Headache and Pain 2013, 14(Suppl 1):P194

Introduction: Prophylaxis is challenging in migraine because of the low efficacy/tolerability ratio of most drugs [1]. Abnormal excitability of the cerebral cortex seems implicated in migraine pathophysiology [2]. Transcranial direct current stimulation (tDCS) can durably modify the activity of a target cortex and thus be a promising treatment [3]. We have shown that the cerebral cortex, namely the visual cortex, is hyperexcitatory in migraineurs between attacks and hypothesized that this may be related more to a decreased preactivation level than to hyperexcitability per se [2]. Anodal, rather than cathodal, tDCS might be the stimulation modulation of choice in migraine.

Aims: To explore the effect of anodal tDCS on visual cortex reactivity in healthy volunteers (HV) and migraine patients (EM) and its potentials for migraine prevention.

Methods: Amplitude and habituation of pattern-reversal visual evoked potentials (VEP) were measured between the 1st and the 6th block of 100 averaged waves before and after tDCS (1mA; 15 min) of the visual cortex on HV (n=11) and on EM (n=12) without aura interictally. To study therapeutic potential, we applied tDCS (15 min) on the visual cortex twice/week for 8 weeks in 7 EM with at least 4 attacks/month and a pre-treatment 2 months baseline.

Results: In HV, tDCS significantly increased the habituation slope of the VEP N1P1 component but had no effect on P1N2. In EM, tDCS tended to increase habituation of both N1P1 and P1N2. At the end of tDCS treatment, there was on average a significant reduction in migraine frequency from 9.14 attacks during the baseline to 5.57 during tDCS (-36.65%, p<0.05). Mean attack duration changed from 124 to 97 min after tDCS (-36.25%, p<0.05).

Discussion: Anodal tDCS on the visual cortex is thus able to increase habituation of VEP that is reduced in migraineurs interictally. Moreover, 2 weekly sessions of anodal tDCS may have a preventive effect in patients. Hence larger sham-controlled trials with anodal tDCS of the visual cortex are worthwhile in migraine.

References

P195
Prophylaxis of migraine with aura: a place for acetylsalicylic acid
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Aim: Aim of our study was to assess the efficacy and tolerability of Acetylsalicylic acid (ASA) in migraine with aura (MA) management, in a sample of patients referred to the Headache Centre of San Giovanni Battista University-Hospital of Torino.

Materials and methods: We analyzed the medical records of 196 patients suffering consecutively to our Centre between 1995 and 2007 and receiving a prophylactic treatment, dividing them in two groups: the ones receiving ASA (90) and those who were treated with other therapies (106). Primary endpoint was to evaluate the improvement in MA crisis frequency in the two groups. A binary logistic regression model was used to identify possible factors associated with the positive response to treatment.

Results: The mean age was 32.1 (±9.9) in ASA group and 36.8 (±4.9) in no-ASA group. Positive response to treatment (measured as a reduction of at least the 50% of crisis with aura) was reported by 85.6% of patients in the ASA group and 51.9% in the control group (p<0.001). Multivariate analysis showed, as only variable related with a positive response to treatment, the group (ASA Group: OR 6.26, p=0.006), while there were no relationships with gender, age or typology of aura.

Discussion: In the past, other studies compared the effectiveness of ASA in migraine versus other prophylactic therapies, but they often considered very small samples, mixing MA and migraine without aura (MoA) together. In those setting ASA appeared to be mildly effective. Our results show a large positive response to the treatment with Acetylsalicylic acid, whose probability of success was about six times greater than the one associated with other therapies.

Conclusions: According to our results, asa is not only effective in the majority of MA cases, but the response is usually evident in a short time.
Migraine attacks during menstruation: efficacy of eletriptan and relationship to recurrence after response
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Introduction: Compared with migraine attacks not related to menstruation, migraine attacks during menstruation have been shown to have longer duration and higher recurrence rates, are more resistant to treatment, and are associated with greater functional disability.

Objective: To compare migraine attacks during menstruation to other migraine attacks and assess recurrence of migraine after response in both these groups.

Design/methods: Data for eletriptan 20 mg(E20), 40 mg(E40), 80 mg(E80) were pooled from 5 similarly designed RCTs of eletriptan. Women with migraine beginning within 1 to 4 days of menstrual flow (GI) were compared to women with migraine not associated with menstruation (G2). Headache response within 2 hours to Eletriptan and placebo was compared in women within GI and G2 using logistic regression analyses controlling for baseline headache severity, treatment group(E20, E40, E80, Pbo) and study. Recurrence of migraine after initial response within 2 hours and up to 24 hours post-headache was compared between GI and G2 also using logistic regression. Adverse event frequencies were also compared between groups.

Results: Five studies (N=3217) were included in this analysis. 2796 (86.9%) of the subjects were women. Mean age for GI (N=630) was 36.8 (SD=8.1) and G2 (N=1586) was 37.7 (SD=9.9) years. Headache response within 2 hours was superior in the Eletriptan treated groups vs. placebo in GI (E20: OR=3.8, 95% CI=1.18, 7.7; p<0.0002) (E40: OR=5.3, 95% CI=3.3, 8.7; p<0.0001) (E80: OR=6.5, 95% CI=3.8, 11.05; p<0.0001) and in G2 (E20: OR=1.65,95% CI=1.01,2.7; p=0.045) (E40: OR=2.9, 95% CI=2.2,3.9; p<0.0001) (E80:OR=4.2, 95% CI=3.15,8; p<0.0001). Headache recurrence rates were higher in GI compared to G2 (OR=1.66, 95% CI=1.22, 2.26; p<0.000). Adverse events were comparable between GI and G2.

Conclusions: Eletriptan has similar efficacy in the treatment of migraines occurring within and without a menstrual period. Migraine attacks during menstruation have higher odds of recurrence than migraines occurring at other times. Eletriptan was safe and well tolerated.

Acknowledgements: Study supported by Pfizer. Available upon request. (Complete list exceeds character limit).

P197
OnabotulinumtoxinA for chronic migraine treatment: 75% responder analysis from double-blind, randomized, placebo-controlled phase of PREEMPT
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The Journal of Headache and Pain 2013, 14(Suppl 1):P197

Introduction: Chronic migraine (CM) is a prevalent and disabling neurological disorder. OnabotulinumtoxinA is the only approved therapy specifically for CM. The results from randomized controlled trials often reflect, but rarely define, the spectrum of patient outcomes. The proportion of patients highly responsive to a therapy is an important endpoint and guide for clinicians and patients.

Objective: To determine the proportion of patients who are highly responsive (75% responder rate) to therapy in 2 double-blind, placebo-controlled, parallel studies (PREEMPT 1 & 2).

Methods: PREEMPT (two phase 3 studies: 24-week, double-blind, placebo-controlled, parallel-group phase, followed by 32-week, open-label phase) evaluated the efficacy of onabotulinumtoxinA for prophylaxis of headaches in CM (15 days/month with headache lasting 4 hours/day or longer). Patients were randomized (1:1) to onabotulinumtoxinA (155-195U) or placebo every 12 weeks. The proportions of patients with 75% decrease from baseline in frequency of headache days, headache episodes, migraine days, migraine episodes, moderate/severe headache days, and total cumulative hours of headache on headache days were analyzed.

Results: Pooled analyses (onabotulinumtoxinA n=688, placebo n=696) demonstrated a statistically significant between-group difference favoring onabotulinumtoxinA in the proportion of patients who had a 75% reduction from baseline in headache days at Week 24 (22.8% onabotulinumtoxinA, 15.5% placebo; p=0.002). For all above headache symptom measures, a significantly greater proportion of onabotulinumtoxinA-treated than placebo-treated patients had 75% decreases from baseline.

Conclusions: PREEMPT supports the efficacy and tolerability of onabotulinumtoxinA for the prophylaxis of headache in adults with CM. [1] These data demonstrate that onabotulinumtoxinA treatment results in a significant 75% reduction in multiple headache symptom measures and highly substantial efficacy for a subpopulation of patients studied.

Support: Allergan, Inc.

Reference

P198
Transcutaneous Vagus Nerve Stimulation (tVNS) for headache prophylaxis: initial experience
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Introduction: Neurostimulation is of increasing interest in headache therapy. Invasive neurostimulation methods were found effective in drug-refractory headaches. There is a need for non invasive therapies that could be justified in less disabled patients. Previous case reports suggested that internal Vagus Nerve Stimulation (VNS) might be effective in headache prevention [1-3].

Objectives: We explored efficacy and safety of a transcutaneous VNS device (tVNS, Gammacore®) as preventive treatment in primary headache sufferers. The aim of this pilot trial was to determine a target subpopulation for a multicenter sham-controlled study.

Methods: Eighteen patients accessed to undertake prophylaxis with tVNS: 12 migraine without aura patients (MO, 5 with medication overuse, MOH, 3 chronic), 4 patients with trigeminal autonomic cephalalgia (2 chronic cluster headache, CCH), and 2 with hemicrania continua (HC). tVNS was applied 3 times/day during 90 seconds. Data were collected using headache diaries.

Results: Results are available for 13 patients. Ten patients stopped tVNS after 0.7 to 6 weeks because of lack of efficacy (N=9) and/or side effects (N=6). In one patient with CCH, attacks decreased from 4.5/day to 0.39/day, and in a patient with MOH headache days decreased from 7/week to 3/week and intensity from 8.5 to 4/10. The benefit remains after 5 months of treatment and attack frequency increases when stimulation is interrupted. The last patient had HC with initial intensity decrease from 8.5 to 4/10 but relapsed after 8 weeks. Reported side effects were local discomfort (N=3), tonic muscle contraction (N=1), fatigue (N=1), palpitations (N=1) and cervical muscle spasm (N=1).

Conclusions: Our initial experience suggests that tVNS might help some headache patients. That it was not effective in many patients may be due to the fact that the vagus nerve is not or insufficiently stimulated. There were no serious adverse events but the stimulation could be poorly tolerated.

References

P199
OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all 5 treatment cycles in PREEMPT SK Aurora1, DW Dodick2, RE DeGryse3, CC Turkel4
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A double blind study with a larger sample is needed to ascertain these findings.
Introduction: Chronic migraine (CM) is a prevalent, disabling neurological disorder. PREEMPT demonstrated efficacy & safety of onabotulinumtoxinA (BOTOX®) for prophylaxis of headaches in adults with CM. 

Objective: Assess patients who received all 5 treatment cycles and completed PREEMPT clinical program.

Methods: PREEMPT (two phase 3 studies: 24-wk, double-blind, placebo-controlled [DBPC], parallel-group phase, followed by 32-wk, open-label phase) evaluated efficacy & safety of onabotulinumtoxinA in CM (≥15 days/month with headache lasting ≥4 hr/day). Patients were randomized (1:1) to onabotulinumtoxinA (O) or placebo (P) every 12 wks for 2 cycles, followed by onabotulinumtoxinA for 3 cycles. Multiple headache symptom measures were evaluated. Results for the completer (5 cycles) subgroup of patients are reported.

Results: Of 1384 total patients, 1005 received all 5 treatment cycles [513 received O only (O/O); 492 received 2 cycles of P then 3 cycles of O (O/P)]. Demographics were similar between treatment groups. At Week 56, after all patients were treated with onabotulinumtoxinA, there continued to be significant between-group differences favoring O/O vs P/O group for the following headache symptom measures: mean change from baseline in frequencies of headache days (-12.0 O/O, -11.1 P/O; p=0.035), migraine days (-11.6 O/O, -10.7 P/O; p=0.038), moderate/severe headache days (-11.0 O/O, -10.1 P/O; p=0.042). Treatment-related adverse event rate was 28.5% for O vs 12.4% for P in the DBPC phase and 34.8% for patients treated with O for all 5 cycles throughout the 56-wk trials.

Conclusion/relevance: This subgroup analysis demonstrated statistically & clinically meaningful improvements with onabotulinumtoxinA treatment (5 cycles) vs placebo (2 cycles)/onabotulinumtoxinA (3 cycles) for multiple headache symptom measures & suggests that at Week 56, patients treated earlier with onabotulinumtoxinA had better outcomes. OnabotulinumtoxinA is an effective, safe, well-tolerated long-term (3-5 cycles) treatment for prophylaxis of headache in adults with CM.

Support: Allergan, Inc.

P200
The percent of chronic migraine patients who responded to onabotulinumtoxinA treatment per treatment cycle in the PREEMPT clinical program
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Introduction: CM is a prevalent, disabling neurological disorder. OnabotulinumtoxinA is the only approved therapy specifically for CM. In patients who do not respond to the first onabotulinumtoxinA injection cycle, it is unclear whether subsequent injections cycles will be effective.

Objective: To determine the proportion of first-time responders with chronic migraine (CM) who demonstrate a clinically meaningful response to onabotulinumtoxinA in the first 3 treatment cycles of the PREEMPT clinical program.

Methods: PREEMPT (two phase 3 studies: 24-wk, double-blind, placebo-controlled, parallel-group phase, followed by 32-wk, open-label phase) evaluated onabotulinumtoxinA for prophylaxis of headaches in CM (≥15 days/month with headache lasting ≥4 hours/day). Patients were randomized (1:1) to onabotulinumtoxinA (155-195U) or placebo every 12 weeks for 2 cycles. We evaluated 50% responder rate for three treatment cycles across multiple efficacy variables. This rate exceeded the previously suggested clinically meaningful response rate of 30% in patients with CM.1

Results: Pooled analyses demonstrated high responder rates among onabotulinumtoxinA-treated patients (n=688) after Treatment Cycle 1 in frequency of headache days (49.3% of patients), moderate/severe headache days (33.0%), and cumulative hours of headache on headache days (54.2%) and a 21.5-point improvement in HIT-6 (56.3%). After Treatment Cycle 2, an additional 11.3-14.5% of patients who did not respond to Treatment Cycle 1 became responders. With a third treatment, an additional 7.4-10.3% of patients became responders.

Conclusions/relevance: These data demonstrate that a high proportion of onabotulinumtoxinA-treated patients are responsive (50% improvement) to the first treatment cycle, and patients who were not responders to the first cycle may become responders with a second and/or third treatment cycle.

Support: Allergan, Inc.

Reference:

P201
Acute treatment optimization for migraine: results of the American migraine prevalence and prevention (AMPP) study
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Objectives: To assess and compare acute treatment optimization as measured by the Migraine Treatment Optimization Questionnaire (M-TOQ) within a population-based sample of persons with migraine.

Methods: AMPP is a longitudinal, US-population-based study for which questionnaires were mailed to 24,000 severe headache sufferers and followed annually. Respondents with ICHD-2 migraine were stratified as either CM (≥15 headache-days/month) or EM (<15 headache-days/month).

Using M-TOQ, a valid/reliable patient-report tool assessing 5 domains: functioning, rapid relief, relief consistency, recurrence risk, tolerability over preceding 4 weeks. Respondents rated statements in each area as either occurring: never, rarely, < or ≥ about half the time. An item response theory (IRT) model used to define scaled treatment optimization scores as function of M-TOQ item set; lower scores-less/problematric optimization; higher scores—greater optimization. The model was expanded to incorporate persons with CM/EM on scaled scores and explored demographic adjustments for age and gender.

Results: 8612 persons met criteria for migraine (CM=539; EM=8073) and completed M-TOQ. IRT model parameters indicated excellent M-TOQ psychometric properties. Scaled treatment optimization scores were significantly lower for persons with CM (3.25 vs EM (4.01, b= -0.757; p<0.001), corresponding to a 0.5 standard deviation (SD) difference between CM and EM. After adjustment, mean difference on scaled-optimization score remained significantly lower (worst) for CM (b= -0.751; p<0.0001).

Discussion: Treatment regimens were less well-optimized and more lacking in domains measured by M-TOQ (ie, functioning, rapid relief, consistency of relief, risk of recurrence and tolerability) among persons with CM vs EM. Funding: The AMPP study was funded through a research grant to the NHF from Ortho-McNeil Neurologics. Additional analyses were supported by Allergan, Inc.

P202
Flunarizine is more effective than topiramate in patients with chronic migraine and medication overuse headache
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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 month and chronic migraine CM is the most common subtypes of MOH in specialty care [1]. Flunarizine and topiramate are considered as first-choice drugs in prophylactic treatment of episodic or transformed migraine[2]. Topiramate is considered as first-choice drug in treatment of CM [1].

Objectives: We analyze two independent case-series with (CM) and (MOH) according to ICHD-II criteria treated with topiramate or flunarizine as first intention and compare the results.

Methods: Patients were medication over users and naïve to (oral) prophylactic therapy. In both groups, the main effectiveness variables (reduction in the number of seizures and days with headache at four months of treatment and responder rates) were analysed.

Results: The study included 348 patients: 186 with flunarizine (88.2% females; mean age: 43.8 ± 13.6) and 160 with topiramate (88.0% females;
mean age: 40.2 ± 13.2). No significant differences were found between groups as regards mean age, sex and number of migraines and days with headache in the previous month. There was a significant decrease (0.0001) in the mean number of crisis in the fourth month of treatment, but with no significant difference between them: topiramate (9.3 ± 7.1 to 4.6 ± 6.1) and flunarizine (9.9 ± 7.3 to 4.1 ± 5.0). Mean of days with headaches at four month of treatment, topiramate 9.7±8.5, flunarizine 6.9±8.4 (0.0106); the respondent rate was: topiramate 57.9%, flunarizine 72.6% (p = .0391). The mean reduction in the number of days with headaches: topiramate 48.2%, flunarizine 63.3% (p = .0040).

Conclusions: Both drugs showed effectiveness when used as the preferred drug in the preventive treatment of (CM) and (HOM). Flunarizine offered better results on reduction in the number of days with headaches and minor side effects than topiramate.

Reference

P203
The ideas of people referred to neurologists about managing their headaches: A qualitative study
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Introduction: Headache is the commonest reason for General Practitioner (GP) referrals to neurologists, accounting for 25% of all referrals. Those that are referred, however, constitute only 2% of patients who consult GPs with headache. Previous research has suggested that referred patients are more fearful and anxious about their symptoms than those managed without referral. GPs described pressure to refer, often for a brain scan. We now report patients’ perspectives.

Aims/objectives: The aim of this study was to explore the view of people consulting GPs with headache who were referred to neurologists.

Methods: A qualitative study using semi-structured interviews with nineteen adults aged 23-63, referred by their GPs for primary headaches. Audio-recorded interviews were transcribed and analysed thematically.

Results: Participants described recuring concerns about secondary organic causes for headache, like a brain tumour. They described their headaches as stressful and a vicious cycle, with further headaches occurring. Some reported catastrophic fears, leading them to attend A&E. Many believed they needed a brain scan, and over half had had a scan, all of which were normal. Many reported dissatisfaction with care and use of alternative therapies.

Conclusion: People referred to neurologists for headache described fear and distress, particularly about the possibility of a brain tumour. GPs now have open access to scanning. This may relieve physical concerns. Interventions to address health-related anxiety may help some consulters for headache too.

References

P204
OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients without medication overuse
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Introduction: CM is a prevalent, disabling primary headache disorder. Most patients in CM clinical trials overuse AHM. The efficacy of prophylactic medications in CM patients without overuse of AHM is unclear.

Objective: To evaluate the efficacy and tolerability of onabotulinumtoxinA in a chronic migraine (CM) subgroup without acute headache medication (AHM) overuse (MO-No).

Design/methods: PREEMPT (two phase 3 studies: 24-week, double-blind, placebo-controlled, parallel-group phase, followed by 32-week, open-label phase) evaluated onabotulinumtoxinA for prophylaxis of headaches in CM (≥15 days/month with headache lasting ≥4 hours/day). Patients were stratified based on AHM use during 28-day baseline and randomized (1:1) to onabotulinumtoxinA (155-195U) or placebo every 12 weeks. Multiple headache-symptom measures were evaluated at Week 24, including mean change from baseline in headache-day frequency (primary). Pooled results from MO-No subgroup are reported.

Results: 480 (n=243 onabotulinumtoxinA; n=237 placebo) of 1384 patients met MO-No criteria. At Week 24, onabotulinumtoxinA treatment significantly reduced headache-day frequency compared to placebo (-8.8/ onabotulinumtoxinA; -7.3/placebo; p=0.013). Significant improvements from baseline (p=0.027) also favored onabotulinumtoxinA at Week 24 for frequency of migraine-days, moderate/severe headache-days, total cumulative hours of headache on headache-days, and percent of patients with severe (>60) headache impact test (HIT-6) scores. Improvements in total HIT-6 and migraine-specific questionnaire scores all significantly favored onabotulinumtoxinA over placebo at Week 24 (p<0.032). Few patients in this subgroup discontinued because of an adverse event (AE); AEs were consistent with overall PREEMPT tolerability.

Conclusion/relevance: OnabotulinumtoxinA is effective and well-tolerated for prophylaxis of headache in CM patients who do not overuse AHM.

Support: Allergan, Inc.

P205
Association of lower level of physical activity with primary headaches
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Background and aims: Low physical activity has been associated with higher prevalence of headaches. The primary aim of the study was to assess the association of pure migraine, pure tension-type headache (TTH) and coexistent headache with the level of leisure-related physical activity. The secondary aim was to study the association between the level of leisure-related physical activity and episodic and chronic mixed headache.

Methods: Total of 1300 subjects was invited to participate in a cross-sectional population study. A total of 805 eligible subjects completed a diagnostic headache interview, provided self-reported data on neck pain and back pain, leisure-related physical activity, demographics and self-rated health. Levels of leisure-related physical activity were classified according to activities performed as low, medium and high (reference).

Results: Multinomial logistic regression analysis adjusted for gender, age, education, neck pain, back pain, poor self-rated health demonstrated that primary headache (mixed headache ) was associated low physical activity (OR=2.54, 95% CI=1.47-4.39, p=0.001) followed by medium physical activity (OR=1.62, 95% CI=1.05-2.52, p=0.03). Low physical activity was significantly associated with pure TTH (OR=2.80, 95%CI=1.38-5.68, p=0.004) and coexistent headache (OR=2.97, 95%CI=1.27-6.99, p=0.01) in the adjusted analysis. Association of pure migraine with low (OR=1.95, 95% CI=0.86-4.43, p=0.11) and medium physical activity, and coexistent headache and pure TTH with medium physical activity did not reach statistical significance. Low activity level is highest in chronic headache (OR=2.97, 95%CI=0.94-9.44, p=0.07) compared to episodic headache (OR=2.42, 95%CI=1.37-4.28, p=0.002).

Conclusions: Lower level of leisure-related physical activity is associated with primary headaches. Furthermore, the association is strongest for coexistent headache followed by pure TTH and pure migraine. The causal relationship of low activity level to headache chronicity cannot be assessed in this cross-sectional study.
P206
Sumatriptan and dihydroergotamine in proximal and distal human isolated coronary arteries
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Sumatriptan and dihydroergotamine (DHE) are both 5-HT receptor agonists and two of the most widely used drugs for the acute treatment of migraine. These drugs are contraindicated in people with cardiovascular disease because of their vasoconstricting properties, as has previously been assessed in proximal coronary arteries. The effect of DHE in distal coronary arteries, however, has never been reported, although smaller coronary arteries might also account for angina-like symptoms, especially in women.

The aim of this study was to compare the contractile effects of sumatriptan and DHE in proximal and distal human coronary arteries, and to relate our findings to the plasma concentrations obtained in clinical practice. Segments of proximal (Ø 3-5 mm) and distal (Ø 0.5-1 mm) human isolated coronary arteries were mounted in organ baths and concentration response curves for sumatriptan and DHE were constructed. In proximal coronary artery segments, maximal contractions to sumatriptan (16+/−18% of contraction to 100 mM KCl) and DHE (5+/−4%) were not significantly different. In contrast, in distal coronary arteries, the contractile responses to sumatriptan (18+/−11%) were significantly larger than those to DHE (4+/−2%). At clinically relevant concentrations (Cmax after different formulations), contractions to both sumatriptan and DHE in proximal as well as distal coronary arteries were below 6%. Thus, our results indicate that coronary artery contractions to DHE in distal coronary artery are smaller than those to sumatriptan, although in the clinical situation both drugs are likely to induce only a slight contraction.

Reference

P207
Application and efficacy of levetiracetam in prophylactic treatment of migraine without aura
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Introduction: In connection with necessity of extension of therapeutic possibilities of migraine treatment the study of efficacy of Levetiracetam for prophylactic treatment was conducted. There are not data in literature on undertaking big randomized studies on this topic.

Background: With a glance for pharmacotherapeutic peculiarities of action of traditional anticonvulsants, that limit their application due to side-effects (valproic acid and topiramate are meant), there is a necessity of enlargement of the range of drugs, that can be used for the prophylactic treatment of migraine.

Objectives and methods: The study was conducted on the base of Headache Center on patients that applied with migraine without aura [1] with attacks resistant to NSAID or triptans, or frequent attacks (4-8 per month). Patients were randomized on gender, age, duration of the disease. 30 patients took Levetiracetam (1000 mg/day) like prophylactic treatment for 6 months, 30 patients took valproic acid (1000 mg/day) for 6 months, and 30 patients took Topiramate (200 mg/day) for 6 months.

Efficacy of the treatment was assessed by quantity of days with headache during the month, quality of life index [2].

Results: Levetiracetam showed efficacy comparable with traditionally used anticonvulsants. The efficacy of Levetiracetam was unequally lower than the efficacy of valproic acid, and it was reliably higher than the efficacy of Topiramate.

References

P208
Efficacy of MAP0004 in treating severe migraine
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The treatment needs of migraine patients are often unmet by available therapies, due in part to the incapability to completely relieve symptoms consistently across a broad spectrum of migraine attacks. MAP0004, an investigational drug that delivers dihydroergotamine (DHE) systemically via oral inhalation, was superior to placebo for the acute treatment of migraine in a Phase 3 trial. A subgroup analysis of subjects with severe migraine pain at baseline during the double blind period is reported here. Severe baseline pain was reported in 366 of the 794 subjects. Subjects with severe migraine pain treated with MAP0004 experienced statistically significant pain relief (p<0.05) as early as 10 minutes and at all subsequent pre-scheduled evaluation time points compared to placebo. These subjects were significantly pain free (p<0.05) by 60 minutes and at all subsequent time points following treatment compared to placebo. Sustained pain relief and sustained pain free values, both between 2 and 24 hours and 2 and 48 hours, were statistically significantly higher for MAP0004 relative to Placebo. Headache recurrence over 24 hours occurred in 6.2% of severe migraine subjects treated with MAP0004 compared to 18% when treated with placebo. In summary, this analysis describes the baseline presentation of the severe migraine patient population and shows that MAP0004 was effective in the acute treatment of severe migraine in this Phase 3 trial.

References

P209
EUROLIGHT project: impact of primary headache disorders from a population-based study conducted in Pavia
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Introduction: Headache disorders, including migraine and tension-type headache, are very common in the general population but there is very little recognition of their public health impact [1]. In Italy, there are relatively few studies on the prevalence of primary headaches. We conducted a survey in the population of the Pavia province, in Northern Italy, which is a part of a global project performed at the European Union level, the Eurolight Project (http://www.eurolightonline.eu), to estimate the impact of headaches using a validated tool (the Eurolight questionnaire).

Material and methods: The Eurolight questionnaire, including 103 items, was distributed to a stratified sample (n=3500) of the adult inhabitants of Pavia province, randomly selected in cooperation with Azienda Sanitaria Locale (ASL). Of these questionnaires, 500 were returned completed correctly.

Results: 487 questionnaires were considered for the analysis (51% by women and 49% by men). Nearly 80% of our study population reported to suffer from episodic headaches in their life and 91.7% had episodic headaches in the last year. Medication Overuse Headache (MOH) was diagnosed in 1.9%. Up to 80.0% of responders suffering from headache never received a diagnosis by a doctor and only 2.4% of them were taking preventative medication. Almost 12% of headache sufferers reported a moderate or severe negative interference of pain in many aspects of the life (education, career and earnings, family planning).

Headache influenced the mood state and there was a correlation between the monthly headache frequency and anxiety or depression symptoms. In MOH patients the presence of anxiety and depression disorders was indeed very high.
Conclusions: Despite a high prevalence of primary headaches in Italian adult population, the majority of affected people are primarily self-treating without receiving the advice of health professionals. Education of patients and health care providers should be a high priority issue in public health.

References:

P210
The effect of sumatriptan on cecalic arteries - 3T MR-angiography study in healthy volunteers

Introduction: The triptans, serotonin receptor 8/D agonists, are the mainstay in the acute treatment of migraine [1]. Sumatriptan, the first triptan, was originally developed as a cranial vasconstrictor by acting on the 5-HT1B/1D receptors in cecalic vessels [2]. However, several modes of action as well as multiple sites of action have been proposed. [3]

Objectives: To explore a possible differential effect of sumatriptan on extra-versus intracerebral arteries, we examined the superficial temporal (STA), middle meningeal (MMA), extracranial internal carotid (ICAextra), intracranial internal carotid (ICAItra), middle cerebral (MCA) and basilar artery (BA).

Methods: The arterial circumference were recorded by high resolution magnetic resonance angiography before and after subcutaneous sumatriptan injection (6 mg) in 18 healthy volunteers.

Results: We found significant constrictions of MMA (16.5%), STA (16.4%), ICAItra (15.2%), MCA (5.5%) and BA (2.1%) (p < 0.0012). ICAItra changed by 1.8% (p = 0.179). Analyses of the relative changes between the intracerebral and extracerebral arteries revealed significantly larger constriction of the extracerebral than of the intracerebral (MCA, BA, ICAItra) arteries (p < 0.00001).

Conclusion: Sumatriptan constricts more extracerebral than intracerebral arteries. We suggest that sumatriptan exerts its anti-migraine action outside the blood-brain barrier by constricting the extracerebral arteries and blocking the nociceptive inputs from sensory afferents.

Conflict of interest: JO has received grants/research support from, has been a consultant/scientific adviser for, and has been in the speakers bureau of Allergan Inc, AlexanZenea Pharmaceuticals LP, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical Products, Lundbeck, Merck and Pfizer. MA has received grant support/honoraria for lecturing from Merck, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical Products, Lundbeck, Merck and Pfizer. MA has received grant support/honoraria for lecturing from Merck, honoraria for lecturing from Pfizer, GlaxoSmithKline, Norpharma and AstraZeneca, is a consultant/scientific adviser for Merck and Allergan. FA has received honoraria for lecturing from Allergan.

References:

P211
Bilateral jaw dislocation following botulinum toxin type A treatment for chronic migraine

Background: Botulinum Toxin Type A is a licenced treatment for chronic migraine. We describe a case of bilateral jaw dislocation which occurred following Botulinum Toxin Injection. Case Description The patient is a 46 year old lady with a 25 year history of chronic migraine and no previous history of joint dislocations. She was injected following the 155 unit fixed-dose, fixed site protocol with no immediate complications. 8 days later the patient developed acute bilateral jaw pain and an inability to close the mouth. An x-ray confirmed bilateral temporomandibular joint dislocations and this was reduced the following day by an oral surgeon. There has been no recurrence, however she continues to complain of jaw pain. As her initial injection was associated with an improvement in headache, she consented to further treatment on the basis that the temporalis muscle was not injected. To date there has been no recurrent dislocation.

Conclusion: We believe that injection of the temporalis muscle in this patient predisposed to bilateral temporomandibular joint dislocation. To our knowledge this has not previously been reported. Regulatory authorities have been notified but treating neurologists need to be aware of this rare occurrence.

P212
Consistency vs. switching triptan treatment and headache-related disability: Results of the American migraine prevalence & prevention study

Introduction: To quantify changes in headache-related disability for migraineurs who switched from a triptan to another acute treatment in a population-based sample.

Methods: AMPP study surveys were mailed to a sample of 24,000 persons with “severe headache” identified in 2004 and followed annually through 2009. Eligible subjects had ICHD-2 migraine, reported triptan use one year and medication data in the subsequent year (a couplet). We examined 4 patterns: a) consistent triptan use, b) switching to another triptan, c) switching to an opioid/barbiturate, or d) switching to a NSAID. Change in disability was measured with MIDAS change from the second to the first year (negative change scores reflect reduction in disability).

Results: 146 respondents met inclusion criteria and reported a switch pattern of interest. Mean MIDAS change in the consistent triptan use group was -7.4. For those switching to another triptan the mean change was -3.5 (NS difference between groups; b=4.0, p=0.23). For those switching to an opioid or barbiturate the mean change was 3.4 (NS difference compared to consistent group; b=-10.9, p=0.079). For those switching to an NSAID, the mean change was 10.3, reflecting significantly higher disability (b=17.7, p=0.002), particularly among those with HFEM/C.

Conclusion: Switching from a triptan to another acute medication may be an indicator of unmet treatment need.

References:
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P213
Prophylactic treatments of migraine and GPs in the north of France: evaluation of practices

Introduction: Prophylactic treatments of migraine are an important part of the management of the disease. Only one survey concerning this topic
was performed in 2000 in France among GPs. This survey was however performed before the French migraine guidelines with a large use of dihydroergotamine at this time.

**Purpose:** To evaluate the practices of GPS in the North of France concerning the prophylactic treatments of migraine management and to compare them with the French Guidelines.

**Methods:** A self-administered questionnaire concerning prophylactic treatments of migraine was mailed in 2011 to 307 GPs in two big cities in the North of France (Lille and Roubaix). We analysed the data and compared them with the French Guidelines.

**Results:** 142 GPs answered to the questionnaire (46.2 %), 85% of GPs use prophylactic treatments of migraine when the patient has 4 to 5 migraine attacks per month. The first line treatment are beta-blockers (BB) (60%). The first objective is to reduce the migraine attacks frequency by 50% at 3 months for 53% of the GPs and the second to increase the quality of life in 45%. 59% of GPs prescribe prophylactic treatment of migraine for a 6-12 months duration.

**Discussion:** GPS in the North of France take into account the bad quality of life of migrants to start a prophylactic treatment. They use in majority the recommended prophylactic treatments of migraine and during a correct duration according the French Guidelines.

**Conclusion:** There is a dramatic increase since 2000 of the use of BB in France as first line prophylactic treatment of migraine. French guidelines of migraine seems to be useful for GPs.

**References**

**P214**

Adding acute treatments for patients on triptans: Results of the American Migraine Prevalence & Prevention (AMPP) study

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**Background:** Augmenting a triptan regimen with another acute medication may be an indicator of suboptimal treatment.

**Objectives:** To quantify changes in headache-related disability for migraineurs who added an acute treatment to an existing triptan regimen in a population-based sample.

**Methods:** AMPP study surveys were mailed to a sample of 24,000 persons with “severe headache” identified in 2004 and followed annually through 2009. Eligible subjects had ICHD-2 migraine treated with a triptan one year and data in the subsequent year (a couplet). We examined 4 patterns of treatment: (a) consistent triptan treatment, (b) adding another triptan, (c) adding an opioid or barbiturate or (d) adding an NSAID. Change in disability was measured by MIDAS from the second to the first year (negative change scores reflect improvement). Change scores were modeled via ANOVA for all couplets and for a 3 average headache-day frequency strata: low (0-4 days/month), moderate (5-9 days/month), and high frequency episodic/chronic migraine ([HFEM/C]≥10 days/month). ANOVAs were estimated for each possible adding pattern relative to the consistent triptan use group. The values of (b) represent change in MIDAS score.

**Results:** 327 respondents met inclusion criteria and reported an add pattern of interest. Adding another triptan was significantly associated with increased headache-related disability (b=10.4, p=0.01) over one year, as was adding an NSAID. The NSAID effect was greatest in those with HFEM/C compared to those with 0-4 days/month (b=24.1, p=0.03), and even greater for those with HFEM/C compared to 5-9 days/month (b=29.3, p=0.02). Adding an opioid or barbiturate was not significantly associated with changes in disability.

**Conclusion:** Adding an opioid or barbiturate was not associated with significant change in headache-related disability; however, adding a triptan or an NSAID was associated with increased disability. The effects for NSAIDs were greatest among the HFEM/C group. Improvement in options for migraine management is needed, especially for persons with high frequency headache.

**P215**

Zonisamide is effective in the preventive therapy of chronic migraine

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**Introduction:** Topiramate is the only approved oral preventive drug for chronic migraine (CM). However, we usually use other preventive drugs of prevention of frequent episodic migraine. Zonisamide is a neuromodulator that has showed efficacy in prevention of CM.

**Objectives:** To evaluate the efficacy of zonisamide after three months of therapy in CM patients (IHS-2006 criteria) that present inefficacy/ intolerance/contraindication to topiramate, sodium valproate, â-blockers and flunarizine.

**Methods:** Doses ZNS: 50-200mg. Primary end-point: Number of migraine days-NMD: Ineffective response-Inef(reduction of days<50%), good-G(50-75%), excellent-Exc(>75%). Secondary end-points: number of migraine episodes-NME; number of headache-days-NHD; drug overdose; consumption of triptans and NSAIDs; EVA and MIDAS score, effective mean dose of ZNS, adverse events.

**Results:** We prospectively included 27 patients (May 2011-May 2012), 85.2% women. Twelve patients (44.4%) presented 16 adverse events (100% mild). Four of them-14.8% left the therapy. NMD, in the 23 patients who finished the three months follow-up, was Exc-39.1%, G-43.5%, and Inef-17.4%; NME was Exc-30.4%, G-43.5%, and Inef-26.1%; and NHD was Exc-34.8%, G-39.1%, and Inef-26.1%. Drug overdose disappeared in 47.8% of overusers. The consumption of triptans and NSAIDs decreased 54.3%, and 65.7%. The EVA score decreased 3.7 points (36.2%), and MIDAS scale score decreased 14.6 points (48.7%). Effective mean doses of ZNS: 106.6mg/night.

**Conclusion:** Zonisamide presents a good profile of efficacy (70.3% of responses) and an acceptable tolerance. It could be a useful therapeutic option in CM patients intolerants, refractory, or with contraindications for topiramate, and the other drugs preventive drugs of migraine.

**References**

**P216**

Real-world economic impact of onabotulinumtoxinA in patients with chronic migraine

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**Introduction:** Compared to episodic migraine, chronic migraine (CM) is associated with greater disability, worse quality of life, and higher costs related to healthcare resource use (HRU). OnabotulinumtoxinA can be used effectively for headache prophylaxis in CM patients with CM, but the effect of treatment on HRU is unknown.

**Objectives:** Quantify the reduction in migraine-related HRU among CM patients treated for 6 months with onabotulinumtoxinA.

**Methods:** We analyzed data from 223 CM patients who presented to a university-based headache specialty clinic in Birmingham, AL between January 2007 and April 2011 and who were treated with 2 cycles of onabotulinumtoxinA (155-195U per cycle). Frequencies of migraine-related hospitalization and utilization of emergency departments (EDs) or urgent
care centers for acute migraine treatment over the 6 months preceding initial treatment with onabotulinumtoxinA were collected retrospectively. Migraine-related HRU data following initial treatment were recorded prospectively. Change in HRU after onabotulinumtoxinA was assessed using paired student’s t-test with α=0.05. Costs of treatment and HRU were based on the 2011 Medicare physician fee schedule and publicly available national ED and hospital costs (HCUP.net). The cost of an urgent care visit was approximated to be 1/4 the cost of an ED visit. The estimated cost for two cycles of onabotulinumtoxinA therapy (including physician administration fee and two 100U vials, to account for wastage) was $2601.

Results: Patients demonstrated a mean reduction of 0.92 ED visits (p=0.001), 0.33 urgent care visits (p<0.001), and 0.11 hospitalizations (p=0.003) following initiation of treatment; application of conservative national estimates for related costs yielded a reduction of $1025 per patient. The reduction in HRU offset 39% of the estimated cost for 6 months of onabotulinumtoxinA.

Conclusions: A reasonable proportion of the cost of onabotulinumtoxinA. A treatment for CM may be offset by a reduction in migraine-related ED visits, hospitalizations, and urgent care visits. Support: Allergan, Inc.

**P217**

**Nitric oxide synthase, Calcitonin Gene-Related Peptide and inflammatory mechanisms are involved in GTN induced neuronal activation**

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**Introduction and objective:** Infusion of glyceryl trinitrate (GTN), a nitric oxide (NO) donor in awake freely moving rats closely mimics a universally accepted human model of migraine and responds to sumatriptan treatment [12]. Here we analyse the effect of nitric oxide synthase (NOS) and calcitonin gene-related peptide (CGRP) systems on the GTN induced neuronal activation in this model.

**Methods:** The femoral vein was catheterized and rat allowed recovering for ten days before infusion of GTN (4 μg/kg/min, for 20 min, i.v.). Immunohistochemistry was used to measure Fos, nNOS and CGRP protein expression. Western blot was done to re-confirm the nNOS expression. Olcegepant (1 mg/kg) for 3 mins was given both as a pre-treatment and post treatment to analyse its effect on Fos activation. The response to pre-treatment with L-NAME (40 mg/kg) and NK-1 antagonist, L-733060 (1mg/kg) was also measured at the activation level.

**Results:** GTN treated rats showed a significant increase of nNOS and CGRP in dura and CGRP in trigeminal nucleus caudalis (TNC). Upregulation of the nociceptive marker Fos was observed in TNC at 2 and 4 hrs after the infusion. The activation at 4 hrs was inhibited by pre-treatment with olcegepant. However, post treatment with olcegepant could not inhibit this activation. Pre-treatment with L-NAME and L-733060 also significantly inhibited the GTN induced Fos expression.

**Conclusion:** The present study indicates that inhibition of CGRP, NOS and inflammatory systems all block GTN induced neuronal activation. These findings also predict that pre-treatment with olcegepant may be a better option than post-treatment to study inhibitory effect on GTN migraine models.

**References**


**P218**

**High frequency headache prevalence and management in primary care. A survey among general practitioners of the Liege area, Belgium**

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**Introduction:** Headache is among the most frequent neurolologic symptoms that lead patients to consult a general practitioner (GP). High frequency headaches (HFH) are very disabling and their management can be a real challenge even for a neurologist, which is likely due to CNS changes occurring with chronic headache and to frequent comorbidities. FHF patients need a multimodal therapeutic approach that is quasi non-existing in Belgium.

**Objectives:** The aim of this survey was to determine the prevalence and management of patients with FHF (min 2 headache days/week) in a cohort of general practitioners in order to evaluate the need and necessary resources for a ‘Centre for Integrated Multimodal Treatment of Chronic Headaches’ (CIMIC) in Liege.

**Methods:** A short questionnaire (10 questions) was distributed to 250 GPs of the Liege area (population: 616 491) with the help of the representatives of a pharmaceutical company.

**Results:** The responder rate was 26% only (N=65). In the last 2 months most GPs examined 1 to 50 patients with FHF. Eighty percent of these FHF patients were also followed by a neurologist, 16.9% consulted a headache specialist and 23% a pain clinic. The majority of GPs (86.1%) reported that at least 50% of their FHF patients had acute medication overuse (>2 tablets/week). About 50% of FHF patients were considered by their GP to be depressed but a minority had other chronic pain disorders. Interestingly, few patients (0-25% on average) had a multimodal headache management (for example a preventive drug treatment combined with behavioural therapy) and most FHF patients were dissatisfied with their current headache management.

**Conclusions:** This short survey among GPs practicing in the Liege area confirms that high frequency headache patients are not rare and in need of improved management, in spite of the fact that many of them are followed by a neurologist. Indeed, most of them are dissatisfied with current care, have acute drug overuse (which is a known aggravating factor for headaches), and are depressed. These patients are likely to benefit from integrated care with multimodal management in a centre like CIMIC. Unfortunately, the low participation rate might reflect the lack of interest and/or time GPs have for chronic headache sufferers. Acknowledgements The authors thank the medical representatives of Grunenthal for the delivery of the questionnaires to GPs.
the ponderous increase, a common side effect among prophylactic migraine treatments.  

Conflict of interest: none.  

References  

**P220**  
Changes in clinical migraine picture and in headache frequency in adolescence. Three year prospective study  
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Background: The clinical picture of migraine in children was different from that in adolescents. The objective of the study was to examine factors which might contribute to an increase or decrease in headache frequency from the age of 13-16 years old. We compared the clinical findings at the first consultation at the age 13, and finally at the age of 16 years.  

Patients and methods: A population –based prospective study comprising a screening questionnaire at the age of 13 (n=717, response rate – 81%) by interview and clinical examination of randomly selected 182 children from migraine headache and adolescents with no headache. The patients followed in a Outpatients Pediatric Neurology Clinic between January 2009 and December 2011. Finally, at the age of 16 years, 132 (73%)/182 adolescents could be re-examined. We checked the male/female ratio, side of the pain, nature of the pain, vertigo and/or dizziness and daily appearance of attacks.  

Results: The ratio of males was 43.2% and 34.1% in that order. Unilaterality of the headaches was 56.6% and 73.2%, respectively. Pulsating quality was 36.4% and 47.3%. Vertigo and/or dizziness associated with headache were 10.2% and 8.6%, and morning dominant attack cases 26.1% and 14.3%, respectively. Headaches increased clinically significantly in 22% (29% of girls and 14% of boys) and decreased in 17% (12% of girls and 23 % of boys).  

Conclusion: The present study revealed that the clinical picture of migraine in childhood and adolescents gradually changing to that for adults with aging. There are no reports on the correlation between the clinical picture and aging. Headache of migraine increases in girls, but decreases in boys in adolescence.

**P221**  
First demonstration of the neuroimmune link in humans using IV Endotoxin and Intradermal Capsaicin in the face and arm  
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Introduction: Animal studies convincingly show that glial activation through immune stimulation has an important role in pain generation and maintenance[1]. However demonstration of whether this pathway is relevant in humans is lacking.  

Objectives: 1) to determine whether low-dose intravenous endotoxin in healthy volunteers alters baseline pain sensitivity 2) to determine whether low-dose intravenous endotoxin in healthy volunteers enhances the response to intradermal capsaicin in the forehead and forearm.  

Methods: Study 1. 9 healthy volunteers (6M) received 0.2 ng/kg intravenous endotoxin or saline placebo in a two-way crossover study with assessments of cutaneous hyperalgesia (von Frey hairs) and allodynia (brush) as well as thermal pain thresholds and cold pain test. Study 2. 12 healthy male volunteers received 0.4 ng/kg intravenous endotoxin or saline on placebo in a two-way crossover study and received 50µg id capsaicin at 2 or 3.5 hours with assessments of flare, spontaneous pain, area of hyperalgesia and allodynia for 1 hour post injection. Core body temperature was assessed by Vitalsense capsule, standard haematology performed and circulating cytokines TNFα, IL-1β, IL-6,10 measured. Peak and area under the curve (AUC) were analysed by mixed effects modelling (study 2).  

Results: In study 1, despite a rise in core temperature and changes in circulating neutrophils and lymphocytes, there was no change in pain sensitivity except a reduction in cold pain tolerance following endotoxin (p=0.045). In study 2, endotoxin enhanced the peak and AUC of allodynia (p=0.005 and .02), hyperalgesia (p=.04 and .05) and flare (p=.0005 and .001) and AUC of pain (p=.05) at the forehead and enhanced peak and AUC flare in the forearm (p=.03 and.04).  

Conclusion: Low dose intravenous endotoxin, a TLR4 receptor agonist on immune cells enhances the objective and subjective response to neurogenic-like stimulus with greater sensitivity on the face compared to the arm. This model is suitable for screening for new immune directed analgesics, including for headache.  

Reference  

**P222**  
Post market pilot programme with single pulse transcranial magnetic stimulation (sTMS) for acute treatment of migraine: SpringTMS™ use in migraine  
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Introduction: Some patients suffer disabling, frequent migraine without effective treatment as current pharmacological options are either contra-indicated, poorly tolerated or overused. A post market pilot programme with the sTMS device was initiated for patients with migraine.  

Aims and objectives: To evaluate patient response to sTMS in an open outpatient setting - To assess the impact of treating migraine attacks with single pulse sTMS on pain and associated migraine symptoms over an extended period (minimum three months) - Understand patient support and educational needs for using sTMS - Assist patients in establishing an optimal sTMS treatment scheme for their migraine patterns - Review options for sTMS within the UK headache care pathway.  

Methods: Clinicians selected patients and prescribed the device. Patients subsequently received the device to use for a minimum period of three months. A clinical liaison had first contact with the patient to discuss treatment and use. Monthly telephone reviews were conducted to support and monitor the patients’ treatment and progress. Survey data was collected monthly over the treatment period. The patients’ progress with treatment was reported to their clinician.  

Results: Sixty-one patients have been prescribed sTMS from which 37 (61%) have been using the device for a minimum of three months and completed surveys. A reduction or alleviation of pain was reported by 73%. Assessed symptoms were improved in 62% of patients or for some, did not develop. A reduction in the number of headache days was reported by 53%. When using the combination of sTMS and a medicine, 30% reported no headache recurrence. Quality of sleep improved in 17%. The treatment was well tolerated with no adverse events reported. Conclusion: The sTMS device is a new and effective acute migraine treatment. This CE marked device is safe to use in clinical practice and has reliable, reproducible effects on migraine over time.

**P223**  
LB07 Role of Psychiatric disorders in association of headache and temporomandibular disorders  
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Introduction: Temporomandibular Joint Disorders(TMD) is a heterogeneous group of symptoms with a multifactorial etiology, affecting 5-7% of general population. Its association with migraine has long been discussed [1], but exact relationship between these two diseases is not clear yet [2]. It is well known that depression and anxiety are common in both TMD and HA patients, so we hypothesized that headache patients with anxiety and
In this case-control study, cases consisted of 65 migraine patients (13 Male, 52 Female) referred to Neurology clinic and 52 healthy controls (14 Male, 38 Female) referring to dental school were matched with them. Migraine patients were classified according to 2nd edition of International Classification for Headache Disorders (ICHD-II). We examined signs and symptoms of TMD using RDC/TMD (Research Diagnostic Criteria for Temporomandibular Disorders) and HADS-14 (Hospital Anxiety and depression Scale) was used to screen anxiety and depression, stratification was performed on the basis of depression and anxiety with cut-off score of 7, and scores more than 7 were considered anxious and/or depressed. Data were analyzed by chi-square test with a significance level of 5% and Odds Ratio (OR) test with a 95% Confidence Interval (CI).

**Results:** In anxious group, migraine patients had a seven times risk of headache compared to non-anxious group, such a relationship was not found between headache and TMD (chi-square test, p=0.05). In depressed group, OR for TMD in migraine patients in contrast to controls was 8.5 (95% CI: 2.5-28, p=0.001), this relationship was also true for non-depressed group with the OR of 3.6 (95% CI: 1.1-11.6, p<0.001).

**Conclusions:** Migraine patients with high level of anxiety seem to have a bigger chance of developing TMD, while high level of depression doesn’t seem to have such an effect. Anxiety should be considered while treating migraine patients with signs of TMD.

**References**


P224 PEI imaging in healthy subjects and migraineurs suggests CGRP receptor antagonists do not have to act centrally to achieve clinical efficacy

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Calcitonin gene-related peptide (CGRP) is a potent vasodilator and sensory neuropeptide implicated in the pathophysiology of migraine headache. CGRP-R antagonists, including telcagepant, have shown clinical efficacy in treating migraine. CGRP-Rs are expressed in the CNS, particularly in the brainstem and cerebellum as well as in the periphery on vascular smooth muscle cells. To investigate whether central CGRP-Rs were likely to be involved in the anti-migraine effects of CGRP-R antagonists we examined central CGRP-R occupancy (CGRP RO) at an efficacious dose of telcagepant in healthy volunteers and in migraineurs during ictal and interictal periods using the novel PET tracer [11C]MK-4232. CGRP RO was evaluated in healthy subjects (n=3) at the lowest clinically efficacious dose (140 mg, PO) of telcagepant ~2h after dosing, coinciding with the time point of efficacy evaluation in clinical migraine studies; PET imaging showed only low CGRP RO (4% - 10%) which is within test-retest variability, suggesting no activity in the CNS. In addition, we examined a CGRP-R agonist activity in healthy volunteers, suggesting similar low RO and no significant differences between states. In conclusion, PET studies with the CGRP-R PET tracer [11C]MK-4232 after therapeutic doses of telcagepant in healthy volunteers and migraineurs suggest that central antagonism of CGRP-R is not necessary for therapeutic efficacy in migraine pain relief and that migraine pain is therefore at least in part peripheral in origin.

**Reference**


P225 Facial spasm and headaches: should we call it “IIH-Spasmod syndrome”? S Muzerengi 1, C Moor 2, M Davies

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The Journal of Headache and Pain 2013, 14(Suppl 1):P225

**Introduction:** Idiopathic intracranial hypertension (IIH) typically manifests with headaches and visual disturbance. Unusual presenting features of IIH are sometimes described. Hemi facial spasm (HFS) in women has an incidence of 0.81 per 100,000 compared to an IIH incidence rate of 3.5-20 per 100,000. We describe the 4th case of HFS induced by IIH and we propose a new nomenclature.

**Case:** We present a case of a 33 year old right handed woman with sequential new onset headache causing secondary HFS. Neurological examination revealed bilateral papilloedema and confirmed right sided facial spasms. Cerebrospinal fluid examination showed an opening pressure of 33cm H2O and normal CSF constituents. High resolution brain MRI and MRV were normal including no evidence of neurovascular compression in the cerebello-pontine angle. EEG was entirely normal. The headache and HFS resolved after lowering CSF pressure. At three months post lumbar puncture she remained asymptomatic with no further episodes of HFS. Conclusion: There are only three prior cases of IIH associated with HFS in the published literature. We describe a further case of a very rare clinical manifestation of IIH and propose a possible pathophysiological mechanism and a new name for this entity “IIH-Spasmod syndrome”.

**References**


P226 In-patient/out-patient detoxication is highly effective in Medication Overuse Headache: report from a multicentric, multinational study C Tasorelli 1, R Jensen 2, M Alena 3, R De Icco 4, Z Katsarava 5, M Lainez 6, JA Leston 7, R Fadic 8, G Nappi 9

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**Introduction:** Medication overuse headache (MOH) is a common and disabling disorder, potentially treatable but with a high rate of early relapse. Detoxification from the overused drug(s) is rationally and ethically considered as the first and main step in the management of MOH patients, however consensus protocols as well as multicenter studies confirming the efficacy of detoxification are lacking in the literature. The aim is to propose and test on large population a consensus protocol for managing MOH.

**Methods:** A consensus protocol for the management of MOH was devised by an expert group. The protocol was based on consolidated clinical expertise and publication records of the members of the group and it foresaw in-patient and/or out-patient detoxication associated with pharmacological treatment and regular follow-up visits over a period of 6 months. The protocol was tested in 6 Centres from Europe and Latin America, which enrolled a total of 387 MOH subjects (313 F, 74 M).
Results: A marked reduction was observed in both outcome measures was observed already during the first month and tended to improve over the following months. Headache days/month: Baseline 23.2, M 13.7, M 12.2, M 10.6, M 10.3, M 10.2 (p<0.001 at all time points vs Baseline). Numbers of days of drug intake/ month: Baseline 23.2, M 11.0, M 12.0, M 9.7, M 9.4, M 9.5, M 8.9, M 6.9 (p<0.001 at all time points vs Baseline). Notably, out-patient detoxification was also effective, performing a little less than in-patient detoxification only at M1 in the two outcome measures considered (Days of headache: in-patients 12.0, out-patients 14.7, p<0.03 days of intake: in-patients 7.3, out-patients 12.6, p<0.001).

Conclusion: The proposed protocol proved effective in reducing headache days and days of symptomatic drug intake in a large population of MOH sufferers distributed in different clinical and geographical settings. These findings confirm the efficacy and the usability worldwide of a consensus protocol for MOH management.

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P227 Disability caused by medication-overuse headache can be considerably reduced by detoxification. Results from multinational COMOESTAS study
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The Journal of Headache and Pain 2013, Volume 14 Suppl 1 P227

Introduction: Medication overuse headache (MOH) is a common, disabling and costly disease that it is potentially treatable. Several studies have demonstrated significant reductions in headache frequency after detoxification. From the patients perspective, the effect on disability, anxiety and depression is often equally important. This has been less often examined and mainly in single centre studies.

Objectives: To investigate whether headache-related disability, depression and anxiety can be reduced by detoxification. Methods Patients with MOH were included from 6 centres in South America and Europe. Before and 6 months after detoxification, the degree of disability was measured by the Migraine Disability Assessment (MIDAS) score, while anxiety and depression were measured by the Hospital Anxiety and Depression Scale (HADS).

Results: A total of 692 patients with MOH were included of which 519 completed the study. Headache days were reduced from 23.6 to 9.8 per month (p<0.001). The MIDAS score was reduced from baseline 59.8 to 25.5 at 6 months after detoxification (p<0.001). HADS depression score was reduced from 6.6 to 4.1, while HADS anxiety score was reduced from 9.3 to 7.1 (both p<0.001).

Conclusion: Disability, depression and anxiety were considerably reduced in patients with MOH by detoxification. This emphasizes the urgent need for increased awareness about avoiding overdose of headache medications both among the public and professionals and demonstrates that not only headache frequency but also quality of life are remarkably improved by detoxification.

Conflict of interests: None.

P228
MRI compatibility of the Autonomic Technologies Inc (ATI) SPG Neurostimulator – New Treatment for Cluster Headache (CH)
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Introduction: The ATI SPG Neurostimulator is designed to be implanted in the mid-face anatomy and to electrically stimulate the SPG. The results from the multicenter European Pathway CH-1 study indicate that patient-controlled SPG stimulation provides statistically significant CH pain relief and is also associated with a reduction in CH frequency.

Methods: MR safety testing was performed according to ASTM standards governing force, torque, image artifact, and RF heating. The SPG Neurostimulator has a mass of 1.5 grams, a thickness of less than 5mm, and is available in four lengths. All four lengths were used during RF heating and image artifact testing in both 1.5T and 3T MRI environments. Force and torque were measured using the longest Neurostimulator in a 3T environment, which represents the worst case scenario.

Results: The maximum mean force generated (for both displacement and torque) was 6.7 grams-force, which is less than the mass of a 50 euro cent coin. Once anchored in the anatomy, the SPG Neurostimulator would require forces and torques an order of magnitude greater than those generated from the 3T MR field before displacement could occur. Diagnostic MR imaging near the implant location is affected by image artifacts extending 40mm from the SPG Neurostimulator, including the integral lead, with a spin and gradient echo pulse sequence. The shape of the distortion varied in all three planes, but the magnitude of distortion was similar. A temperature rise of 0.5°C and 2.4°C at a whole body average specific absorption rate (SAR) of ≤ 2 W/kg was measured at the SPG Neurostimulator in a 1.5T and 3T environment, respectively. The ATI SPG Neurostimulator has also been successfully imaged in multiple patients without any apparent side effects.

Conclusions: Results from this testing has enabled the ATI SPG Neurostimulator to be labeled as MR conditional in the European Union, and is currently the only whole body MR conditional CE marked neurostimulator available.

Conflict of interest: All authors are employees of Autonomic Technologies, Inc.

P229
Headaches in the elderly, in an out-patient population over 60 years of age
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Headache in community-living adults age 65 and older is the 10th most common reported symptom in women and the 14th most common in men. Although the prevalence of migraine declines with age, approximately 10% of women and 3% of men aged 70 experience severe recurrent or constant headaches. Much less is known about the evolving clinical profile of migraine over the life span. The present study aimed to investigate every type of headaches in elderly people and was carried out on a group of patient over 60 years of age, selected from 771 consecutive patients to the Headache Centre in the period January 2011-December 2011.

Methods: This study was conducted in a university-based outpatient headache clinic. The study population consisted of 771 consecutive headache patients treated by the authors in one year. Variables studied included gender, headache duration in years, aura, headache characteristics, associated symptoms, presence of allodynia, headache frequency, headache days, and disability. Amedical history of these patients was also recorded. The headache diagnosis were made according to ICHD-2 criteria. Patients were stratified by age into 3 groups: group 1, 16 to 39, group 2, 40 to 59, and group III, 60 years and older.

Results: A total of 605 patients were female and 166 were male, mean age was 36.9 ± 13.6 years (range 16 to 84), average headache duration 18.4 years, and headache days/month 7.9. The average age of older headache sufferers was 66.5 years. There were 48 female patients (7.9%) and 6 male patients (3.6%) in the older age group. There were no differences between these groups in gender and other characteristics. The 60+ age group tended to have more chronic migraine and to use more acute medication. Discussion In our population chronic migraine and medication overuse don’t decline over time. We found that, compared with younger patients, older headache patients had not a “lesser migraine” as reported in previous studies. Studies of community-based headache population are warranted to define the influence of age on the full spectrum of migraine.
P230
Treatment of hemicrania continua by non-invasive vagus nerve stimulation in 2 patients previously treated with occipital nerve stimulation
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Introduction: Hemicrania Continua is an indomethacin sensitive chronic primary headache syndrome consisting of constant unilateral pain with severe cranial autonomic exacerbations. Long-term indomethacin use can be associated with side effects, resulting in discontinuation of the drug in some patients. Current neuromodulation approaches to treatment, including occipital nerve stimulation (ONS), all require surgical implantation. A novel alternative treatment for this disorder is therefore needed.
We assessed the usefulness of a new non-invasive, portable vagus nerve stimulation (VNS) device, the GammaCore, in two patients who were unable to take indomethacin. Both had previously responded to ONS with the Bion implant1, but had subsequently had it explanted.
Results: Patient 1 (male, 61) had been using the device both prophylactically and acutely for 24 weeks at last follow up, with an overall improvement in his baseline condition, estimating a 30% improvement in background pain and 20% improvement in painful autonomic exacerbations. Acutely the device was able to abort exacerbations within 15 minutes most of the time, and it significantly improved the pain for the remainder of attacks. He felt satisfied with the device, although did not feel it was as helpful as the Bion implant. Patient 2 (female, 56) had been using the device following an exclusively prophylactic regimen for 32 weeks at last follow up, with an overall improvement in her baseline condition, estimating a 75% improvement in both background pain and painful autonomic exacerbations. She felt very satisfied with the device and felt it to be superior to the Bion implant.
Both would recommend non-invasive VNS to other patients.
Conclusions: This is the first evaluation of an entirely new treatment modality for cluster headache. We have developed a paradigm that appears to be well-tolerated and effective in both the acute and preventive treatment of episodic and chronic cluster headache. These preliminary findings suggest a formal clinical trial is warranted to further establish the efficacy of this treatment.
Conflict of interest: This work was supported by an unrestricted grant from ElectroCore Medical, LLC.

P231
Non-invasive vagus nerve stimulation for the treatment of cluster headache: a case series
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Introduction: Cluster headache is a highly disabling primary headache syndrome. A need exists for a novel, safe and practical approach to add to the current therapeutic armamentarium.
We assessed the usefulness of a new non-invasive, portable vagus nerve stimulation (VNS) device, the GammaCore, which has been developed for the treatment of headache.
Methods: Patients attending headache centres in the UK and Ireland were offered non-invasive VNS treatment in an unbiased fashion. Case notes were reviewed, and patients questioned during routine follow up about their experience with the device and the impact they perceived it had.
Results: Of patients given the device 14 of 17 (9 male; 7 chronic, all medically intractable, 7 episodic; median age 46, range 13-84) had sufficient data available during a median device use period of 13 weeks (range 2-26) to include in analysis. Thirteen felt there was an overall improvement in their condition since using the device, stating a mean estimated subjective improvement of 60% (SD 30) from baseline. One patient’s condition remained the same. Seven were able to reduce significantly or stop their previous abortive treatment, five had reduced it and two required the same amount as previously. Five were very satisfied, eight satisfied and one equivocally satisfied after using the device. All 14 would recommend the treatment to others.
Ad hoc analysis suggests that treatment can both abort and significantly improve attacks, as well as having secondary effects of reducing attack frequency when used prophylactically.
Conclusions: This is the first evaluation of an entirely new treatment modality for cluster headache. We have developed a paradigm that appears to be well-tolerated and effective in both the acute and preventive treatment of episodic and chronic cluster headache. These preliminary findings suggest a formal clinical trial is warranted to further establish the efficacy of this treatment.