Kynurenine pathway (KP), the quantitatively main branch of tryptophan metabolism, has long been considered a source of nicotinamide adenine dinucleotide, although several of its products, the so-called kynurenines, are endowed with the capacity to activate glutamate receptors, thus potentially influencing a large group of functions in the central nervous system (CNS). In fact, Kynurenic Acid and Quinolinic Acid are able to interact with ionotropic glutamate receptors and Cinnabarinic Acid has been reported as an orthosteric agonist of metabotropic glutamate receptors (mGlU4), and Xanthurenic Acid has been recently demonstrated to be a putative agonist of metabotropic glutamate receptors 2/3 (mGlU2/3). Moreover, 3-HK and 3-HANA have mainly been studied, since they have been shown to induce neurotoxic effects by increasing oxidative stress and the production of free radicals or through excitotoxicity. Migraine has a complex pathophysiology in which both central and peripheral components of the trigeminal pain pathway play a central role. The trigemino-vascular activation during the attack has largely been described, and recently the brainstem nuclei, called "migraine generators", have been reported to be involved in migraine. Moreover, a series of destabilizing events within the brain trigger a cortical spreading depression (CSD), responsible for the aura phenomena and for trigeminal activation. The role of glutamate is heavily supported both in the trigemino-vascular as well as in brainstem nuclei activation, and furthermore in the CSD initiation and propagation. Some of the KP metabolites able to interact both with ionotropic and metabotropic glutamate receptors might be involved in migraine pathophysiology. Despite the large number of studies conducted on migraine etiopathology, the KP has only been recently linked to this disease. Nonetheless, some evidence suggests an intriguing role for some kynurenines, and an exploratory study on the serum kynurenine levels has been helpful to better understand possible alterations of the kynurenine pathway in patients suffering from migraine.

When defining the burden of migraine it is important to consider patients’ disability and clinical and public health perspectives. Migraine sufferers often have severe under recognized and underdiagnosed health burden and reductions in social activities and work capacity. Health professionals focus on diagnosis as a key element to effective treatments, however the majority of clinicians still tend to perceive migraine, and headache disorders in general, as minor complaints. Ten years ago a possible way to increase awareness and diminish the burden was described[1]. However epidemiological data of headache disorders, despite the international Lifting the Burden Campaign, is still scarce in many parts of the world and inconsistent because of the sampling frames and of how prevalence rates are defined and the physical, emotional, social and economic burdens of headaches are still poorly acknowledged. Uncertainty about the prevalence distribution reflects that there is still need of instruments for classifying migraine in a comparable manner across populations and that more studies must be undertaken to classify the disability due to the disorder using reliable outcome measures[2]. Estimation of needs for health services, their costs and effectiveness require indicators that go beyond measures of death rates or of diagnosis alone, and include the “functioning” of people. The biopsychosocial model of the WHO Classification of Functioning, Disability and Health (ICF) provides the model, as well as the classification system, that allows to measure all dimensions of functioning and disability[3]. More than ten years of research with ICF in migraine sufferers shows that it allows data comparability and the evaluation of the role of environment. According to ICF construct any health condition, in an unfavourable environment, can cause disability. Environmental barriers for migraine sufferers are lack of health care facilities, of accurate diagnosis, of drugs, but also difficulty in being taken seriously. Steiner[4] drew attention to the high number of people with disability due to headache who do not receive health care. The barriers responsible for this might vary throughout the world, but poor awareness of headache in a context of limited resources generally was still constantly among them. Describing and accounting the burden of migraine worldwide is not enough anymore, we need to change our paradigm again and to move towards new pathways. The opportunity is provided by the biopsychosocial approach of the ICF. To reduce the burden of millions of migraine and headache sufferers once we cannot change the disease, we should change the environment and global efforts should focus on the new development of drugs but mainly on improving the response of health care systems.

Conflict of interests: The authors certify that there is no actual or potential conflict of interest in relation to this article.

References
The impact of headache disorders is a problem of enormous proportions, both for the individual and the society. Medical literature has tried to assess its effects on individuals, by examining prevalence, distribution, attack frequency and duration, and headache-related disability, as well as effects on society, looking at the socio-economic burden of headache disorders. The issue of costs represents an important problem too, concerning both direct and indirect costs. Direct costs concern mainly expenses for drugs. Migraine has a considerable impact on functional capacity, resulting in disrupted social activities: many migraineurs do not seek medical attention because they have not been accurately diagnosed by a physician or do not use prescribed medication[1].

Indirect costs associated with reduced productivity represent a substantial proportion of the total cost of migraine as well. Migraine has a major impact on the working sector of the population, and therefore, determining the indirect costs outweighs the direct costs. This study will explain the notion of cost of illness, examining how it could be applied in such a framework. Then, an overview of the studies aimed at measuring direct and indirect costs of migraine and headache disorders will be carried out, later shifting on to the relationship between costs and quality of life for people affected by headache disorders.

As it has been seen, there are still many unresolved problems in disease costing, to the point that it still appears as a set of method that may lead to extremely different outcomes depending on the evaluation approach being used. Moreover, given the social relevance of migraine, together with the assessment of therapeutic options, it is important to increase the knowledge related to the economic consequences of prevention. From the analysis of prevalence, incidence, morbidity and the state of health caused by headache, it is important to stimulate the scientific community and policy makers to analyze the problems connected to the economic costs of headache. Costs of headache could be contained by observing their trends implementing specific “observatories”. Overall, the bottom-up approach, applied in the Eurolight study, would seem the preferable and most comprehensive method to assess the societal burden of headache. However, a crucial factor is the attainment of a higher participation to the survey.

Reference

Disability and quality of life in patients with different forms of migraine

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Background and state of the art: Migraine (M) is the seventh leading cause of years of life lost to disability (YLDs) worldwide, responsible for 2.9% of all YLDs, more than half of all YLDs attributable to neurological disorders[1]. Its negative effects result from several studies, particularly in surveys carried out by our research group, through the application of patient oriented outcome measures (PROMs), and in their development and validation[2-4]. Administration of MIDAS (a migraine-specific tool) demonstrated that: the disability level is rather high (particularly in chronic M); social, family and leisure activities are more impaired than work activities; days spent at work with reduced effectiveness are more than days of absence[3-5]. A better understanding of the pervasive impact of migraine has been achieved using the WHODAS 2.0, a questionnaire based on the International Classification of Functioning, which captures the interaction between the individual’s health status and the context of life. Our data, together with many results deriving from the application of quality of life tools (e.g., SF-36 and MSQ), showed that migraine influences physical and emotional domains, causes restriction and avoidance of activities also outside the headache episodes[6-11].

Measuring the impact of migraine: a relevant issue in different fields: Migraine has to be considered both as a clinical and as a public health problem: therefore, at least two perspectives need to be taken into account:

1. Epidemiological and healthcare perspectives: to evaluate the burden of migraine in the population, understand patients’ needs in implementing appropriate treatments and address healthcare interventions.
2. Clinical practice and research perspectives: to assess the severity of migraine in an individual patient, to better tailor treatment plans, and eventually to evaluate their global outcome, and to assess the efficacy of new treatments in RCTs and observational studies.

Concluding remarks and future directions: Migraine is a common condition, whose impact is not constant on individuals, in terms of personal suffering and reduced health, and on societies, in terms of reduced productivity and increased costs for the health system [7,8,12]. The systematic use of PROMs should be encouraged both in the clinical and in the research fields, particularly in RCTs to quantify the potential benefits of treatments. Further (ongoing) research is needed to understand the potential application of the different tools in the different contexts, as well as to develop new instruments to assess the qualitative aspects of migraine-related disability, particularly in the workplace.

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References
The use of diagnostic imaging in the evaluation of patients with headache is an almost mandatory step. Although there are specific conditions (the so-called red flags) indicating the need of diagnostic imaging, daily experience shows that a study of the brain and, often, of the intracranial vessels, is part of the routine of many of these patients. The most common and appropriate study is the MRI integrated with the angiographic evaluation (MRA). An MRI and MRA, properly performed, are able to exclude most of the organic pathologies potentially causing headaches, although all of these conditions is long and not useful in this context. It is important to remember that significant MRI changes are found in about 4% of patients with chronic headache but this percentage can rise up to 14% in the atypical forms. The MRI evaluation also allows to define whether the patients, especially the young ones, have a condition of brain signal alterations (multiple bright spots). Some studies reported that these are more frequent in patients with migraine especially with aura and mostly in females. The clinical significance and role of these changes remains to be proven. Another approach of imaging is related to the possibility of assessing, by means of functional studies, the pathophysiological moments responsible for the symptoms. These studies are based mainly on functional MRI which includes cerebral perfusion, cortical activation (induced or by means of resting state techniques) and metabolic studies with spectroscopy. The last approach is the one that assesses the consequences of long standing symptom analyzing morpho-volumetric brain “in toto” or inside the cerebral cortex. These are techniques like computed voxel based morphometry (VBM) or Free Surfer able to evaluate small volumetric changes between groups of healthy subjects and patients.

A6

Functional neuroimaging: the adaptive mechanisms in migraine

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Migraine is a common neurological disorder characterized by a primary brain dysfunction subtended by an episodic activation and sensitization of the trigemino-vascular pain pathway. Although migraine attacks are clinically well-defined, the underlying pathophysiology of the more complex migraine scenario is largely unknown. Functional brain changes, that occur because of repeated migraine attacks, may be explained through a maladaptive feedforward allostatic cascade model. The fundamental assumption is that “the brain is a central organ of stress” [1], able to detect stressful or potentially stressful situations and react in form of behavioural and/or physiologic responses. These brain responses, mediated by the autonomic nervous system and neuroendocrine mechanisms, could be either adaptive or maladaptive. In this context, allostatic is the ability to protect the body through adaptation [2]. Contrariwise, the allostatic load and overload, resulting from repeated stress and/or allostatics[3], refers to the wear and tear on the systems that normally support adaptation. Compelling evidence suggests that the brain of migraine patients is significantly different from healthy controls. Some of these differences are related to abnormal cortical activity during painful stimulations, suggesting an “adaptive” response observed in the course of moderate or high noxious trigeminal stimulations. Conversely, other differences relate to abnormality in responses that should be adaptive but become impaired or maladaptive, such as altered brainstem processing. More recently, a decreased functional connectivity was demonstrated within the fronto-parietal network (FPN) in patients with migraine without and with aura in the absence of clinically relevant executive deficits. FPN represents the neural substrate of executive functions and FPN functional abnormalities might be a part of a complex cascade that terminates in a migraine attack. Specifically, FPN functional connectivity changes could underlie a defective executive functioning in which high-demanding conditions cannot be correctly processed and solved by patients with migraine, escalating the brain adaptive response, likely resulting in a risk factor for headache attacks. In conclusion, we believe that in migraine an internal state of dysregulation creates an allostatic load with maladaptive consequences on brain, behaviour, physiological regulation and systemic physiology that progress in a feedforward cascade. Thus, we suggest that migraine should be considered a brain disease and not simply a recurrent acute pain syndrome.

References

A7

Genomics and epigenomics

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Migraine with (MA) and without aura (MO) is a common brain disorder that affects 15% of the general population. Genetic studies on twins have shown that MA and MO heritability spans between 50% and 60% [1]. Despite the high degree of heritability the genetic basis of MA and MO has not been elucidated and on the whole their etiology is far from being resolved. Several years ago it has been hypothesized that also epigenetic mechanisms such as DNA methylation, miRNA and histone modifications could play a relevant role in MA and MO. In particular epigenetic mechanisms have the potential to link early life events, neuro-inflammation and estrogen activities in the etiology of migraine and in its chronification [2] and pharmaco-epigenetics could be implicated in the wide spectra of different drug treatment responses [3]. In recent years the technologies for studying nucleic acids have literally exploded, opening to new possibilities for study of genetics and epigenetics of MA and MO [4]. One of the most significant results is the sharp cost decrease for the whole genome DNA sequencing, since the psychological threshold of 1000$ for a 30x genome is about to be achieved. This cost reduction is fostering a wealth of large sequencing campaigns that will allow overcoming all the limitations due to the poor knowledge of human genetic variability that has slowed the ability of identifying the genetic basis of all sporadic diseases including MA and MO [5].

The reduction of nucleic acids sequencing costs and the availability of cost effective microarray solutions for the analysis of DNA methylation has favored the implementation of epigenomic studies, in particular DNA methylation microarray has been thoroughly used providing new insight regarding the variability and the role of such epigenetic agent. DNA

metylation, miRNA and histone modifications have proven to be a potential source of powerful and robust biomarkers. Taken together both the new genetic and epigenetic omics approaches have the potential to provide new molecular insights in the etiology of MA and MO. Moreover, from such approaches we expect to obtain tools to improve migraine diagnosis, patient stratification, and therapy.

Conflict of Interest: None.

References

A8
Proteomic research of proteins involved in pain expression in an animal model of chronic pain
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Background: Pain is defined as an unpleasant sensory and emotional experience, associated with a real or potential tissue damage. Chronic pain can arise from tissue injuries or inflammation (inflammatory pain), or from lesions of the peripheral or central nervous system (neuropathic pain). The purpose of this study was to search proteins potentially involved in the expression or mediation of pain utilizing proteomic techniques, in an animal model of CP obtained by the ligation of the sciatic nerve.

Methods: The rats (Wistar) used in this study were divided into 4 groups: two control groups, one treated with saline and the other with Indomethacin (2 mg/kg for 3 consecutive weeks), and two groups with the ligation of the sciatic nerve[1], subjected to the same treatment. Initially, two behavioral tests ("Plantar test" and "Von Frey test") were carried out to confirm the presence of pain in operated animals. Subsequently, the proteomic analysis was performed on serum samples, first by one-dimensional protein separation (SDS-PAGE) and then by two-dimensional gel electrophoresis (2-DE). The differentially expressed proteins among the different groups were identified by mass spectrometry (ESI-Q-ToF/MS).

Results: The most significant result obtained by SDS-PAGE analysis was observed in the group of operated rats treated with saline, where the expression of 6 protein bands was significantly increased, compared to rats treated with Indomethacin. The 2-DE analysis confirmed these data and allowed to identify 6 additional different proteins, which included typical inflammatory proteins, antioxidant enzymes and proteins with neuroprotective function, implicated in the degeneration/regeneration of peripheral nerves (e.g., ApoE). Particularly, a prostaglandin with a pivotal role in central sensitization, involved in induction of hyperalgesia and cutaneous hyperesthesia, was identified. This protein was also detected in our previous study on medication-overuse headache (MOH) patients, where we found it significantly increased in urine of NSAIDs, mixture and triptans abusers, in respect to the healthy control group[2].

Conclusions: The presence of these proteins may be due to an attempt of functional recovery of the nerve and, at the same time, of pain reduction. For this reason, they could be a potential target for the understanding and treatment of peripheral neuropathy. These findings need to be validated by other experiments, such as using molecular biology techniques.

References

A9
Integrated OMICS tools for personalised medicine
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System-wide adoption of Personalised Healthcare requires an active and flexible but highly integrated infrastructure, joining many different competences and technologies and allowing continuous upgrading, also through self-learning processes. In this system, clinics and diagnostics would no longer be partitioned, according to a stepwise scheme, from other disciplines as basic science, information technologies, ethics and policies. Each player constitutes a node of a cabled network, where input and output from each node are automatically transferred to all nodes, to systematically retune and coordinate the global activity. Since 2005 the Sant’Andrea Hospital of Rome is an in-house built model of Personalised Healthcare Service, which auto-catalytically drives its own development, which may furnish good evidence that translation of Personalised Medicine into clinical practice is not so elusive. The interaction between usually distant academic departments and wards (as Biochemistry, Internal Medicine, Psychiatry, Oncology), favoured by a farsighted management of hospital resources by the administrators, allowed to create a shared, innovative laboratory, the Advanced Molecular Diagnostics Unit (DiMA). The availability of advanced technologies, as mass spectrometry and medium-to-high throughput DNA analysis paved the way to a “real-time” evaluation of the benefits brought into the “real-world” clinical practice by implementation of new diagnostics aimed to therapy tailoring. This allowed the start up of a health service based on the principles of personalised medicine, in order to optimize the amount of tests necessary to evaluate the patient, to interpret the results correctly and, finally, to plan a personalised therapy and to periodically evaluate and/or modify it, to obtain the best clinical results with the least side effects.

Our OMICS platform for personalised medicine offers the following combined approaches:

i) Epigenetics, to obtain information on the regulation of gene expression and to evaluate the methylation profile change during hypomethylation therapies;
ii) Functional genomics, to measure genetic expression in normal and pathologic conditions, in order to define genetic expression profiles;
iii) Structural genomics, which defines genomic differences with clinical impact in the patient populations;
iv) Metabolomics and therapeutic drug management, to define all molecules of interest in a specific clinical context and the actual drug and metabolite concentration during therapies.

The MIFAR (Metabolismo Integrato FARMaci – drug metabolism integration) including about 60 gene variants has been developed. The data interpretation is ruled out using the Charité Bioinformatic platform (Berlin DE) and allows adaptation of drug therapies to the individual MIFAR profile, improving efficacy and safety of treatments. The DiMA Unit provides pharmacogenomics and theranostics report for at least 5,000 patients/year.

References
A10  Migraine and functional connectivity: an innovative pathophysiological perspective

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Migraine is a chronic disorder of neuro-vascular origin, characterized by abnormal neuronal excitability and altered processing of multimodal stimuli. Methods able to detect subtle changes of EEG rhythms under painful stimulation may improve the knowledge of mechanisms of pain processing in normal subjects and patients with chronic pain syndromes. The study of the dynamical relationships between signals recorded at different scalp locations can help to confirm and formulate hypotheses on the physiological mechanisms related to stimuli processing. Correlations, spectral coherence and phase synchronization, which allow to understand the extent to which two variables are statistically connected or shared, influenced by a third variable, together with analyses of the directional aspects of these dynamical interactions, may potentially contribute to understanding the mechanism of pain processing in migraine. Functional and effective connectivity in terms of synchronization and information transfer were able to reveal differences in visual reactivity between migraine patients and controls, so these methods may presumably outline a different way to process nociceptive laser stimuli in migraine, giving further knowledge on how the cortex changes its inter-connections under painful inputs.

Thirty-one migraine without aura outpatients (MwoA) were evaluated and compared to 19 controls (CONT). The right hand was stimulated by laser. In the pre-stimulus phase, the vertex complex of averaged laser evoked responses (LEPs) showed reduced habituation compared to controls. In the post-stimulus phase, the same cortical areas were more connected in MwoA vs CONT. In the totality of patients and controls, the habituation index was negatively correlated with the Granger Causality scores.

A different pattern of cortical activation after painful stimulation was present in migraine. The increase in cortical connections during repetitive painful stimulation may subdue the phenomenon of LEPs reduced habituation.

Brain network analysis may give an aid in understanding subtle changes of pain processing under laser stimuli in migraine patients. Written informed consent to publication was obtained from the patient(s).
consequence of a genetic substrate. This chronic hyperexcitability may contribute to their susceptibility to develop recurrent pain attacks. In the chronic form of migraine, as well as in cluster headache during the active phase of the disease, the hypersensitivity of the pain system is related to a dysfunction in central supraspinal antinociceptive pathways modulating pain processing [2,4,5]. In migraineurs, a high frequency of migraine attacks coupled with an overexposure to symptomatic medication contributes to a further impairment in nociceptive control, leading to the progression from episodic to chronic form of migraine and medication-overuse headache. This hypothesis is supported by a recovery to a normal functioning of both the supraspinal antinociceptive system and pain sensitivity after withdrawal treatment or clinical improvement. In cluster headache, the state-dependent facilitation in pain processing is linked to a state-dependent defective supraspinal control of pain, which is normally operating during the remission phase of the disease. On these bases, an imbalance of excitatory and inhibitory systems supports the development of episodic, remittent and chronic pain conditions in subjects with a pro-nociceptive profile. Interestingly, a series of studies demonstrated morphologic and metabolic abnormalities in pain-related brain areas in subjects with chronic form of migraine and cluster headache. Our recent data have demonstrated that the facilitation in pain processing and the related defective supraspinal control of pain are linked to a dismodulation of the default mode network.

References

A13 Is lack of habituation a biomarker of migraine? A critical perspective
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Processing of sensory stimuli has been supposed to be dysfunctioning in migraine. A basis for such abnormality has been identified in a defective ability to habituate to repetitive sensory stimulation. Habituation, i.e. the way the nervous system attenuates response to repeated non noxious stimuli is a fundamental function of sensory systems, that allows appropriate adaptation of neural responses to the relevance of incoming stimuli. In humans, habituation can be studied by evoked potentials where it is indexed by a reduction of amplitude of the evoked response to repeated stimulation. After the first evidence by Schoenen et al in 1995 [1] of reduced habituation to visual evoked potentials in migraine the defect was confirmed in other studies, not only with visual stimuli, but also with other sensory modalities (acoustic, somatosensory) and even with nociceptive stimulation. For such a consistency lack of habituation has been considered a neurophysiological hallmark of the disease. However, critical aspects concerning this statement have been recently raised because the requirement for a disease hallmark appeared not to be met by lack of habituation [2,3]. A disease hallmark should be intrinsic to the pathophysiology of a disease and as such ubiquitous or quite so and specific for that disease. This however, does not seem to be the case for lack of habituation in migraine. Some authors indeed were not able to find defective habituation in this disease and recently relevant criticism about this dysfunction has been raised by the group of Sand and Omland [2]. These authors indeed applying a different methodological approach (with a blind procedure for both VEP recording and analysis) in a series of studies (exploring a wide range of stimulation parameters) were not able to replicate, at least for visual modality, the habituation defect and attributed this to a likely expectancy bias not adequately controlled in previous studies. Moreover, dysfunctions of habituation is not specific for migraine as it has been found in several other diseases ranging from chronic pain states, to deafferentation diseases like tinnitus, or different supraspinal pathologies like Parkinson’s disease. Thus, more than strictly related to migraine pathophysiology, lack of habituation could represent a more general marker of neural dysfunction that migraine can share with several other diseases.

References

A14 Controversies about the role of the deficit of habituation of evoked potentials in migraine: a disease biomarker? PROS
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In most studies, episodic migraineurs have an interictal habituation deficit of cortical evoked potentials to repeated monotonous stimuli. It has been found by applying almost every modality of sensory stimulation for evoked potentials (visual - VEP, auditory - AEP, somatosensory - SEP), as well as in visual evoked magnetoencephalographic (MEG) responses [1], thus it is considered as a biomarker of the interictal status, which normalises during the migraine attacks and cannot be found in chronic migraine. A reduced habituation deficit, however, was not confirmed in migraineurs in some studies [1], which was attributed to low reliability and repeatability [2,3], and to a reduced specificity to migraine pathophysiology.

Nonetheless, some studies that demonstrated an interictal deficit of cortical habituation were conducted blindly, both for VEP[4,5] and AEP [6]. Moreover, when the same VEP data were analysed independently by two investigators, one of them totally blinded to the diagnosis and the migraine state (ictal vs interictal), blinded and non-blinded analyses were strictly intraindividually correlated and both confirmed the presence of interictal deficit and ictal normalization of VEP habituation. Repeated intraindividual recordings were also strictly correlated, which suggests a good test repeatability [7].

The habituation deficit in VEP has been demonstrated up to now only in pediatric photosensitive epilepsy (which may share some cortical abnormalities with migraine) [8] and in healthy subjects with a high analytic score [9], suggested to be increased in migraineurs [10]. Although the latter may play a role in the habituation deficit found in migraineurs, it cannot explain its variations during the migraine cycle and its absence in chronic migraineurs. On the other hand it has been demonstrated that at least two different electrophysiological phenotypes may be found in migraineurs [11] and that the deficit of VEP habituation may be slightly different when the same tests are performed in different countries [12].

The discrepant findings in the literature can thus most likely not be explained by the presence or absence of blinding nor by low repeatability. Other methodological issues might be responsible, such as, for instance, online averaging - commonly used in the “negative” studies - that is associated with short interruptions of the visual stimulation, possibly allowing a recovery of habituation. Also, the recruitment of patients, usually performed in headache centers in the “positive” studies,
may have contributed to a better selection of patients. Alternatively, phenotypic and/or genotypic differences in cohorts of patients could result in different neurophysiologic patterns.

References


A15

Molecular bases of neurophysiologic dysfunctions in migraine
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In past years, several studies evidenced neurophysiologic dysfunctions in sporadic episodic (during both the ictal and the interictal period), and chronic migraine patients. These dysfunctions could reflect a genetic susceptibility that exposes patients to recurrence of migraine attacks. Recently, several studies were performed in order to explore the role of genetic polymorphisms on neurophysiologic dysfunctions that were already known to be related to migraine. These studies evidenced that neurophysiologic features, such as interictal habituation deficit and ictal response sensitization, are influenced by genetic polymorphisms involved in neural plasticity (brain derived neurotrophic factor (BDNF)), in vascular homeostasis (angiotensin converting enzyme [ACE] and methylenetetrahydrofolate reductase [MTHFR]), and in monoaminergic modulation (monoamine oxidase type A [MAO-A]). Moreover, we have recently found that a glutamatergic polymorphism, Glutamate receptor ionotropic AMPA 3 (GRIA3), already known to be related to central sensitization mechanism and then to migraine pathophysiology, can also influence neurophysiologic features of chronic migraine due to medication overuse.

The study of the influence of genetic polymorphisms on migraine-related neurophysiological dysfunctions could be regarded as an “in vivo” human experimental model in which the different genetic background could predict different neurophysiologic “endophenotypes”. This experimental model could lead to understand, for instance, the way different drugs act on migraine, or to unveil in which way some risk factors, such as for instance drug overuse, induce transformation from episodic to chronic migraine.

A16

Neurophysiologic peculiarities of pediatric primary headaches
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In spite of the high prevalence of primary headaches in pediatric age, most neurophysiologic studies in these diseases have concerned only adulthood. The neurophysiologic investigation of the pathophysiological mechanisms subtending migraines and tension-type headache in children and adolescents could be particularly interesting, since during the developmental age the migraineous phenotype is scarcely influenced by many environmental factors that can typically act on adult headache patients. Reduced habituation of evoked potential amplitude, that represents the neurophysiologic abnormality most frequently found in adult migraineurs, was confirmed also in migraine children, although it was shown to involve also children with tension-type headache. Some studies have shown abnormalities in the maturation of brain functions in migraine children and adolescents. While the visual system maturation is slowed in young migraineurs, the psychophysiological mechanisms subtending somatosensory spatial attention in migraine children are more similar to those of healthy adults than to those of age-matched controls. There are still some unexplored fields that will have to be subjects of future studies. In particular, the technique of transcranial magnetic stimulation, which has given an important contribution to our knowledge of primary headache pathophysiology in adults, has not yet been used in young migraineurs. It will possibly provide further elements about brain excitability in migraine children.

A17

Laser evoked potentials and central sensitization in migraine
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Migraine is a disabling disorder of neuro-vascular origin. An abnormal neuronal excitability, largely based on genetic nature, is a predisposing factor to attack onset. A reduced habituation to multimodal repetitive non nocebo stimuli was observed in migraine. The pattern of reduced habituation to nociceptive stimuli may favor the increase of pain and the phenomena of central sensitization. Central sensitization is a phenomenon of pain processing, which may predispose to chronic pain. Alloodynia occurring during migraine attack and persistent pericranial tenderness in migraine are symptoms of central sensitization [1,2]. CO2 laser evoked potentials (LEPs) have been used in migraine research, proving very useful in demonstrating functional abnormalities of the central nociceptive system which might be linked to the pathophysiological mechanisms of this disease. Abnormalities of pain processing seem to characterize children with migraine. Reduced habituation and progressive amplification of cortical responses under laser stimuli indicate an overactive nociceptive system just at the onset of migraine, which may subtend symptoms of central sensitization and allodynia and pericranial tenderness. An abnormal pattern of habituation to nociceptive stimuli may favor the increase of pain and the phenomena of central sensitization. Central sensitization is a phenomenon of pain processing, which may predispose to chronic pain. Alloodynia occurring during migraine attack and persistent pericranial tenderness in migraine are symptoms of central sensitization [1,2]. CO2 laser evoked potentials (LEPs) have been used in migraine research, proving very useful in demonstrating functional abnormalities of the central nociceptive system which might be linked to the pathophysiological mechanisms of this disease. Abnormalities of pain processing seem to characterize children with migraine. Reduced habituation and progressive amplification of cortical responses under laser stimuli indicate an overactive nociceptive system just at the onset of migraine, which may subtend symptoms of central sensitization and allodynia and pericranial tenderness. An abnormal pattern of habituation to nociceptive stimuli may favor the increase of pain and the phenomena of central sensitization.
aspects may guide therapeutic approach: in a recent work in which we explored the efficacy of botulinum toxin in the treatment of chronic migraine, we found a correlation of the clinical effect with an improvement of the LEPs habituation deficit. The modes of action of pharmacological or nonpharmacological interventions, such as neuromodulation methods, should therefore be reconsidered in terms of their ability to normalize the complex abnormalities of brain hyperresponsivity and the central sensitization phenomena.

References


A18

Non invasive neurostimulation
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Neurostimulation has been used in pain management for a long time. Several non-invasive neurostimulatory techniques were developed to manage headaches unresponsive to medical treatment, in particular for preventive treatment. Recently, novel non invasive neurostimulation approaches have been used successfully for different forms of headache: they represent a promising opportunity in headache management useful for acute and preventive treatment of migraine. Among the different non invasive approaches, transcutaneous supraorbital electrostimulation device (Cefaly), transcutaneous magnetic stimulation (TMS), transcranial electrical stimulation (tDCS), and non-invasive vagus nerve stimulation device (n VNS) have shown efficacy in a consistent number of pilot studies (lack of placebo condition). Vagus Nerve Stimulation (VNS) was a well known surgical procedure approved for treatment of refractory epilepsy and depression, with a peripheral mechanism of action. It has been used in selected intractable migraine cases if associated with comorbid depression, with promising results. A hand-held patient controlled non-invasive vagus nerve stimulation device (Gammacare) has been developed to treat migraine attack and has contributed to an easier treatment of migraine episodes. Goadsby et al reported significant results from treatment of migraine attacks by non-invasive transcutaneous vagal nerve stimulation in a population of 30 patients with a 2-hr pain-free rate of 22%. In our open-label, single arm, multiple attack, 27 patients, 18-65 years old, with a diagnosis of migraine without aura according to the IHS beta 2013 classification, with a high frequency, were enrolled and participated in the study with 112 attacks treated. Treatment consisted of one stimulation, 90-second dose, delivered to the right cervical branch of the vagus nerve. In forty-four attacks (39.2%) 9 resolved within 30 minutes; 50 attacks (44.6%) did not resolve in the first 2 hours, so patients used rescue medication; in 18 attacks (16.2%) there was no complete resolution of pain, but a significant relief in the first 2 hours (40% in the VAS scale) and patients did not use any rescue medication. No adverse events were recorded, the therapy was well tolerated. Non-invasive vagus nerve stimulation (nVNS) offers a novel approach to acute migraine attack. For patients with high frequency of migraine attacks, nVNS may represent a suitable tool to decrease the risk of medication overuse. The variety of non-invasive neuromodulatory approaches has opened new strategies for treatment of patients suffering from drug-refractory forms of headache. Randomized sham controlled studies and larger and multicentre trials are needed in order to determine the optimal dosage and to clarify the mode of action.

A19

Biological substrates of migraine
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Migraine episodes are probably originated by central mechanisms in brain areas able to cause the classical neurological symptoms of prodrome and aura. Conversely, the headache phase begins with the activation of meningeal nociceptors at the origin of the trigeminovascular system. Recent information has postulated that the occurrence of aura can activate nociceptors in the meninges. Conversely, the mechanisms by which common prodrimes initiate the headache phase or what sequence of events triggers activation of the meningeal nociceptors is not yet understood. However, a mechanistic analysis for a common factor in migraine clinical features strongly suggests a genetic predisposition to generalized neuronal hyperexcitability.

Hypothalamic neurons are sensitive to changes in physiological and emotional homeostasis and they might activate meningeal nociceptors by altering the balance between parasympathetic and sympathetic influence in the meninges. Accordingly, hypothalamic neurons that contain dopamine, histamine, and orexin, and brainstem neurons that contain noradrenaline and serotonin send inputs to trigemino-thalamic neurons in sensory thalamic nuclei. These neurotransmitters can shift the activity of thalamic neurons. Clinical and preclinical studies suggest that migraine aura is caused by cortical spreading depression (CSD), a slowly propagating wave of depolarization/excitation followed by inhibition in cortical neurons and glia. In the cortex, the initial membrane depolarization is associated with a large efflux of potassium, influx of sodium and calcium and release of glutamate. Interestingly, endogenous CGRP is released in the cortical tissue during CSD, and CGRP receptor antagonists have an inhibitory effect on CSD, suggesting a critical role of CGRP in this phenomenon. The demonstration that CGRP antagonism reduces CSD supports the possible use of drugs targeting central CGRP receptors as antimigraine agents. Finally, among the various pathophysiological conditions controlling the expression and the features of headache in migraine, medication-overuse headache (MOH) plays a central role. MOH is a clinically important entity and it is now well documented that the regular use of acute symptomatic medication by people with migraine increases the risk of aggravation of the primary headache. MOH is one of the most common causes of chronic migraine-like syndrome. We have analyzed the possible mechanisms underlying sensitization in MOH by comparing these mechanisms with those reported for other forms of drug addiction. Recent data support the evidence for cognitive impulsivity in drug overuse in headache and in other forms of addiction associated with dysfunction of the frontostriatal system and an integrative hypothesis for compulsive reward-seeking in MOH.

A20

Cortical spreading depression and familial hemiplegic migraine 2015
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The molecular and cellular mechanisms of the primary brain dysfunction leading to the onset of a migraine attack and to susceptibility to cortical spreading depression (CSD), the neurophysiological correlate of migraine aura and a likely trigger of the headache mechanisms, remain largely unknown and major open issues in the neurobiology of migraine. Our approach to these open questions is the study of the functional consequences of mutations causing familial hemiplegic migraine type 1 and type 2 (FHM1 and FHMM2), FHM1 is caused by gain-of-function mutations in the neuronal CaV2.1 channel, a voltage-gated calcium channel that plays a dominant role in controlling neurotransmitter release at brain excitatory and inhibitory synapses. FHMM2 is caused by loss-of-function mutations in the glial alpha2 Na-K-ATPase, an isoform that is thought to have specific roles in K+ and glutamate clearance by
astrocytes and in astrocyte Ca2+ homeostasis. Knockin (KI) mouse models carrying FHMI or FHMI2 mutations show a lower threshold for CSD induction and a higher velocity of CSD propagation. We have investigated the cortical mechanisms underlying the facilitation of experimental CSD in FHMI1 and FHMI2 KI mice by studying synaptic transmission at cortical excitatory and inhibitory synapses and the rate of glutamate and K+ clearance by cortical astrocytes in acute cortical slices. Our findings are consistent with the conclusion that increased activation of NMDA receptors due to enhanced cortical glutamatergic synaptic transmission in FHMI1 and to reduced rate of glutamate clearance at cortical excitatory synapses in FHMI2 contributes to the facilitation of CSD in FHMI1 mice. The data from FHMI mouse models support the view of migraine as a disorder of brain excitability characterized by dysregulation of the excitatory-inhibitory E/I balance, and point to episodic disruption of the E/I balance and neuronal hyperactivity due to excessive recurrent glutamatergic transmission as the basis for vulnerability to CSD ignition in FHMI.

A21

CGRP receptors and TRP channels in migraine

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Calcitonin gene-related peptide (CGRP) seems to play a major role in migraine mechanism. Overwhelming data report the efficacy of small molecule CGRP receptor antagonists in the treatment of migraine attacks. If some CGRP receptor (CGRP-R) antagonists could theoretically cross the blood brain barrier (BBB) one of them, ocipant, due to its peptoid nature could not. However, the clinical development of such otherwise well tolerated compounds has been spoiled by their hepatic liability that has been considered an off-target effect. In the last few years the identification of monoclonal antibodies (Ab) for CGRP or the CGRP-R has provided an alternative strategy to maintain a good efficacy profile and circumvent the severe liver toxicity of classical small molecules CGRP-R antagonists. Indeed, data from phase-II trials are showing that the therapeutic gain between active treatment with the various anti-CGRP Abs and placebo varies from about 20% to 40% and adverse reactions are limited to irritation at the site of injection and few other minor effects. Anti-CGRP mAbs predictably may cross the BBB at a minimum extent, thus making unlikely the hypothesis that they act at sites of action with the central nervous system. This observation is associated with the prevalent localization of the complex multimeric assembly of CGRP-R in the vascular smooth muscle where they mediate the inflammatory neurogenic vasodilatation. Thus, the most parsimonious hypothesis proposes that blockade of the CGRP/CGRP-R receptor system within the cranial neurovascular system produces the desirable analgesic effect in migraine pain. If the mechanism and the genetic background that by promoting cranial neurogenic vasodilatation generate migraine pain remain a mystery, some insights on the triggers that may activate this pathogenic pathway are now better understood. A series of agents known to provoke migraine attacks have been identified as activators of certain transient receptor potential (TRP) channels expressed by a subpopulation of peptidergic nociceptors. In particular, the subtypes ankyrin 1 (TRPA1) and vanilloid 1 (TRPV1) are activated by migraine provoking agents. Nitric oxide, umbellulone and acrolein gate TRPA1 and alcohol TRPV1. All stimuli by channel targeting generate CGRP release from perivascular terminals of cranial sensory neurons, thus producing the neurogenic effect blunted by CGRP-R antagonists and by anti CGRP mAbs. More importantly, antimigraine medicines, such as metaximole (dipyron), propyphenazone and parthenolide exert their analgesic effect by antagonizing TRPA1.

Reference

A22

Osmophobia in adult and juvenile headache patients

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Introduction: Osmophobia (Os), defined as a perception of odors as unbearable during the headache attacks, has been described since ancient times as an accompanying symptom of migraine. More recently authors demonstrated that Os is much more relevant in migraine patients (M), with (MA) or without aura (MO), than in various primary headaches (PH). It has also been put in evidence that Os is very specific in the differential diagnosis between M and tension-type headache (TTH). Consequently, the 2004 edition of ICHD included in the Appendix (A1.1) Os among the proposed alternative diagnostic criteria of MO. In January 2013, a provisional revised version (ICHD-3 beta) of the previously released classification was offered for the approval of the scientific community. In this version Os disappeared from the Appendix, without any explanation.

Aim and methods: To understand this choice, we reviewed and analyzed the available scientific data on Os features in M, and more specifically the usefulness of Os in the differential diagnosis of various types of primary headaches. An open search was performed on MedLine, which yielded 50 articles listing among their keywords “Osmophobia”. We considered the papers issued after the release of ICHD-2, finding 42 articles which appeared between 2005 and 2015, of which 19 had been published since 2013. Among these, 29 were eligible: while 18 papers investigated Os only as an accompanying symptom in M and/or various PH, 11 also focused on its relevance for differential diagnosis. We calculated the cumulative values of sensibility and specificity of Os in the differential diagnosis of M vs TTH.

Results and conclusions: Literature reports a much higher prevalence of Os in M than in various PH, particularly TTH[1]. Even if sensibility and specificity range from 25% to 86% and 69% to 100% respectively in different papers, all published data support the usefulness of Os in the differential diagnosis between M and TTH. Calculated cumulative values demonstrate a high specificity, between 87% and 98%, of Os in the diagnosis of M in adulthood. As far as Os in children is concerned, it appears to have an even more important role since the presence of Os in a child presenting as suffering of TTH results to be a prognostic marker of the future clinical development of MO[2]. In conclusion, published data consistently support the inclusion of Os among the M diagnostic criteria. On this ground of robust evidence, the unexplained decision to remove Os from the diagnostic criteria of M in ICHD-3 beta appears methodologically unjustified. A revision of this choice is therefore strongly recommended.

References

A23

Menstrual migraines

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The third edition of the International Classification of Headache Disorders (ICHD-3 beta), published in 2013, includes recommended criteria for “A1.1.1 Pure menstrual migraine without aura” (PMMA) and “A1.1.2 Menstrually related migraine without aura” (MRMA). The criteria are in the appendix while it is debated whether menstruation should be considered as a migraine trigger, or if menstrual migraine is a distinct clinical entity. Based on the ICHD-3 beta
diagnostic criteria, menstrual attacks must occur on day 1 ± 2 (i.e., days -2 to +3) of menstruation in at least two out of three menstrual cycles, even though some studies have proposed a wider perimenstrual window. PMM and MRM may occur even in women taking combined oral contraceptives or hormone replacement therapy. In such cases, the mechanisms of migraine may be different, with endometrial bleeding resulting from the normal menstrual cycle and bleeding as a result of the withdrawal of exogenous hormones. When PMM or MRM are considered to be associated with exogenous oestrogen withdrawal, both codes A1.1.1 or A1.1.2 and “8.3.3 Oestrogen withdrawal headache” should be used. Menstrual attacks concern mostly migraine without aura (MO). However, cases of PMM and MRM with aura have been observed, both in clinic-based and population studies. In a recent population-based study carried out in Norway [1], menstrual migraine (MM) accounted for 22% of migraine among female migraineurs aged 30-34 years (5% of the general population), being in most cases MRM (16.6%). Besides MO, several MM with aura (2.7% of migraineurs) were observed and the addition to appendix of MM with aura was proposed. Several studies have found that, in women with MRM, menstrual attacks are longer, more severe, more disabling, and less responsive to symptomatic treatment [2]. In women from the general population, menstrual attacks would differ from nonmenstrual attacks only in women who fulfill the ICHD criteria for MM[3]. Other issues, as the relationship of menstrual attacks would differ from nonmenstrual attacks in women with menstrually related migraine referred to headache centres. Cephalalgia 2004, 24:707-716.


References

A24
Migraine in pregnancy
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Migraine is a predominantly female disorder. Evidence suggests that migraine activity is influenced by hormonal factors, and particularly by estrogen levels and fluctuations. During pregnancy, estrogen may reach one hundred times the normal level, whilst progesterone levels decrease, rising again towards the end of the pregnancy; however, hormonal fluctuations are not as pronounced as during the non-pregnant state [1]. Most women with migraine report an improvement of their attacks during pregnancy, from the first to the third trimestre, particularly women with a history of menstrual migraine and with migraine without aura[2]. This improvement may be due to the lack of hormonal fluctuations but also to the increased levels of natural pain-killing hormones (endorphins) induced by pregnancy [1,2]. If no improvement is seen toward the end of the first trimestre, migraine is likely to continue throughout pregnancy and postpartum. Most women with migraine improving in pregnancy will experience attack recurrence shortly after delivery, likely in the first weeks [2]. This decline might be due to the precipitous drop in estradiol and endorphin levels occurring in the postpartum period [1,3]. A small number of pregnant women experience a worsening of their migraine while a few others may even develop de novo migraine symptoms. In this context, migraine usually occurs during the first trimester and is most often with aura[2]. Women continuing to experience migraine attacks throughout pregnancy may require treatment but we need to consider that not all medications used for migraine in pregnancy. Paracetamol is the preferred drug for acute treatment throughout pregnancy. If paracetamol is not sufficiently effective, sporadic use of sumatriptan can be considered. NSAIDs such as ibuprofen can also be used under certain circumstances, though their intake in the first and third trimesters is associated with specific risks and contraindications. For prevention, non pharmacological approaches are always first-line treatment, and should also be used to complement any drug treatment. Some vitamins and dietary supplements have been proposed, such as, magnesium, riboflavin and coenzyme Q10. Preventive drug treatment should only be considered in the most severe cases and should include low doses of β-blockers and amitryptiline[4]. A personal history of migraine headaches can affect pregnancy outcomes. There is increasing evidence showing that migraine is a risk factor for several vascular complications during pregnancy, including gestational hypertension and preeclampsia, stroke, myocardial infarction, and venous thromboembolism; therefore, migraine should be considered a potential cardiovascular risk factor in obstetric care[5]. Further research is warranted to understand the mechanisms underlying the increased risk of vascular disease in pregnant migraineurs. Better understanding of those mechanisms could lead to potential treatment and earlier intervention, thereby reducing the health care costs of morbidity and mortality associated with adverse vascular events in this population.

References

A25
Migraine during perimenopause
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Migraine affects the female sex to a greater extent than the male, with a female: male ratio of 3:1. Hormonal fluctuations during the reproductive life may influence migraine occurrence and intensity, both in a positive or negative way. Many women experience migraine approaching menopause, but the trend of migraine symptoms may vary according to the different stages of the perimenopause. If a woman is already a migraineur subject, the attacks often worsen during both the early and late phases of menopausal transition, whereas an onset of migraine is quite rare [1,2]. According to some authors, women with premenstrual syndrome (PMS) before menopause have increased prevalence of migraine in late menopausal transition, and a subsequent reduction of the attacks in postmenopause [2]. The presence of PMS can be considered one of the predictors of migraine trend during the menopausal transition, since women with PMS are more sensitive to hormonal fluctuations and more prone to develop moderate to severe menopausal symptoms [3]. Hormone replacement therapy (HRT) can be used during the late premenopausal phase and the first years of postmenopause in order to counteract climacteric symptoms [4]. The effect of HRT on migraine has been investigated, either in its role of provoking or preventing the attacks. HRT should be administered continuously, without intervals, to avoid sudden estrogen deprivation and the consequent possible onset of migraine [5]. Treatment with estradiol-based gels and transdermal patches is preferable to oral formulation as it maintains constant serum hormone levels. In contrast to guidelines on the use of estroprogestinic contraceptives, migraine with aura is not an absolute contraindication to HRT when the way of administration is topical with a low dose of natural estrogens. If the aura recurs or worsens, HRT should be in any case discontinued [6]. When the effect of tibolone versus continuous combined HRT regimen in migraine is compared, a significant reduction in the hours with pain-limiting daily activities and of the amount of analgesics intake can be observed, even if there is no reduction of the days with migraine [7]. Natural menopause is associated with a lower incidence of migraine as compared with surgical menopause [8]; data on migraine prevalence in relation to the type of surgical procedure are till now unclear and contradictory [9].

Conflict of interest: None to declare.
References


A26
Neural plasticity and migraine
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Background: During recent years, various experimental data suggested that the functional state of the migraineur's brain fluctuates in relation with the cyclical recurrence of the migraine attack. This was historically observed with the methods of clinical neurophysiology that revealed interictal deficient habituation of any kind of sensory responses - with the notable exception of the olfaction - that was attributed to abnormal thalamo-cortical interactions and its normalization during an attack. On the other hand, studies with repetitive transcranial magnetic stimulation (rTMS), have reported interictal paradoxical cortical responses in reaction to both depressing or enhancing rTMS and their changes up to the bending point of an attack when cortical responsivity behaves differently. Such recurring changes were confirmed recently with morphological and functional neuroimaging methodologies. For instance, fMRI BOLD responses induced by painful stimuli differ between ictal and interictal scans in episodic migraine. We recently showed that cyclic changes can also be demonstrated at rest, i.e. without any sensory input, in anisotropy of thalamic microstructure, in grey matter density of temporo-parietal areas, and in interconnectivity among large scale cortical networks. The conjunction of neuroimaging and neurophysiological data can be considered as robust evidence favouring cycling morphological and functional brain alterations as prominent features of migraine pathophysiology.

Conclusions: Both the abnormal neurophysiological information processing and morphological brain changes point to altered neural plasticity mechanisms, which prevent the immediate and longer-lasting cortical changes that allow multimodal sensory integration and reflect adaptation to headache recurrence.

A27
Secondary headache in emergency
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Headache is one of the most common causes of access to Emergency Departments (ED). Primary headaches and headaches secondary to benign conditions (e.g. headache attributed to acute sinusitis) represent the majority of cases, while secondary life-threatening headaches are less frequent. The primary objective in the ED setting is to decide whether the headache is primary or secondary and recognize serious life-threatening conditions presenting with headache and requiring prompt medical diagnosis and care, such as subarachnoid hemorrhage (SAH), intracerebral hemorrhage, cerebral venous sinus thrombosis (CVST), cervical arterial dissection (CAD), brain tumors, pituitary apoplexy, spontaneous intracranial hypotension, or intracranial infections. Careful history taking and physical examination remain the most important part of the assessment of the headache patient [1]. A thorough history should investigate the onset of headache, quality, location and irradiation of pain, associated symptoms experienced before and during the headache, comitant medical conditions, medication use, recent trauma or interventions. The examination should then target areas identified as abnormal during the headache history; fundoscopy evaluation should be performed when symptoms may suggest an increased intracranial pressure; in addition, a complete neurological assessment including level of consciousness, cranial nerve testing, pupillary responses, motor strength and sensorial testing, and signs of meningeal irritation is essential [2]. Based on historical and physical findings “red flags” for secondary headache disorders are sudden onset, onset after 50 years of age, increased frequency, severity or significant change in the usual headache pattern, new onset with an underlying medical condition (such as cancer or immunodepression), comitant signs of systemic illness (such as fever, neck stiffness, rash), focal neurologic signs or symptoms, papilledema, and head trauma [2]. In headache patients with one or more “red flags” a diagnostic workup is indicated including blood tests, neuroimaging studies, and cerebrospinal fluid (CSF) examinations, which are selected depending on the patient’s history and findings. Blood testing and dosage of inflammatory indexes (erythrocyte sedimentation rate, C-reactive protein) should be performed in all headache patients especially when an infective or inflammatory condition is suspected. In the ED, non-contrast computed tomography (CT) is the preferred imaging study and is used to rule out hemorrhage, while most patients should perform a magnetic resonance imaging (MRI) brain scan followed by CT/ MRI angiography if brain vessel disease is suspected (such as, CAD, aneurysms, and CVST). Lumbar puncture with CSF analysis may help to diagnose SAH, infection, tumor and disorders related to CSF hypertension or hypotension [3,4]. Treatment and prognosis depend on the etiology of the headache. Prompt recognition and early treatment of secondary headache are essential to avoid some preventable complications.

References


A28
Obesity, diet and nutraceuticals
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Migraine is the most prevalent neurological disorder worldwide, affecting on average 12% of the general population. Recent data support migraine as part of the metabolic syndrome (MetSyn) spectrum. The evidence of an association between obesity, insulin resistance, and migraine, all having in common the ability to favor a general pro-inflammatory state, reinforces this view. Under a neuronal point of view, another possible link between migraine and MetSyn is, other than the inflammatory state, the cellular energetic deficit. Indeed, it is well known that a mitochondrial energetic dysfunction may play a role in migraine pathogenesis, that MetSyn could further impair mitochondrial metabolism increasing oxidative stress, and that nutraceuticals involved in mitochondrial oxidative phosphorylation (OXPHOS) metabolism (Riboflavin, CoQ10, and magnesium) can be used as migraine prophylactic treatments. Here we review the evidence of MetSyn and migraine association and possible therapeutic implications.

There is a close relationship between migraine and MetSyn, especially insulin resistance and obesity. More in detail, obesity is regarded as an important factor of chronification for migraineur patients, while weight-loss seems to have a protective effect. The main player of this association seems to be the obesity-related inflammation and an adequate slimming diet can act to reduce this inflammatory mechanism. In fact, inflammatory cytokines are higher in obese subjects and normalized by weight reduction. Moreover, several foods could act as triggers for some patients by inducing inflammation or a sub-threshold mediated pathway, by a direct histamine or other vasoactive peptides effect, or by modifying the quality and quantity of fat intake. Also, altered insulin metabolism could be related to leptins and nitric oxide (NO) stress, both inducing inflammatory effects involved in migraine pathogenesis. Some prophylactic treatments induce increase of weight, insulin and leptins that can counteract the therapeutic effect; it is the "prophylactic paradox": a long lasting migraine could be worsened by the drug-induced obesity.

Therefore, there is the rationale for the adoption of specific dietetic patterns as complementary treatment in migraine management. In particular, the ketogenic diet is worthy of mention because of its multiple effects on the above-mentioned mechanisms, since it induces a significant weight-loss (when prescribed as very-low calorie diet), normalizes leptins and hyperinsulinemia, improves mitochondrial OXPHOS metabolism, and has a ketone bodies induced anti-inflammatory effect.

In summary, more attention should be paid to metabolic implications of migraine and its treatment to further improve, or at least not worsen, patients’ conditions and reduce migraine-related comorbidities and complications.

A29
Invasive neurostimulation
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Chronic migraine afflicts 1-5% of the global population and poses a substantial burden on subjects’ quality of life and on health services utilization [1]. Although most patients benefit from abortive and preventive drugs, a subgroup of patients remains refractory to treatment. Refractory chronic migraine is one of the greatest challenges in headache medicine and, in these patients, innovative techniques should be considered. In the past 20 years neuromodulatory approaches, already proved effective in other chronic pain syndromes, have been increasingly used for refractory primary headaches. Neuromodulation, a reversible and adjustable manipulation of pain pathways is an evidence-based invasive treatment for chronic pain conditions and it may be applied to any neural structure: spinal cord, deep brain, and peripheral nerves.

Recently, three 12-week follow-up prospective, randomised trials have been conducted to validate occipital nerve stimulation in chronic migraine and intractable chronic migraine associated to occipital localization of pain. Considering the primary outcomes (50% reduction in pain intensity, 50% decrease of headache days) all the three trials have failed. In one of these studies [2], although the second follow-up at 52 weeks has shown important effects on pain severity, headache days, HIT-6 and MIDAS scores (65% of patients achieved 30% reduction in headache days and/or pain, 50% achieved 50% reduction in headache days and/or pain, 70% reported excellent or good headache relief and improved QoL, 70% would undergo the procedure again), it has also shown high incidence of adverse events related to the procedure (70% of patients experienced at least one AE, 41% of AEs required supplemental surgery, 8.6% of AEs required hospitalization).

A more recent prospective, open-label, exploratory study [3] assessing the long-term (6-months) safety, tolerability and efficacy of cervical high frequency (10 kHz), paresthesia-free, spinal cord stimulation in a cohort of 14 refractory chronic migraine patients (refractory also to Onabotulinumtoxin-A) has shown good results on reduction of headache days, medication intake, HIT-6 and MIDAS scores. The patients were carefully selected, for refractory chronic migraine, not considering topographic criteria for localization of pain, and were assessed by two different psychologists before eligibility. A significant reduction in headache days was observed at 24 weeks (average 7.0 days). Seven (50%) subjects recorded a >30% decrease in headache days, while 5 (36%) subjects reported a reduction in headache days greater than 50%. Eight subjects (57%) reverted to an episodic pattern of headache (<15 days a month). Medication intake reduced significantly, and four subjects discontinued triptans. Few adverse events have been reported.

HF10-SCS deserves further clinical investigations to evaluate its possible role in the management of rCM.

References

A30
Molecular genotype in migraine
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Migraine is an episodic brain disorder with disabling attacks of headache that are associated with nausea, vomiting, and hypersensitivity to light, sound, and smell. According to major criteria of the International Classification of Headache Disorders (ICHD-II) from the International Headache Society (IHS), migraine is divided into two main subtypes that are based on the absence (migraine without aura, MO) or presence (migraine with aura, MA) of an aura. Migraine has a profound effect on wellbeing and general functioning, not only during attacks, but also in terms of work performance, family and social relationships, and, mainly in children, school achievement, thus explaining why the WHO expert panel rates migraine among the most disabling and costly chronic disorders.

There is a strong genetic component in migraine as evidenced by observations that the disorder runs in families and that about 50% of the patients have close relatives also affected by a similar condition. However, migraine risk is also conferred by environmental factors and epidemiological evidence suggesting a tight gene-environment interaction (endogenous or exogenous), among which several predisposing or triggering factors have been defined.

In the past decades, our growing understanding of the genetic contributions in migraine disorders has been translated in better knowledge of the pathophysiology but needs to grow further and to be
translated into more effective treatments. Indeed, several genes involved in syndromic and monogenic forms of migraine have been defined, allowing a significant contribution to the mechanisms generating the attacks, but the timing and specific contribution of secondary hits remain largely unclear.

A31
Psychopathological phenotypes in childhood migraine
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Migraine headache represents a frequent reason for neurological evaluation in developmental age. Many studies in the last decades have been focused on the role of psychopathological profiles among migraineur children. On the other hand, conflicting results have been reported about the different psychopathological profiles among subjects affected by migraine. The role of psychopathological aspects on clinical findings among children may be relevant particularly for severity and frequency of attacks. A recent review showed the higher prevalence in migraine children of psychological symptoms, detected by using the Child Behavior Checklist (CBCL), than healthy controls [1]. Moreover, clinical and population-based studies suggest that children with migraine are more likely to have internalizing symptoms (i.e., particularly anxiety and depression traits), as well as psychological comorbidities [1]. Nevertheless it is still a matter of controversy whether children with migraine have specific psychological vulnerabilities or if they only cope differently with stressful situations. In 2015 Arruda et al reported that children with migraine are more likely to present emotional symptoms, conduct problems, hyperactivity, peer problems, and total difficulties in psychosocial adjustment stressing the role of psychological adjustment styles as predisposing factors for developing psychopathological troubles among migraine children [2]. In this perspective we could speculate that the psychopathological profile of migraine children could be influenced by environmental or familiar elements such as, by specific psychological vulnerabilities of migraine children [2]. In this light, some studies pinpointed the role of parenting styles effects on migraine severity and frequency in children, related to parental stress levels, while a preliminary study indicated the potential value of maternal personality assessment for better comprehension and clinical management of children affected by migraine [3,4].

According to the analysis of specific psychopathological vulnerabilities in migraine children, a higher prevalence among migraineur children of the avoidant attachment style (type A) and the significantly lower prevalence of the secure style attachment (type B) than controls was found [5]. Moreover, also significant differences among temperamental characteristics of MwA children respect to the comparisons [6], suggesting that the study of psychopathological comorbidities in pediatric headache may be enriched by these new aspects.

References

A32
Non headache phenotypes in pediatric age
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Although headache represents the main symptom of migraine, it is a very complex disease and can be manifested by a number of other symptoms. This is particularly evident in pediatric age where clinical conditions different from headache can involve children who are already suffering or will suffer from migraine headache. In the International Classification of Headache Disorders 3rd edition (ICHD-III), these conditions, occurring as repeated attacks with complete remission between episodes, are defined as "Episodic syndromes which may be associated with migraine". They include “Cyclical vomiting syndrome” (1.6.1.1), “Abdominal migraine” (1.6.1.2), “Benign paroxysmal vertigo” (1.6.2) and “Benign paroxysmal torticollis” (1.6.3). Though not included in the ICHD-III, other clinical entities, such as motion sickness and limb pain, have been associated with migraine. In order to underline the strict relationship between all these non headache symptoms and migraine, they are also known as “migraine equivalents”. We investigated the migraine equivalents prevalence in a large population of children referred to our pediatric headache centre [1]. A total of 1,134 of children/adolescents (73.2% with migraine and 26.8% with tension-type headache) were included. We found that migraine equivalents could equally involve children with either migraine or tension-type headache and that high frequency of headache attacks correlated with migraine equivalents presence. It was concluded that migraine equivalents should not be considered merely as headache precursors, but they are part of the migraine syndrome. In a more recent study, we showed that anxiety and somatization levels were higher in migraine children with migraine equivalents, as compared to those without migraine equivalents [2]. Our findings, together with those issued from the literature, suggest that in children and adolescents migraine equivalents should be considered as symptoms of the migraine disease, thus their inclusion among the diagnostic criteria for pediatric migraine/tension-type headache would be hopeful.

References

A33
Metabolism and headache
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Background: In the past decade, several studies have shown a significant association between migraine and several features of the metabolic syndrome (MetS), including insulin resistance, systemic hypertension, and obesity. In addition, headache is a highly prevalent symptom in several metabolic disorders. The purpose of this review was to discuss recent findings regarding the relationship between headache, migraine, and metabolic disorders.

Methods: A computerized search of the PubMed and Cochrane Library databases was performed to identify English-language articles published between January 1, 2000, and June 30, 2015. Search terms included
migraine, headache, diabetes, hypertension, obesity, and metabolic syndrome. Out of 241 articles screened, 41 were selected for review.

Results and discussion: MetS is characterized by a cluster of metabolic abnormalities including insulin resistance, hypertension, dyslipidemia, obesity, and a proinflammatory state. Over the last two decades, different definitions and diagnostic criteria for MetS have been proposed, like the EGI, the NCEP ATP III and the AACE criteria. Migraine, as defined by the International Headache Society (ICHD-3 beta), is a chronic neurovascular disease characterized by recurrent, disabling headache attacks. Met5 and migraine are highly prevalent medical conditions, affecting 15-20% of the population. Both conditions are associated with increased risk for atherosclerotic cardiovascular disease. The two conditions often coexist, but the pathophysiological mechanisms of this comorbidity are still under investigation. Several studies have clearly shown that insulin sensitivity is impaired in migraine, even in young, non-obese, non-diabetic, normotensive patients. Association between polymorphism of the insulin receptor gene and migraine provided inconclusive results. Prevalence and characteristics of headache in patients with diabetes have been scarcely investigated. Elevated blood pressure is a frequent clinical feature of MetS. Few studies investigated blood pressure (systolic or diastolic) abnormalities in migraine. Recently, a large demographic study found a positive association between migraine and cardiovascular risk factors may be of relevance for prevention and treatment of both conditions.

A34
Rehabilitation from symptomatic drugs overuse: yes, no, may
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In predisposed subjects with migraine or tension-type headache increasing intake of acute medications is associated with a progressive clinical worsening. When the days of symptomatic drug use reach a given threshold (10 or 15 days/month, depending on the classes of drugs, ICHD-III) and the headache has become chronic for at least three months, a causal relationship is deemed to exist between the medication overuse and the clinical worsening, and the headache is termed medication-overuse headache (MOH). MOH affects nearly 2% of the general population. It represents a highly disabling condition that impacts considerably on the quality of life of sufferers and on the society in general because of high levels of disability and use of healthcare resources.

MOH is treatable: withdrawal from overused drugs leads to a clinically significant improvement in the majority of patients. Even more so, when it is performed within an integrated approach aimed at targeting frequent associated features (i.e., muscle tenderness and contractures, psychological disturbances, increased stress levels) and in the most appropriate clinical settings (i.e., outpatients clinics for simple MOH, hospitalization for complex MOH). Some Authors also report improvement with prophylactic medication (topiramate, botulinum toxin) alone.

Increasing amount of evidence suggests that the clinical process leading to MOH is paralleled by the establishment of chronic sensitization, which is partly reversed by withdrawal of overused drugs. In addition, several experimental reports confirm that frequent use of analgesics or triptans facilitates nociception, probably via the overexpression of CGRP and neuronal NOS in the trigeminal ganglion. Clinical practice and analysis of the literature suggest that the beneficial effect of drug withdrawal tends to be more marked and abrupt as compared to the reported slower reduction of headache days when prophylactic medication alone is used. Direct comparison trials are however lacking.

A major issue to be addressed is the high risk of relapse into overuse and pain chronicity following improvement. A good wealth of literature findings has allowed precise quantification of the rate of relapse into overuse and pain chronicity following drug withdrawal (alone or in combination with prophylactic mediation), while data are missing as regards relapse rates following prophylactic treatment alone for MOH.

Taking all these observations into consideration, and awaiting for the necessary evidence from comparative trials, presently the optimal approach to MOH seems to be provided by a multistep process that possibly includes all of the following procedures:
1. Patient’s education regarding the need to stop overuse;
2. Withdrawal from overused drugs;
3. Management of comorbid conditions;
4. Optimization of symptomatic medications;
5. Personalization of prophylactic medication.

A35
Hemicrania continua and unilateral headaches: are they still together in the IHS classification?
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Sjaastad & Spierings described “Hemicrania continua” (HC) in 1984 [1]. In 2001, succinct criteria were presented [2]: permanent hemicrania, pain intensity: mild-moderate, (but occasionally - severe) and indomethacin dosage < 150 mg daily. In addition, relative shortage of “local” autonomic phenomena, relative lack of “migraine symptoms” and of “cervicogenic” features. Such patients generally had tried legion drugs, with little effect. Such trials equal the usage of placebo. These guidelines seemed to function close to optimally. Then, criteria of the International Headache Society (IHS) (ICHD-III beta classification) came along. Surprisingly, they were transferred from a recent review article by Goadsby [3], almost word by word, despite the existence of a committee of intelligent and knowledgeable colleagues. There is an abundance of failures in the actual scheme. It is unacceptable to include as mandatory criteria, facial/forehead autonomic features. In this way, e.g. sweating becomes prominent - 33%, against a subjective feeling of sweating in only 6% of our series (ratio: 5:5). Objectively, by quantitative evaporationometry, there was no facial asymmetry in all our 8 cases. There were 12 autonomic phenomena in this category [3], with a mean ratio between Goadsby’s/our figures of 4:4. When made mandatory, autonomic features will create bogus cases. Bogus cases necessitate ultra-high indomethacin dosages; such dosages have an unspecific, analgesic effect, on various headaches. Our mean indomethacin continuation dosage was: 83 mg (range: 50-150), while in Goadsby’s series it was 176 mg (25-500). HC is the unilateral headache with the least “local” autonomic features, “migrainous” and “vascular” components. It is a rather “pure” headache. The present classification brings HC nearer to other unilateral headaches with local autonomic symptoms, a misunderstood policy. CPH is exceptional with clinical similarities; the absolute in HC is paralleled by the establishment of chronic sensitization, which increases the pain threshold (10 or 15 days/month, depending on the classes of drugs, ICHD-III) and the headache has become chronic for at least three months, a causal relationship is deemed to exist between the medication overuse and the clinical worsening, and the headache is termed medication-overuse headache (MOH). MOH affects nearly 2% of the general population. It represents a highly disabling condition that impacts considerably on the quality of life of sufferers and on the society in general because of high levels of disability and use of healthcare resources.

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A major issue to be addressed is the high risk of relapse into overuse and pain chronicity following improvement. A good wealth of literature findings has allowed precise quantification of the rate of relapse into overuse and pain chronicity following drug withdrawal (alone or in combination with prophylactic mediation), while data are missing as regards relapse rates following prophylactic treatment alone for MOH.

Taking all these observations into consideration, and awaiting for the necessary evidence from comparative trials, presently the optimal approach to MOH seems to be provided by a multistep process that possibly includes all of the following procedures:
1. Patient’s education regarding the need to stop overuse;
2. Withdrawal from overused drugs;
3. Management of comorbid conditions;
4. Optimization of symptomatic medications;
5. Personalization of prophylactic medication.

References
A36
Choosing the safest acute combination therapy during prophylactic treatment: pharmacokinetic and pharmacodynamic considerations
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Drugs used in the treatment of migraine have been recently reported to be highly associated with the occurrence of clinically significant drug-drug interactions (DDIs). The multiple drug therapy regimen is widely used for migraine treatment, particularly for chronic migraine. In fact, additional pharmacological agents are usually administered during an acute migraine attack in patient chronically treated with prophylactic therapy. The wide variety of drugs available for migraine prophylactic and acute treatment, and consequently their pharmacological interactions, might complicate the choice of a safe combination therapy. The most frequently used drugs for the prophylactic therapy of migraine belong to the antidepressants, β-blockers, tricyclic, SSRI and SNRIs antidepressants and antihistamine medications while acute migraine attacks are treated with triptans, NSAIDs and ergot derivatives. Moreover, in the last few years several of the latter drugs have been combined in new formulations for clinical use in order to improve treatment efficacy and, consequently, the compliance of the patient. Drug-drug interactions might occur at receptors level, both in the Central Nervous System (CNS) and in the peripheral, at the major metabolic pathways levels (i.e., CYP450 enzymes) and at the protein binding level. One of the most widely known examples of the severity of such interactions is represented by the serotonergic syndrome induced by the co-administration of serotonergic antidepressants and triptans. In the management of chronic migraine, usually prophylactic treatment is already administered, therefore the choice of an additional drug for the acute attack should be decided considering the specific DDIs. Therefore, the aim of this study was to schematically discuss the prophylactic-acute drug-drug interactions from a pharmacokinetic and pharmacodynamic point of view.

A37
Chronic migraine: nosographic and epidemiological issues
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The term “chronic migraine” (CM) was officially introduced in 2004 in the second edition of the International Classification of Headache Disorders (ICHD-2), which included it in the chapter on migraine at the three-digit level (code 1.5.1) among the complications of the disorder [1]. The latest edition of the classification (ICHD-3 beta version) published in 2013 still uses the term in the chapter on migraine but moves it to the two-digit level (code 1.3), after migraine without aura (1.1) and migraine with aura (1.2) [2]. According to the ICHD-3, a diagnosis of CM must be made when a patient who has been suffering from migraine for some time has had “headache occurring on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month”. The major drawbacks in the current systematization of this important chapter are the following: (a) the term used (CM) is ambiguous; and (b) the time pattern indicated in the diagnostic criteria is not adequate to define a homogenous case series of patients. In order to solve these drawbacks and be more adherent to the reality of clinical practice, CM as it is currently known should be separated into two parts, depending on the severity of the headache [3]. One thing is having had headache on 15-20 days a month for 3-4 months. Quite another is having had headache each day of the month for several years. In the former case, we could use the term “high-frequency migraine”, including it at the three-digit level of migraine without aura. In the latter case, it would be better if we used the term “transformed migraine”, which is already well known in the literature and should be included at the three-digit level among the complications of migraine. This division of CM as we know it into two separate subgroups could be very helpful both in improving the clinical and healthcare management of patients and in providing much-needed availability of homogeneous case series for basic and pharmacology research. Partly due to the nosographic ambiguities mentioned above, current epidemiological data are still scarce and rather conflicting. Based on the indications from the ICHD-2 and the ICHD-3, CM would have a 1-4% past-year prevalence rate in the general population, showing an even more marked predominance in women than does episodic migraine. More than half the CM cases would also have medication-overuse headache.

References

A38
Pathogenesis of chronic migraine: the role of neuromodulators
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The pathogenesis of chronic migraine (CM) remains largely unknown. We hypothesized that anomalies of tyrosine metabolism, found in migraine without aura (MwoA) patients, play an important role in the transformation of MwoA into CM, since the increase in the number of MwoA attacks is the most predisposing factor for the occurrence of CM. To test our hypothesis we measured the plasma levels of dopamine (DA), noradrenaline (NE) and trace amines, including tyramine (TYR) and octopamine (OCT), in a group of 73 patients with CM, 13 patients with chronic tension-type headache (CTTH) and 37 controls followed in the Headache Centres of the Neurology Departments of Asti, Milan and Vicenza hospitals in Italy. The plasma levels of DA and NE were several-fold higher in CM patients compared with control subjects (p > 0.001). The plasma levels of TYR were also extremely elevated (p > 0.001); furthermore, these levels progressively increased with the duration of the CM. Our data support the hypothesis that altered tyrosine metabolism plays an important role in the pathogenesis of CM. The high plasma levels of TYR, a potent agonist of the trace amine associated receptors type 1 (TAAR1), may ultimately down-regulate this receptor because of loss of inhibitory presynaptic regulation, therein resulting in uncontrolled neurotransmitter release. This may produce functional metabolic consequences in the synaptic clefts of the painmatrix implicated in CM. Written informed consent to publication was obtained from the patient(s).

A39
Chronic migraine: treatability, refractoriness, pseudo-refractoriness
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Chronic migraine (CM), a highly disabling condition affecting 2-3% of the general population, represents a difficult-to-treat disorder for its unclear pathophysiology, complex comorbidities, and disappointing response to available pharmacological treatments [1]. High quality evidence (≥ 2 RCTs) recommends the prophylactic use of onabotulinumtoxin A (155-195 IU) and topiramate (100 mg) in CM, while lower quality evidence (1 RCT) supports the treatment with sodium valproate (800-1500 mg), gabapentin (2400 mg) and tizanidine (18 mg) [2]. Amitriptyline, memantine, zonisamide and pregabalin may also be of help in CM but their use has been suggested only
in open studies [2]. CM patients may show poor or no response to preventative therapies. The consensus statement of the European Headache Federation (EHF) defines CM refractory to treatment (rCM) when it does not respond to adequate dosages of at least 3 drugs from the classes of beta-blockers, anticonvulsants, tricyclics, onabotulinum toxin A and others (e.g., flunarizine, candesartan) for at least 3 months each, in absence of medication overuse [3]. This rCM definition has been questioned by some authors who stressed the need of using drugs from different classes, not limited to 3, before making rCM diagnosis [4]. Labeling a patient as affected by rCM may profoundly modify his/her life with heavy psychological, social, work and medico-legal consequences, potentially leading to expensive and still unsatisfying surgical procedures such as occipital nerve stimulation [5]. We point out the risk that the current rCM EHF definition could indeed also include pseudo-refractory CM patients, due to potential bias: firstly, a significant proportion of CM patients may spontaneously reverse to episodic migraine, as clearly evidenced in population-based study [6]; secondly, rCM patients may present underlying psychiatric disturbances (e.g., personality disorders) not easily recognized, classified and treated by headache specialists; thirdly, rCM diagnosis could be biased by unproven evidence as current rCM criteria do not specify who should attest patient's headache history (theoretically self-reported or stated by unqualified physicians). We suggest that 1) rCM is probably more rare than presently stated; 2) before formulating a diagnosis of rCM, psychiatric disorders should be carefully ruled out by appropriate and thorough psychiatric investigations; 3) when assessing CM patient's past medical history, only clinical data coming from certified headache centers should be considered; 4) CM patients should be followed up for an adequate period of time before making a definite rCM diagnosis.

References

A40
A proposal for a national registry on chronic migraines
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According to the existing classification chronic migraine (CM) is a primary headache that occurs on 15 or more days per month for more than 3 months and has the features of migraine on at least 8 days per month. In Europe, CM prevalence ranges from 2.7% to 4.7%. CM is an extremely disabling disorder associated with significant functional impairment. The 2010 Global Burden of Disease Survey conducted by the WHO listed migraine as the 7th cause of disability in the world, responsible for 2.9% of all years of life lost to disability. Unfortunately, however, in its current definition CM includes subgroups of patients with very different levels of severity and outcome. Failing to recognize them entails highly negative repercussions on research and clinical practice, with inadequate patient management and lack of cost-effectiveness. Therefore, it is essential that these subgroups of subjects be clearly identified to optimize clinical management, rationalize the allocation of economic resources, provide specific clinical and health care procedures, and clarify pathogenetic mechanisms. The clinical registry will include the data of all patients with CM, aged 18 or over, seen at the Headache Centres of Parma, Bologna, Rome, and Milan. The diagnosis of CM will be made by a headache specialist based on the diagnostic criteria of the ICHD-III beta (2013) and on the CM classification proposed by Manzoni et al [1]. The principal aim of the clinical registry will be to identify still undefined subgroups of subjects with CM through a specially designed clinical registry to be applied in a large number of outpatients. The registry will make it possible to collect personal and social patient data, as well as data about their physiological conditions and non-essential habits; clinical features of headache (before and after its evolution to chronicity); any factors concomitant with the headache’s evolution to chronicity (i.e., medication overuse, life events, hypertension); comorbidity and injuries; headache-related disability (MIDAS, WHO-DAS-II, MSQ); quality of life (SF36); symptomatic and preventive treatments; medication overuse; visits and hospitalizations for CM; and recognized sickness and invalidity allowances. The creation of a large-scale registry will make it possible to identify specific CM (i.e., refractory CM) subgroups, based on clinical and biological features. It will also make it possible to identify areas with lack of or inadequate health care provision and waste of resources (i.e., useless examinations or treatments), eventually helping to improve CM management and ensure health care procedures that are more appropriate.

Reference

A41
Headache and psychopathology: DSM-V vs ICHD-3\(b\) vs ICD10
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A strict relationship between migraine and psychiatric factors has been suggested, but the exact role and the influence on evolution of headache is unknown. The most frequent diagnosis was a comorbidity of anxiety and mood disorders. The comorbidity of psychiatric disorders and headache has important implications as far as treatment is concerned. In comparing DSM-V, ICHD-3\(b\) and ICD10 criteria on headache and psychopathologic, diagnostic criteria agree on pre-existing headache with the characteristics of a primary headache disorder becoming chronic, or made significantly worse, in close temporal relation to a psychiatric disorder, both in the initial headache diagnosis and psychiatric diagnosis. Headache attributed to psychiatric disorder should be given, provided that there is good evidence that that disorder can cause headache. When a causal relationship cannot be confirmed, the pre-existing primary headache and the psychiatric disorder are diagnosed separately. Thus, the diagnostic categories are limited to those few cases in which a headache occurs in the context and as a direct consequence of a psychiatric condition known to be symptomatically manifested by headache. Diagnostic criteria must be restrictive enough not to include false positive cases, but must set the threshold low enough to admit the majority of affected patients. Headache disorders occur coincidentally with a number of psychiatric disorders. Although criteria for headaches attributed to psychiatric disorders have suggested that headache may be considered exclusively in association with several psychiatric disorders, such as, depressive, anxiety and trauma/stress-related disorders, might be considered as attributed to these disorders, because of uncertainties concerning the causal relationships and relative lack of evidence in this context. Evidence suggests that the presence of a comorbid psychiatric disorder tends to worsen the course of migraine and/or tension-type headache by increasing the frequency and severity of
the headache and/or making it less responsive to treatment. Thus, identification and treatment of any comorbid psychiatric condition is important for the proper management of these headaches. It should be noted that somatization disorder per se is not included in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). It has been replaced by the category Somatic Symptom Disorder, characterized by one or more somatic symptoms. Thus, ICHD-3 beta continues to refer to the DSM-IV definition of somatization disorder. Using WHO’s criteria and methods for measuring burden of disease in DALYs, headache disorders can be placed correctly in the context of other mental and neurological disorders and other chronic illnesses. In order to know the full burden attributable to headache disorders, however, further epidemiological work must be conducted around the world and this must encompass assessments of clinical, economic and humanistic impacts.

A42 Trigeminal neuralgia
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The International Association for the Study of Pain (IASP) defines trigeminal neuralgia as a sudden, unilateral, severe, brief, stabbing, recurrent episode of pain in the distribution of one or more branches of the trigeminal nerve. Trigeminal neuralgia (TN) can be distinguished in classical TN and symptomatic TN [1]. Classical TN is due to a vascular compression of the trigeminal root by tortuous or aberrant vessels. Symptomatic TN can be related to cerebello-pontine angle tumours which compress the trigeminal nerve root. Multiple sclerosis (MS) is typically associated with TN (2-4% of patients with TN) [2]. Whether produced by multiple sclerosis or chronic compression exerted by a blood vessel or a benign tumour, demyelination increases the susceptibility of the nerve fibres to ectopic excitation, ephaptic transmission, and high-frequency discharges. Although the primary cause of TN must necessarily affect the primary afferents, the pathophysiological mechanism may or may not secondarily involve the central neurons.

Recent epidemiological studies of general practice research databases reported a TN incidence ranging from 12.6 to 26.8 per 100,000/year, with the incidence increasing with age (16.3 in the fourth decade, 30.6 in patients older than 80 years) [3,4]. Pain distribution is unilateral (bilateral TN may sometimes occur in MS). The maxillary division is the most frequently affected, both in classic and symptomatic TN. Pain, usually referred to as stabbing or electric-shock-like, is brief and paroxysmal, lasting a few seconds. Paroxysms may be provoked by stimulating cutaneous or mucous trigeminal territories (trigger zones), regardless of the distribution of the perceived pain. Carbamazepine, still remains the gold standard drug with the highest efficacy was shown to be very similar but tolerability is better with oxcarbazepine [1].

References

A43 The value of epidemiology in headache
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Headache is the commonest neurological condition worldwide. According to the Global Burden of Disease 2010, tension-type headache is the second most common clinical condition (prevalence, 20.8%) preceded only by dental caries and followed by migraine (prevalence, 14.7%) [1]. Globally, migraine is the leading cause of disability-adjusted life years (DALY) and years living with disability (YLD). This information was obtained from epidemiological studies in developed and in developing countries where well-defined populations were investigated in search of people suffering from headache. Epidemiological studies estimate the frequency, spectrum and burden of a disease in a population. Headache, in this regard, has peculiar aspects that cannot be fully explored when studying referral patients (i.e., individuals seen in hospital, headache centers and other outpatient services) as the majority of patients do not have access to hospital facilities and several individuals do not even ask for medical consultation. However, in light of the frequency of headache in the population, the disease has a high impact on the society in terms of functional disability and indirect costs [2]. As several epidemiological studies are based on telephone interviews, the full spectrum of the disease can be easily captured on a population basis. Epidemiological studies are also instrumental when addressing the role of personal and environmental risk factors and their association with headache (migraine) types [3]. However, the representativeness of the study population is a pre-requisite for the external validity of the results. In addition, in the absence of valid and reliable biomarkers, the diagnosis of headache still relies mostly on clinical findings [4]. In this regard, epidemiology largely contributes to the identification of symptoms and signs most likely to differentiate the main diagnostic categories of the disease.

References

A44 Migraine and epilepsy: what value today?
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More than 100 years of investigation have found that seizures and migraine co-occur in some affected individuals and families, and there is much evidence that these diseases share genetic susceptibility. In particular, in a recent review, the prevalence of migraine in epileptic patients was about 12% [1]. On the other hand, epilepsy exhibits a prevalence of about 6% in migraineurs [2]. Moreover, epilepsy has also been reported in patients with familial hemiplegic migraine (FHM),
Although few studies showed a prevalence of epilepsy of about 7% in FHM, currently no conclusive data are available. Certainly, epilepsy and migraine share common characteristics that the underlying pathophysiology relates to alterations in ion channels or ion transporters. In these episodic functional diseases, in which susceptible brain regions are hyperexcitable, the attacks begin with hypersynchronous neuronal firing [3]. In epilepsy, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors play a predominant role in mediating the generation and spread of seizure activity whereas in migraine mainly N-methyl-D-aspartate (NMDA) receptors are involved in triggering CSD. However, the nature of the ionic conductance changes leading to the massive but transitory neuronal depolarization underlying CSD has not yet been define [4].

Genetically determined dysfunction of ion transporters seems to point to a common underlying mechanism for both paroxysmal disorders. In the last two decades the mutations in the ion transportation genes CACNA1A, ATP1A2 and SCN1A have been identified for FHM. Conversely, only a few genes have been reported in patients with sporadic hemiplegic migraine (SHM). These cases can be caused by a de novo mutation or by inheritance of a gene mutation from asymptomatic carrier and are usually characterized by early-onset, severe and complex disorders.

Certainly, genetic analysis can provide greater insight into the potential causes of both disorders and it could contribute to better treatment choices.

References

A45 Migraine and fibromyalgia
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Fibromyalgia is a chronic pain syndrome of unknown etiology characterized by diffuse pain, sleep disorders, fatigue, cognitive dysfunction and a cohort of different symptoms implying comorbidity with diseases with common pathophysiological basis. There is a growing body of evidence that abnormal pain processing at a central level has a role in FM pathogenesis, though recent evidence supports the coexistence of a peripheral nociceptive fibers sufferance. In recent years, clear phenomena of temporal summation of pain (or windup) and central sensitization have been extensively reported. Neurophysiologic methods able to explore the nociceptive afferent system suggest that FM syndrome is heterogeneous, with pain processing dysfunction at both peripheral and central level. Reduced habituation to multimodal and especially painful stimuli characterizes FM, as well as associated conditions, one of the most common is migraine. A genetic dysfunction of ionic channels may possibly explain neuronal abnormalities at both central and peripheral level in FM, opening a new scenario also in the comprehension of pathophysiological basis of associated conditions.

A46 Medication-overuse headache: an update
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Medication-overuse headache (MOH) is a chronic daily headache evolving from an episodic primary headache (mainly migraine) due to overuse of one or more classes of migraine abortive medication. The development of MOH is associated with both overuse of one or more classes of migraine abortive medication and behavioral predispositions. MOH causes a significant decline in the quality of life and reduces functioning in patients affected. In the same MOH patients, the presence of psychopathological disturbances may be a predictor of relapse and poor response to treatment. In a recent study of our group, we found that MOH patients had a more complex profile of psychiatric comorbidity compared to episodic migraine (EM) patients. Furthermore, clinically relevant obsessive-compulsive disturbances for abused drugs assessed by Yale-Brown Obsessive Compulsive Scale Y-BOCS, appeared to be more represented in the MOH group, while the prevalence of this trait in the EM group was comparable to that of healthy controls (unpublished results).

Management of MOH represents a difficult challenge for clinicians and headache experts, particularly because of the high percentage of relapse after a successful withdrawal treatment. This can be addressed if the patient is followed over a prolonged period of time with a combination of prophylactic pharmacotherapy and use of abortive medication with minimal risk of MOH, avoiding previously overused medications.

With the aim to verify the efficacy and safety of sodium valproate in the short-term treatment of MOH, we recently carried out a multicentre study (SAMOHA study) which demonstrated a superiority of the drug compared to placebo after detoxification [1]. In an ancillary study of SAMOHA, analysing responders and non responders to detoxification and advice to withdraw a benefit was excluded in patients with a long history of MOH [2]. In a further ancillary research we found a significant correlation between MOH relapse and the total MSQ score, the Role Preventive and the Emotional Function sub-scales, suggesting a poorer quality of life in non responders [3]. Recent evidence suggests an involvement of genetic factors in predisposition to medication overuse. In a recent study of our group involving a subsample of MOH patients enrolled in the SAMOHA study, we sequenced all exons, intron/exon junctions and 3’-UTR regions of HDAC3 gene which had been implicated in excessive medication consumption in MOH patients. Univariate analysis showed that the G allele of the exonic SNP rs2530223 was significantly associated with the number of acute medications/month used and with the number of days/month in which acute medication were used (unpublished results).

References

A47 The multimodal treatment in headaches
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Primary headaches are common debilitating disorders with high prevalence and significant socioeconomic and personal impacts. Idiopathic headaches affect all aspects of the individual’s life and are the result of complex interaction of biological, psychological, and environmental factors. In patients with chronic headaches the efficacy of pharmacological
treatments is often not satisfactory. Pain and disability can potentially induce an escalation of analgesics/triptans intake leading to medication-overuse headache [1]. Experiencing pain can trigger a cascade of neurological events that lead to an altered psychological state and therefore to aberrant behaviors. Moreover, prior psychological states and psychiatric comorbidities can confer a heightened risk for pain chronicity, due to processes such as cross sensitization, where exposure to stress in the past results in greater sensitivity to other seemingly unrelated stimuli [2]. Accordingly, the processes of sensitization in headache patients, can be expressed both in the peripheral and central nervous systems, contributing to pain chronicization. Given the multidimensional nature of chronic pain, efficacious assessment and treatment requires a comprehensive, multiaxial approach considering every aspect of the individual’s life [3,4]. Modification of lifestyle habits could play a role in preventive strategies of primary headaches, especially in childhood and in adolescence [5]. The non-pharmacological therapies can be part of a multimodal treatment or an alternative therapy in the case of pregnancy, breast feeding, multiple therapies for comorbid diseases, poor tolerability of drugs, childhood and elderly [6]. Acupuncture and biofeedback are considered the first-choice for the prophylaxis of tension-type headache [6]. Many other non-pharmacological treatments are useful in the prevention of primary headaches, although further well-conducted studies are needed to support their efficacy. They include physiotherapy/physical exercise, progressive muscle relaxation training, short-term psychotherapy and cognitive-behavioural therapy [6]. Another promising intervention is Mindfulness meditation, which is characterized by deliberately focusing on the present moment in a non-judgmental way [7]. Several recent neuroimaging studies suggest that meditation may modulate pain through several mechanisms [8]. It may reduce the saliency of noxious stimuli through attentional focusing, and promote pain modulation reducing expectations of impending noxious stimuli. Moreover, it could induce beliefs related to the promotion of pain relief and refraining from catastrophic thinking. The headache patient can be difficult to manage. We propose the setting of a multimodal treatment, shared by the patient who has to be considered an integral part of care, aimed at improving all aspects of the individual’s life.

References

A48 Vestibular migraine
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Vestibular migraine (VM) has been increasingly recognized as a frequent cause of episodic vertigo, affecting up to 1% of the general population, with female preponderance [1]. Recently, both the Bárány Society and the Migraine Classification Subcommittee of the International Headache Society have proposed original diagnostic criteria for VM, which have been included in the recent edition of the International Classification of Headache Disorders (ICHD-3 beta version). VM diagnosis implies that vestibular symptoms are present during a migraine attack, with or without headache, in the absence of objectively demonstrated interictal vestibulopathy.

In the last decades, several studies have attempted to identify the electrophysiologic markers that could allow a distinction between VM and other vestibular disorders. Nevertheless, despite a growing body of literature, there is still an ongoing debate regarding whether VM origin is principally central or peripheral. However, during the past few years, the extensive application of advanced MRI techniques has contributed to significantly improving the understanding of VM pathophysiology. Functional and structural abnormalities have been detected in brain areas involved in multisensory vestibular control and central vestibular processing in patients with VM [2-4]. However, functional and structural alterations identified in patients experiencing VM also resemble those previously described for migraine. In conclusion, VM probably represents one of the pathophysiological paradigm of migraine and vestibular pathways connection.

Similarly to migraine pharmacological preventive therapy, VM treatment includes different prophylactic medications such as calcium channel blockers, beta-blockers, antiepileptic drugs and antidepressants, reporting consistent reduction of vertigo spells and or migraine attacks in a high rate of patients.

References

ORAL PRESENTATIONS

A49 O041. GRIA3 (glutamate receptor, ionotropic, ampa 3) gene polymorphism influences cortical response to somatosensory stimulation in medication-overuse headache (MOH) patients

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Introduction: Medication-overuse headache (MOH) is a secondary form of chronic headache developed by migraineurs after prolonged symptomatic medication overuse. Bio-behavioural sensitization is a key mechanism in MOH pathophysiology, as evidenced by cortical somatosensory evoked potentials (SSEPs) studies. While episodic migraineurs, recorded between attacks, showed lower initial SSEP amplitudes and lack of habituation during stimulus repetition, in MOH patients the SSEPs were initially higher and further increased during stimulus repetition, resulting in a persistent sensitisation proportional to the duration of the headache chronification.
phase. The central sensitization seems to be strongly dependent by glutamate. Amongst various gene polymorphisms in the glutamatergic system, only the Glutamate Receptor Ionotropic AMPA 3 (GRIA3) was previously associated with migraine. The aim of our study was to verify whether GRIA3 rs3761555 single nucleotide polymorphism (SNP) could influence processes of central sensitization in MOH patients.

Methods: We measured SSEP amplitudes as a marker of sensitizer, and SSEP habituation over two sequential blocks during uninterrupted peripheral stimulation in a well-characterized group of 50 MOH patients who underwent GRIA3 rs3761555 polymorphism analysis.

Results: Sixty (34 females) MOH patients were enrolled in the study: 27 (9 males) resulted as T/T and 26 C/T and 7 (4 males) T/T. In the comparison among the three genotypes, the grand average of all the neurophysiological data did not emerge in terms of latencies and amplitudes. The analysis of block amplitude averages showed differences in SSEP T (p = 0.028) and 3 (p = 0.023) block amplitude.

Discussion: Our findings are consistent with the hypothesis that the glutamatergic system influences central sensitization processes in MOH patients, by plastic changes in the “pain matrix”, resulting in decreased nociceptive thresholds, increased responsiveness to peripheral stimuli and expansion of the receptive fields of central nociceptors. These phenomena are at the base of migraine chronification, maybe due to the higher levels of glutamate, as it is measurable in the CSF of chronic migraineurs. Indeed, we observed that although MOH patients overall had notoriously larger SSEP 1st block amplitude than controls, and deficient habituation, GRIA3 rs3761555 SNP influenced the amplitude of blocks, according to a decreasing gradient from T/T to C/C subjects. Although the analyzed SNP functional consequences are unknown, it was highlighted as somehow implicated in migraine pathophysiology in two independent cohorts of patients, maybe by an altered transcriptional activity. Hitherto, we are not aware of other disorders potentially related to this SNP.

Written informed consent to publication was obtained from the patient(s).

A50

O071. The association between meteoropathy, depression, hopelessness and quality of life in medication-overuse headache patients

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Background: Medication-overuse headache (MOH) is one of the most common forms of chronic daily headache (CDH) [1], with a prevalence in the adult general population of 1%-2% [2]. MOH is often comorbid with emotional disturbances and disordered personality traits. The aim of the present study was to determine whether depression, hopelessness and quality of life were associated with meteoropathy in MOH patients. The most frequent symptom of meteoropathy is the exacerbation of acute or chronic episodes of pain in many parts of the body, in and of itself inflamed and/or degenerated.

Materials and methods: Participants were 203 consecutive adult outpatients, of which 165 females (81.3%), admitted to the local Headache Centre of the Sant’Andrea Hospital in Rome, Italy. Inclusion criteria were a diagnosis of MOH, and an age of 18 years or older. Exclusion criteria were comorbidity with major disorders of the CNS, delirium and/or any condition affecting the patient’s ability to complete the assessment. The average age of participants was 46.99±11.99. Patients participated voluntarily in the study, and each subject provided written informed consent. Patients were administered the BDI II, BHS, Q-LES-Q, TEMPS-A, SHSS, and CTQ.

Results: The results showed significant associations of meteoropathy with depression, hopelessness, and quality of life in medication-overuse headache patients. The association between meteoropathy and depression was significant (r = 0.253; p < 0.01), hopelessness (r = 0.151; p < 0.05), and with some subscales of the Q-LES-Q (-2.82<r>-.105; p < 0.01) and with the levels of hopelessness. The METEO-Q was significantly associated with any dimensions of the Q-LES-Q when controlling for the presence of other variables.

Conclusions: Our data seem to confirm that patients with MOH are prone to experiment the high levels of meteoropathy both in quality and in intensity, confirming that MOH has a negative impact on quality of life. Moreover, meteoropathy was found to be associated with levels of depression, and with physical health, emotions, social relations, and general activities. Possibly neurophysiological and endocrinological alterations linked to climatic changes play a role in affecting quality of life. An integrated approach that includes the neurophysiological and psychological fields may be particularly useful, because of the bi-directionality of the migraine-depression association, of the crucial role of depression in the transformation of migraine in MOH, and could minimize the risk of chronic headaches, improving the prognosis.

Written informed consent to publication was obtained from the patient(s).

Conflict of Interest: The authors report no conflicts of interest.

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References:

A51

0070. The association between temperament, depression, hopelessness and quality of life in medication-overuse headache patients

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Background: Migraine is one of the major causes of disability and lost working days worldwide [1]. Medication-overuse headache (MOH) is one of the most common forms of chronic daily headache (CDH) [2], with a prevalence in the adult general population of 1%-2% [3]. MOH is often comorbid with emotional disturbances and disordered personality traits. The aim of the present study was to explore the impact of mental illness among patients with migraine. To evaluated if depression, hopelessness, suicide risk and quality of life were associated with temperament and trauma in MOH patients.

Materials and methods: Participants were 135 consecutive adult outpatients, of which 113 females (83.7%), admitted to the local Headache Centre of the Sant’Andrea Hospital in Rome, Italy. Inclusion criteria were a diagnosis of MOH, and an age of 18 years or older. Exclusion criteria were comorbidity with major disorders of the CNS, delirium and/or any condition affecting the patient’s ability to complete the assessment. The average age of participants was 47.59 (SD=12.01). Patients participated voluntarily in the study, and each subject provided written informed consent. Patients were administered the BDI II, BHS, Q-LES-Q, TEMPS-A, SHSS, and CTQ.

Results: The results showed that females present higher levels of anxiety (t= 3.392; p < 0.001). Good correlations were found between temperament and levels of depression (r = -0.65; p < 0.001), hopelessness (r = -0.57; p < 0.05), quality of life (r = -0.28<r>-.105; p = 0.01) and with the risk of suicide (r = -0.36; p < 0.05). Particularly, subjects with suicide ideation showed higher scores on the level of depression, (t = -4.823; p = 0.001) hopelessness, (t = -4.261; p < 0.001) and emotional abuse (t = -3.526; p = 0.001).

Conclusions: Our data confirm that patients with MOH showed an anxiety-related temperament associated with high levels of depression, hopelessness and suicide risk. Suicide attempts seem to be more frequent in patients suffering from migraine than in the general population, especially in females. Suicidal ideation was associated with higher headache frequency and headache-related disability. The evidence of a possible link between chronic headache and psychiatric disorder is not a recent finding. Back in 1895, the occurring depressive mood, irritability, and anxiety in these patients [4] was described. Our findings indicate that patients with a diagnosis of MOH and migraine have severe
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hopelessness, and suicide risk. This evidence suggests that psychologic assessment is necessary in patients with MOH, and also that the presence of headache has to be carefully monitored in patients with mental illness. Written informed consent to publication was obtained from the patient(s).

Conflict of interest: The authors report no conflicts of interest.

Acknowledgements: This study was not supported financially by any grants.

References

A52

O028. Thalamo-cortical network changes during the migraine cycle: insights from MRI-based microstructural and functional resting-state network correlation analysis
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Background: Abnormal structural and functional plasticity in cortical and subcortical brain regions may be an important aspect of migraine pathophysiology. Resting state magnetic resonance imaging allows studying functionally connected brain networks and whether there is a relation between the plasticity of resting state networks and integrity of thalamic microstructure during the migraine cycle is not known. To verify functional connectivity between brain networks at rest and its relationship with thalamic microstructure in migraine without aura (MO) patients during and between attacks.

Methods: Twenty-four patients with untreated MO underwent 3T MRI scans during (n=12) and between attacks (n=14) and were compared to a group of 15 healthy volunteers. We used MRR to collect resting state data among four selected resting state networks, identified using group independent component (IC) analysis. Fractional anisotropy (FA) values of bilateral thalami were retrieved from a previous diffusion tensor imaging study on the same group of subjects and correlated with resting state ICs Z-scores.

Results: We found a significant reduced functional connectivity between the default mode network and the visuo-spatial system between attacks, and between the executive control network and the dorso-ventral attention system during attacks. When HV and migraine groups were combined, ictal and interictal selected ICs Z-scores correlated negatively with bilateral thalami FA values.

Conclusions: The present results are the first evidence supporting the hypothesis that abnormal dynamics of the connectivity between thalamus and functional cerebral networks at rest could contribute to the recurrence of migraine attacks.

Written informed consent to publication was obtained from the patient(s).

A53

O032. Associations between any headache and obesity: results from a systematic review and meta-analysis of observational studies
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Background: Data about the association between migraine and obesity are controversial, but a recent meta-analysis showed an association between the two conditions [1]. As numerous studies addressing the possible association between any headache (including migraine) and obesity have provided conflicting findings [2,3], we therefore performed a systematic review and meta-analysis of observational studies, to assess the associations between any headache and obesity and pre-obesity.

Materials and methods: Data were obtained through multiple electronic databases up to April 2015, using the terms “migraine” OR “headache” in combination with “obesity” OR “pre-obesity” OR “body mass index”. Out of 2,022 records, we finally included 4 studies [4-7]. We obtained pooled adjusted effect estimates (PAEE) of the risk of having any headache in obese and pre-obese subjects versus normal weight subjects, and in obese and pre-obese women versus normal-weight women. To obtain PAEE the natural logarithm of each single estimate was weighed by the inverse of its variance. Only studies written in the English language reporting a clearly, unequivocal definition of exposure and outcome variables were included. To reduce methodological heterogeneity we performed our analyses including only the studies which defined BMI categories according to the World Health Organization (WHO) criteria for Western populations (underweight, <18.50 kg/m2; normal range, 18.50-24.99 kg/m2; overweight, ≥25.00 kg/m2; pre-obesity, 25.00 - 29.99 kg/m2; obesity, ≥30.00 kg/m2).

Results: We found an increased risk of any headache in obese versus normal-weight subjects in 3 studies [5-7]; overall PAEE 1.29, [95% confidence interval (CI) 1.04-1.60; p = 0.022]; in obese versus normal-weight women in 2 studies [4,5]; overall PAEE 1.41, (95% CI 1.23-1.62; p < 0.001) and in pre-obese versus normal-weight women in 2 studies [4,5]; overall PAEE 1.13, (95% CI 1.01-1.25; p = 0.025). When considering pre-obese versus normal-weight subjects in 3 studies [5-7], we did not find an increased risk of any headache (overall PAEE 1.06, [95% CI 0.94-1.18; p = 0.335].

Conclusions: The meta-analysis of the available observational studies suggested an association between any headache and obesity, that was stronger in the female gender, and between any headache and pre-obesity in the female gender; these results are in line with the previous meta-analysis findings [1].

References
**A54**

**0026.** An abnormal transduction of the chromatic stimuli from the outer to the inner retinal layers may contribute to cause photophobia in migraine

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*The Journal of Headache and Pain 2015, 16(Suppl 1):A54*

**Background:** Recent experimental evidence points out a possible involvement of outer and inner retinal layers in hypersensitivity of migraine patients to light stimuli. To investigate the short-wavelength-sensitive (S) and the medium-long-wavelength-sensitive (ML) cone photoreceptors of the visual pathways in migraine without aura (MO) patients between attacks and in healthy volunteers (HV) by using yellow-blue (Y-B) or red-blue (R-B) visual flicker stimuli.

**Methods:** Square-wave focal electroretinograms (FERGs) were recorded in 22 MO patients and 20 HV. For each randomly presented flicker stimulation protocol (Y-B or R-B), 600 sweeps (4 Hz repetition rate) were recorded and partitioned in 6 blocks of 100. Fourier analysis allowed extracting from the FERG data the fundamental (1F) and the second harmonic (2F) components (amplitude and phase) that are related respectively to outer and inner retinal activity. Usual headache severity and photophobia during migraine were scored on a 0 to 10 visual analogue scale.

**Results:** When compared to HV, MO patients had an advanced 1F phase but normal amplitude in all blocks of Y-B FERG. In MO patients, the self-rated intensity of ictal photophobia was positively correlated with attack frequency (r = 0.571, p = 0.01), headache severity (r = 0.508, p = 0.03), 1F Y-B phase (all blocks r = 0.487, p = 0.04), 1F R-B phase (r = 0.521, p = 0.03), 2F Y-B amplitude (all r = 0.610, p < 0.01), habituation slope (r = 0.686, p < 0.01), and 2F R-B phase (r = 0.526, p = 0.03).

**Conclusions:** These results suggest that an abnormal signal transduction from the outer to the inner retinal layers could contribute to the mechanisms by which light causes pain or discomfort during the migraine headache.

Written informed consent to publication was obtained from the patient(s).

**A55**

**0027.** Sub-cortical sources of the somatosensory pathway are hypoactive in migraine interictally: a Functional Source Separation analysis

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**Background:** Recent morpho-functional evidence pointed out that abnormalities in the thalamus could play a major role in the expression of migraine neurophysiological and clinical correlates. Whether this phenomenon is primary or secondary to its functional disconnection from the brainstem remains to be determined. We used a Functional Source Separation algorithm of EEG signal to extract the activity of the different neuronal pools recruited at different latencies along the somatosensory pathway in interictal migraine without aura (MO) patients.

**Methods:** Twenty MO patients and 20 healthy volunteers (HV) underwent EEG recording. Four ad-hoc functional constraints, two sub-cortical (F514 at brainstem and F516 at thalamic level) and two cortical (F520 radial and F522 tangential parietal sources), were used to extract the activity of successive stages of somatosensory information processing in response to the separate left and right median nerve electric stimulation. A band-pass digital filter (450-750 Hz) was applied offline in order to extract high-frequency oscillatory (HFO) activity from the broadband EEG signal.

**Results:** In both stimulated sides, significant reduced sub-cortical brainstem (F514) and thalamic (F516) HFO activations characterized MO patients when compared with HV. No difference emerged in the two cortical HFO activations between the two groups.

**Conclusions:** Present results are the first neurophysiological evidence supporting the hypothesis that a functional disconnection of the thalamus from the subcortical monoaminergic system may underline the interictal cortical abnormal information processing in migraine. Further studies are needed to investigate the precise directional connectivity across the entire primary subcortical and cortical somatosensory pathway in interictal MO.

Written informed consent to publication was obtained from the patient(s).
A57

O046. Color vision and visual cortex excitability are impaired in episodic migraine. Simply coexisting or pathophysiologically related dysfunctions?1
Filippo Brighina1, Viviana Fippo1, Simona Maccoca2, Vittoria Calabò1, Fabio Lombardo1, Giuseppe Cosentino2, Roberta Baschi1, Nadia Bolognini2, Giuseppe Vallar2, Brigida Fierro1

1 Dipartimento di Biomedicine Sperimentali e Neuroscienze cliniche (BioNeC), Università di Palermo, Palermo, Italy; 2 Dipartimento di Psicologia, Università di Milano Bicocca, Milano, Italy
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The Journal of Headache and Pain 2015, 16(Suppl 1):A57

Background and objectives: Evidence of abnormal color vision processing in migraine comes from observation of positive symptoms during visual aura, effects of strong color contrast triggering attacks and of colored-spectacles reducing migraine frequency. Although the central or peripheral basis of such color misperception remains unclear, several authors reported a selective deficit of short-wavelength cones (S-cones) [1]. Sound-induced flash illusions (SIFI) are a simple way to describe visual distortion induced by acoustic perception. SIFI critically depend on excitability of primary visual cortex (V1) as they are reduced by facilitatory anodal transcranial direct current stimulation (tDCS) over V1 in healthy subjects [2]. We observed diminished SIFI in episodic migraine patients, especially in those with aura (MA) and during the attack [3] in agreement with the hypothesis of visual cortex hyperexcitability. Aim of the present study was to explore the potential correlation between cones dysfunction (evaluated by colorimetric scales) and visual cortex hyperexcitability (tested by SIFI) in episodic migraine without aura patients (MoA).

Materials and methods: Twenty-two MoA patients (4 M; mean age 35.8 ± 11.1 years) and 12 unimpaired healthy volunteers with no family history of migraine (9 M; mean age 27.7 ± 13.2 years) were enrolled. Migraine patients were tested interictally. None of the patients enrolled had taken any prophylactic drug during the 3 months prior to the experiment. Every participant took part in two randomized experimental sessions. Experiment 1 consisted of the Farnsworth-Munsell 100-hue test: the disks in 4 different trays had to be arranged to form a smooth color sequence between two reference disks. Experiment 2 consisted in reporting the number of flashes seen on a black screen in isolation or in different combinations with beeps.

Results: Cone deficits were more prevalent in the migraine (72%) than in the control group (0.08%). S-cone defect (56.2%) was still the most frequent alteration detected in our sample. Accordingly with previous results MoA patients as a whole showed no significant difference in SIFI perception as compared to controls even if a trend towards reduced illusory percept was found. However, when performing subgroup analyses, the MoA group with S-Cone defect showed significantly less fission illusions as compared to the group of healthy subjects (p < 0.001).

Discussion and conclusions: S-Cone dysfunction is highly prevalent in migraine; patients with such functional retinal impairment show higher levels of visual cortical excitability. The results of the study seem to establish a correlation between visual retinal and higher visual dysfunctions found in migraine. Further evidence (in migraine with aura and in the ictal phase) is needed to define the role and interplay of such abnormalities in migraine pathophysiology.

Written informed consent to publication was obtained from the patient(s).

References

A58

O017. Cortical functional correlates of responsiveness to short-lasting preventive intervention with ketogenic diet (KD) in migraine: a multimodal evoked potentials study
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The Journal of Headache and Pain 2015, 16(Suppl 1):A58

Background: Ketogenic diet (KD) - a dietary regimen that mimics fasting in producing ketone bodies - seems to have a role in preventing migraine. The molecular mechanisms underpinning ketogenic diet effectiveness are only partially clear.

Aim: With the aim of identifying cortical electrofunctional correlates of responsiveness to short-lasting preventive intervention with KD in migraine, we recorded visual (VEPs) and somatosensory (SSEP) evoked-potentials before and after 1-month intervention with KD.

Methods: Sixteen interictal migraine without aura patients (MO, ICHD-II code 1.1) underwent VEPs (right eye stimulation, 600 sweeps, 3.1Hz reversal rate, 15 min of arc check) and median nerve SSEPs (right stimulation, 500 sweeps, 4.4 repetition rate, 1.2 motor threshold) recordings, before and during ketogenesis, confirmed by urinary sticks. We measured VEPs N75-P100 and SSEPs N20-P25 amplitudes respectively in 6 and in 2 sequential blocks of 100 sweeps, and habituation as the slope of the linear regression between block 1 to 2 for SSEPs or between 1 to 6 for VEPs.

Results: After 1-month of KD, a significant reduction of mean migraine frequency (from a mean of 4.1 to 1.4 attacks/month, p < 0.001) and duration (from 51.9 to 16.3 hours/month, p < 0.001) was observed. KD did not change N1, N2, and P2 amplitude of VEPs or SSEPs block of 100 sweeps, but significantly reduced habituation as the slope of the linear regression between block 1 to 2 for SSEPs or between 1 to 6 for VEPs.

Conclusions: We found evidence for KD-induced changes at cortical level in parallel to an improvement of migraine. Since KD was able to restore normal EPs habituation curves during stimulus repetition without changing significantly early amplitude responses, we hypothesize that KD acts on habituation via an enhancement of late GABA inhibition.

Written informed consent to publication was obtained from the patient(s).

A59

O044. Frequency-dependent habituation deficit of the nociceptive blink reflex in migraine with and without aura
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Background: The habituation phenomenon is a frequency-dependent form of non-associative learning which reflects the excitability level of both sensory and pain systems. We previously demonstrated a frequency-dependent deficit of habituation of the conventional blink reflex in migraine [1]. We investigated the habituation of the trigeminal nociceptive system by studying the habituation of the late component (R2) of the nociceptive blink reflex (nBR) in a wide range of stimulation frequencies in subjects with migraine without aura (MWOA) and with aura (MWA).

Methods: We studied, interictally, 25 MWOA and 17 MWA subjects, as well as 20 healthy control subjects. We delivered a series of 26 electrical stimuli, at different and randomly chosen stimulation frequencies (0.05, 0.1, 0.2, 0.3, 0.5, and 1Hz), subsequently subdivided into five consecutive blocks of
five averaged and rectified responses for each stimulation frequency. Habitation was measured as the percentage decrease of the mean area under the curve of the R2 component across the blocks.

Results: A significant habituation deficit in the R2 component of the nBR was diffusely found at higher (1Hz and 0.5Hz) and intermediate (0.3 and 0.2Hz) frequencies in MWoA when compared to controls. MWA showed a significant habituation deficit at intermediate (0.3 and 0.2Hz) frequencies when compared to controls. No differences in habituation rate were found at lower (0.1 and 0.05Hz) frequencies between patients and controls.

Conclusions: A frequency-dependent habituation deficit in trigeminal nociception was clearly detected in MWoA at higher and intermediate frequencies. It indicates a wide abnormal processing of painful stimuli at the trigeminal level during the interictal period. On the contrary, MWA showed a clear habituation deficit at intermediate (0.3 and 0.2Hz) frequencies, only revealing a less impaired trigeminal nociceptive excitability during the interictal period. Our data provide further evidence for functional differences between MWoA and MWA.

Written informed consent to publication was obtained from the patient(s).

Reference


A60
OO18. The increased flow pulsatility into cerebral arterial network may play a role in the pathogenic mechanism of migraine headache?
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The Journal of Headache and Pain 2015, 16(Suppl 1):A60

Background: It is now well accepted that migraine headache is mediated by the increased sensitivity and ensuing activation of trigeminovascular nociceptive afferents that innervate the dura mater and their related blood vessels. One of the fundamental questions is to determine which processes actually play a role in promoting such condition.

Aim: To evaluate whether patients with episodic migraine with (MA+) and without aura (MA-), during the interictal period of migraine, would have an increased flow pulsatility into cerebral arterial network and whether it would play a role in migraine headache.

Methods: To evaluate the flow pulsatility into cerebral arterial network, we measured the time-delay in milliseconds (ms) between the R-wave of an electrocardiogram and the arterial pulse wave of cerebral microcirculation (R-APWCMtd) on the frontal cortex detected by near-infrared spectroscopy (NIRS) in 10 patients with MA+ (age 39.5±12.2 years), in 10 with MA- (age 40.3±10.2 years), according to the ICHD-3 criteria (2013), during the interictal period of migraine, and in 15 age, sex and height matched healthy control subjects.

Results: The patients with migraine had a significantly longer R-APWCMtd than the control subjects F= 13.4, p < 0.001: MA+: + 38.3 ms; MA-: + 34.7 ms indicating an increased distensibility of the wall of the cerebral arterial network. In multiple regression analysis, R-APWCMtd was significantly associated with migraine (R² = 0.50, p < 0.0001) but not with age, gender, height, migraine attack frequency and disease duration.

Conclusions: The increased distensibility, reducing the impedance mismatch between aorta and first-generation arteries, leads to an increased flow pulsatility into intracranial dural meningeal vessels that may lead to a mechanical stimulation of the nociceptors that innervate the dural vasculature. This condition may play a role in promoting the sensitization of trigeminovascular afferents and sterile inflammation within the dura mater that are fundamental to the pathogenesis of migraine headache.

Written informed consent to publication was obtained from the patient(s).

A61
P043. Hyperechogenicity of the periaqueductal gray in chronic migraine and episodic migraine as a potential marker of progressive dysfunction: preliminary results with transcranial sonography
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1Clinical Neurophysiology Unit, University of Pavia, Pavia, Italy; 2Headache Science Centre, National Neurological Institute C. Mondino, Pavia, Italy; 3Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy
E-mail: grazia.sances@mondino.it
The Journal of Headache and Pain 2015, 16(Suppl 1):A61

Background: It is widely accepted that the brainstem plays a role in migraine pathophysiology. The periaqueductal gray matter (PAG) is a substantial component of the descending pain modulatory network. Previous MRI studies by Welch et al demonstrated that PAG iron levels are abnormally high both in episodic and chronic migraine, suggesting the hypothesis that iron accumulation may be a marker of progressive PAG dysfunction. The increase in iron levels can be investigated with transcranial sonography (TCS) because of heavy metal-induced hyperechogenicity.

Aim: The purpose of our study was to evaluate hyperechogenicity of PAG in patients with episodic migraine (EM) and in subjects with chronic migraine associated with medication-overuse headache (CM+MOH).

Methods: We evaluated 10 patients diagnosed with EM and 10 patients with CM+MOH: one patient from group 1 and one from group 2 were excluded because of unsonable transtemporal window. TCS was performed using Acuson Sequoia ultrasound machine with a 2-MHz transducer. The sonographic parameters were set according to standard literature criteria. Using the transtemporal approach, the midbrain and diencephalic examination planes were visualized in axial section. Echogenicities of raphe midbrain, substantia nigra and PAG, thalamus, lentiform nucleus and head of the caudate nucleus were examined and graded as hyperechogenic. The maximal width of the frontal horns of the side ventricles and the minimal transverse diameter of the third ventricle were measured on a standardized diencephalic examination plane. Hyperechogenicity was considered as the visually rated intensity of the ultrasound signal increase compared to the surrounding brain tissue.

Results: PAG echogenicity was higher in patients with CM+MOH than in those with EM. 6/9 CM+MOH patients showed PAG hyperechogenicity, while only 1/9 in the EM group.

Conclusions: These preliminary findings suggest the occurrence of a progressive degeneration of PAG in migraine. The possibility to reliably detect it with TCS would provide a low-cost, harmless, widely available tool. Evaluation on a larger population is needed to confirm PAG dysfunction in chronic migraine and the reliability of TCS for screening purpose and to predict the evolution of the disease.

Written informed consent to publication was obtained from the patient(s).

Conflict of interest: None.

A62
P038. Effects of non-invasive vagus nerve stimulation on cerebral vasomotor reactivity in patients with chronic migraine during intercritical phase: a pilot study
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E-mail: f.vernieri@unicampus.it
The Journal of Headache and Pain 2015, 16(Suppl 1):A62

Introduction: Different strategies of neurostimulation have been developed as treatment tools for migraine. Among them, vagus nerve stimulation (VNS) can be performed both invasively and non-invasively. Recently, “Gammacore” has been approved as a non-pharmacological and non-invasive tool for headache, and a recent study demonstrated its efficacy in 22% of patients with acute migraine attacks [1].
Although the pathophysiology of migraine is not yet fully understood, many studies have shown a role of sterile inflammation of cerebral vessels and of the change in diameter of the intracranial arteries. Blood flow velocities and vasomotor reactivity (VMR) in patients suffering from migraine without aura in the intercritical phase were found either increased or normal compared to non-migraineurs healthy controls [2,3]. Since the vagus nerve is the largest parasympathetic nerve of the body, it is probable that its neuromodulation can affect cerebral hemodynamics. The purpose of the study was to evaluate the effects of external vagus nerve stimulation on VMR of patients suffering from chronic migraine.

**Study design:** We enrolled 20 patients aged between 18 and 65 years, suffering from chronic migraine and 20 healthy non-migraineur subjects matched for demographic characteristics. None of them assumed vaso-reactive drugs for at least 30 days before registration. Subjects enrolled underwent registration of blood flow velocity in the middle cerebral artery bilaterally through transcranial Doppler (TCD), in the morning and fasting from food and caffeine. The monitoring was performed at baseline, during and after apnea lasting 30 seconds. After the recording, the subjects underwent external stimulation of the vagus nerve with “Gammacore” device for 90 seconds, and 20 minutes after we once again registered VMR through apnea test. VMR was calculated by means of Breath holding index according to the following formula [4]: VMR/apnea duration in seconds.

**Preliminary results:** No statistically significant differences emerged comparing VMR before and after VNS in our population, irrespective of groups. No patient suffered from adverse event during or after VNS.

**Conclusions:** Non-invasive VNS resulted safe and did not seem to influence VMR, neither in migraineurs nor in healthy volunteers. However, the small sample of our study population does not allow to draw definitive conclusions, hence the study will be further continued to extend sample size.

Written informed consent to publication was obtained from the patient(s).

**References**

**A63**
**PO062. Sensory modalities during dreams in migraine**
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*The Journal of Headache and Pain 2015, 16(Suppl 1):A63

**Background:** Migraine is a primary headache characterized by recurrent episodes of unilateral head pain, associated to vegetative symptoms (nausea) and alterations in sensory experiences: photophobia and phonophobia are diagnostic criteria, osmophobia, although not diagnostic, seems to be very specific [1]. Dream is a universal mental activity present during sleep, characterized by hallucinatory production. Subjects may recall experiences in different sensory modalities, such as visual, auditory, olfactory and gustatory sensations [2]. In a previous study, through an anamnestic questionnaire, we found that migraine patients were more prone than non-migraineurs to recall gustatory and olfactory dreams [3]. We designed a study aiming to eliminate the possible bias due to the retrospective analysis.

**Materials and methods:** We enrolled 104 subjects (69 F, 35 M; mean age 35.3±14.10; range 20-76), of which 59 controls not suffering from any kind of primary headache (30 F; mean age 32.7±13.29; range 20-76), 17 migraine with aura (MA, 17 F; mean age 40.5±3±12.27; range 24-59), 28 migraine without aura (MO, 22 F; mean age 37.86±15.87; range 23-70).

**Results:** We included in the same question, as subjects of a previous study reported olfactory/gustatory sensations. Olfactory and gustatory experiences were included in the same question, as subjects of a previous study reported difficulty in discriminating between these two sensory modalities. We examined the prevalence of subjects reporting each sensory experience at least once in 30 days, and compared different diagnostic groups using Chi square test or Fisher exact test when appropriate.

**Conclusions:** With this study, even eliminating the possible bias of retrospective analysis, we confirmed that migraine subjects experience gustatory and olfactory sensations during dreams more frequently than subjects without migraine. These results suggest a peculiar functioning of brain structures such as the amygdala and the hypothalamus in the migraine brain.

Written informed consent to publication was obtained from the patient(s).

**References**

**ORAL PRESENTATIONS**

**A64**
**0050. Chronic daily headache and body mass index: a meta-analysis of observational studies**
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*The Journal of Headache and Pain 2015, 16(Suppl 1):A64

**Background:** Many studies have investigated the association between chronic daily headache (CDH) and normal weight, pre-obesity, and
obesity, with controversial results. A meta-analysis of observational studies was conducted in order to clarify the association between CDH and body mass index (BMI) categories.

**Methods:** Studies published up to April 2015 about the association between CDH and BMI were systematically searched from multiple electronic databases. We included in the analysis observational studies in the English language with CDH as outcome variables, and pre-obesity or obesity as compared with normal weight as exposure variables. Only the studies which defined BMI categories according to the World Health Organization criteria for the Western population were included (underweight, <18.5 Kg/m²; normal range, 18.5-24.9 Kg/m²; overweight, ≥25.0 Kg/m²; pre-obesity, 25.0-29.9 Kg/m²; class I obesity 30.0-34.9 Kg/m²; class II obesity 35.0-39.9 Kg/m²; class III obesity ≥40.0 Kg/m²). Pooled adjusted effect estimate (PAEE) with 95% confidence interval (CI) was calculated to examine the strength of the association using random-effects models.

**Results:** Out of 2,022 records, 4 studies [1-4] met the selection criteria and were included in the meta-analysis. The pooled analysis suggested an increased risk of having CDH in obese subjects (PAEE 1.48; 95% CI, 1.10; 1.98; p = 0.009) as compared to normal weight subjects, while the risk in pre-obese subjects was not different when compared to that of normal weight subjects (PAEE 1.13; 95% CI 0.93-1.39; p = 0.223) (Figure 1). Data analysis according to BMI categories found that subjects with grade II-III obesity had a higher risk of CDH (PAEE 1.94; 95% CI, 1.50-2.51; p < 0.001) than normal weight subjects, while grade I obesity was not associated with a higher risk of CDH (PAEE 1.05; 95% CI 0.43-2.59; p = 0.909) (Figure 2).

**Conclusions:** According to this meta-analysis of observational studies there is an association between CDH and moderate and severe obesity. This association suggests that body weight management may be a viable

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**Table 1:**

<table>
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<td><strong>[0.93; 1.39]</strong></td>
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**Figure 1(abstract A64)**

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**Table 2:**

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<td>Santos, 2014</td>
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<tr>
<td><strong>Overall</strong></td>
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<td><strong>[1.10; 1.98]</strong></td>
<td><strong>100%</strong></td>
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</table>

**Figure 1(abstract A64)**
strategy for the prevention of chronification in patients suffering from both migraine and tension-type headache.

References


**Outcome: chronic daily headache**

**Exposure: grade I obesity**

<table>
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<th>Study</th>
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<td>Winter, 2009</td>
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<tr>
<td>Overall</td>
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</table>

*Heterogeneity: I²=71.9%, p=0.059*

**Outcome: chronic daily headache**

**Exposure: grade II-III obesity**

<table>
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*Heterogeneity: I²=0%, p=0.484*

Figure 2(abstract A64)

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**A65**

**0010.** Migraine aura symptoms last for more than one hour in more than one quarter of patients: results from a prospective diary-aided study

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*The Journal of Headache and Pain* 2015, **16**(Suppl 1):A65
Background: As there are no biological markers, a detailed description of symptoms, particularly temporal characteristics, is crucial when diagnosing migraine aura. In ICHD-II beta, migraine aura duration is considered normal when each symptom is no longer than one hour. A recent systematic review of the topic [1] did not find any article exclusively focusing on the duration of the aura. The pooled analysis of data from the literature on aura duration showed that visual symptoms last for more than one hour occurred in 6%-10% of patients, sensory symptoms in 14%-27% and dysphasic aura in 17%-60%. Here we investigated the duration of aura symptoms, using a prospective diary-aided approach.

Methods: We recruited 176 consecutive patients affected by migraine with aura at the Headache Centres of Pavia and Trondheim. The study received approval by the local Ethics Committees. All patients signed an informed consent form. All the patients prospectively recorded the characteristics of three consecutive attacks in an ad hoc aura diary that included the time of onset and the end of each aura symptom and the headache.

Results: Fifty-four patients completed the study recording in a diary the characteristics of three consecutive auras (n=162 auras). Out of 162 auras that were evaluated, visual symptoms occurred in 159 (97%), sensory symptoms in 52 (32%), and dysphasic symptoms in 18 (11%). The cumulative number of aura symptoms recorded was therefore 229. The median duration of visual, sensory and dysphasic symptoms was 30, 20 and 20 minutes, respectively. Visual symptoms lasted for more than one hour in 14% of auras (n=158), sensory symptoms in 21% of auras (n=52), dysphasic symptoms in 17% of auras (n=17). Twenty-six percent of patients had at least one aura out of three with one symptom lasting for more than one hour.

Conclusions: This is the first study specifically focused on temporal aspects of migraine with aura. We provide data to suggest that aura symptoms may last longer than one hour in a relevant proportion of auras or migraine with aura patients. These findings will contribute to a better phenotypical framing of migraine with aura and may be of help in the review process of the international classification of headache disorders. Written informed consent to publication was obtained from the patient(s).

Conflict of interest: None.

Acknowledgements: This study was carried out in collaboration with UCADH (University Consortium for Adaptive Disorders and Head pain), University of Pavia, Italy. This work was supported by grants of the Italian Ministry of Health to RC 2013-2015.

Reference

A662

O022. Migraineurs: seriously ill or basically healthy?

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The Journal of Headache and Pain 2015, 16(Suppl 1):A662

Background: Some epidemiological studies report many comorbidities in migraineurs compared with head pain patients, and a recent population-based study [1] showed that 61% of patients with migraine (both with and without aura) were involved in at least one of the PD among the general population (6.4%). The aim of the present study was to evaluate if there is at least one symptom lasting for more than one hour in a significant proportion of patients [1]. Here we investigated in a prospective diary-aided study whether patients with "prolonged aura" (PA - an aura in which there is at least one symptom lasting for more than one hour) are different from the patients with a "typical aura" (TA).

Methods: We recruited 176 consecutive patients affected by migraine with aura at the Headache Centres of Pavia and Trondheim. The study received approval by the local Ethics Committees. All patients signed an informed consent form. Fifty-four patients completed the study recording in a diary the characteristics of three consecutive attacks in an ad hoc aura diary that included the time of onset and the end of each aura symptom and the headache. We also collected demographic and clinical variables of each patient including age, gender, presence of headache associated with aura, frequency of migraine with aura attacks, age at onset of migraine with aura, duration of illness, co-occurrence of migraine with aura or tension-type headache, age of migraine without aura onset, use of a migraine preventive therapy, family history for migraine with aura and white matter lesions at MRI in the analysis. We performed an analysis to evaluate if there was any demographic or clinical variable associated with having suffered from at least one PA out of three attacks.

Results: Fifty-four patients completed the study recording in a diary the characteristics of three consecutive auras (n=162 auras). Fourteen out of...
Table 1 (abstract A67) Association between clinical variables and the condition of having suffered of at least one migraine with prolonged aura out of three attacks: univariate analysis

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>All patients (n=34)</th>
<th>Patients without prolonged aura</th>
<th>Patients with at least one prolonged aura</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>45 (83.3)</td>
<td>32 (80.0)</td>
<td>13 (92.9)</td>
<td>0.487</td>
</tr>
<tr>
<td>Male</td>
<td>9 (16.7)</td>
<td>8 (20.0)</td>
<td>1 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Age, years (SD)</td>
<td>39.6 (14.5)</td>
<td>412 (14.4)</td>
<td>34.8 (14.0)</td>
<td>0.153</td>
</tr>
<tr>
<td>Age at MwA onset, years (SD), n=52</td>
<td>23.4 (11.5)</td>
<td>24.2 (12.2)</td>
<td>21.3 (9.1)</td>
<td>0.571</td>
</tr>
<tr>
<td>Frequency of MwA, attacks/year (SD)</td>
<td>23.9 (27.6)</td>
<td>24.1 (29.6)</td>
<td>23.3 (22.0)</td>
<td>0.866</td>
</tr>
<tr>
<td>Duration of MwA, years (SD), n=52</td>
<td>15.6 (12.7)</td>
<td>17.1 (12.6)</td>
<td>11.3 (12.3)</td>
<td>0.079</td>
</tr>
<tr>
<td>Aura with headache</td>
<td>46 (85.2)</td>
<td>32 (80.0)</td>
<td>14 (100)</td>
<td>0.193</td>
</tr>
<tr>
<td>on 3/3 attacks</td>
<td>3 (5.6)</td>
<td>3 (7.5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Co-occurrence of MwoA n=53</td>
<td>5 (9.3)</td>
<td>5 (12.5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15 (28.3)</td>
<td>10 (25.6)</td>
<td>5 (35.7)</td>
<td>0.710</td>
</tr>
<tr>
<td>Yes</td>
<td>38 (71.7)</td>
<td>29 (74.4)</td>
<td>9 (64.3)</td>
<td></td>
</tr>
<tr>
<td>Age at MwoA onset, years (SD), n=38</td>
<td>17.8 (8.6)</td>
<td>18.3 (8.7)</td>
<td>16.2 (8.6)</td>
<td>0.327</td>
</tr>
<tr>
<td>Frequency of MwoA attacks/month (SD), n=38</td>
<td>5.2 (5.3)</td>
<td>5.4 (5.7)</td>
<td>4.6 (1.4)</td>
<td>0.904</td>
</tr>
<tr>
<td>Co-occurrence of tension type headache</td>
<td>46 (85.2)</td>
<td>36 (90.0)</td>
<td>10 (71.4)</td>
<td>0.213</td>
</tr>
<tr>
<td>No</td>
<td>8 (14.8)</td>
<td>4 (10.0)</td>
<td>4 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Familiarity for aura, n=52</td>
<td>40 (76.9)</td>
<td>28 (73.7)</td>
<td>12 (85.7)</td>
<td>0.588</td>
</tr>
<tr>
<td>Yes</td>
<td>12 (23.1)</td>
<td>10 (26.3)</td>
<td>2 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Preventive prophylaxis, n=53</td>
<td>33 (62.3)</td>
<td>26 (66.7)</td>
<td>7 (50.0)</td>
<td>0.434</td>
</tr>
<tr>
<td>No</td>
<td>20 (37.7)</td>
<td>13 (33.3)</td>
<td>7 (50.0)</td>
<td></td>
</tr>
<tr>
<td>White Matter Changes at MRI, n=45</td>
<td>34 (75.6)</td>
<td>23 (71.9)</td>
<td>11 (84.6)</td>
<td>0.604</td>
</tr>
<tr>
<td>Yes</td>
<td>11 (24.4)</td>
<td>9 (28.1)</td>
<td>2 (15.4)</td>
<td></td>
</tr>
</tbody>
</table>

Prolonged aura: aura with at least one symptom lasting for more than 60 minutes
MwA: migraine with aura; MwoA: migraine without aura

54 patients (26%) had at least one PA, while 30 patients (74%) had three TA. In univariate analyses, none of the clinical or demographic parameters was significantly associated with the fact of having experienced a PA (Table 1).

Conclusions: For the first time we demonstrate that patients with prolonged aura have no demographic and clinical differences with patients with typical aura. These data support the need to review the ICHD criteria for migraine with aura.

Written informed consent to publication was obtained from the patient(s).

Conflict of interest: None.

Acknowledgements: This study was carried out in collaboration with UCADH (University Consortium for Adaptive Disorders and Head pain), University of Pavia, Italy. This work was supported by grants of the Italian Ministry of Health to RC 2013-2015

Reference

O035. Headaches in Mitochondrial Disorders
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Background: Headaches are a well known feature of Mitochondrial Disorders (MCDs). However, no systematic epidemiological data are available in large populations of patients.

We aimed to describe the prevalence and the characteristics of headache in a large group of patients with mitochondrial encephalomyopathies.

Methods: We studied all consecutive patients referred to our Neuromuscular Unit, during a 6-month period. Ninety-three patients (aged 15 to 78 years, 31 males) with a typical phenotype of MCDs, underwent a structured diagnostic headache interview, using an operational diagnostic tool following the IHS criteria. If they met the criteria for primary headache, they were included in the “Headache Group” (HEAD+). The other patients were collected in the “No Headache Group” (HEAD-). Clinical, neuroradiological, and neurophysiological data were compared between groups. Mann-Whitney U-test was used to analyze numeric variables; Fisher’s exact test was used to analyze nominal variables. Binary logistic regression analysis was performed to identify risk factors of headache.

Results: Headaches were reported in 35.48% of patients. Migraine was the most common headache. The patients of the Headache Group were younger (HEAD+ = 45.5±17.2 years; HEAD- = 54.5±14.8 years; U-test = 7.393; p = 0.007), increased prevalence of epilepsy (p = 0.0103), myoclonus (p = 0.0309), stroke (p = 0.0209), EEG focal slow abnormalities (p = 0.0359), EEG
Migraine has a higher prevalence in MCDs compared to
Three hundred and thirty-five patients were recruited: 142
Migraine and epilepsy are chronic disorders, often
None of the patients presented identical characteristics on the
We collected AEs of some AEDs - valproic acid
Thirty patients with migraine without aura prospectively
Migraine attacks may have different features with respect to
Our data confirm the extensive safety and
We emphasize the higher prevalence of AEs due to AEDs in migraineurs, suggesting a peculiar

Background: Migraine and epilepsy are chronic disorders, often comorbid, characterized by transient and recurrent neurological disturbances. Sharing pathophysiological and clinical features, both epilepsy and migraine benefit from antiepileptic drugs (AEDs) treatment. However, despite their overlapping, peculiar differences regarding reported adverse events (AEs) of AEDs seem to emerge in clinical practice. In particular, tolerability and frequency of AEs might depend on the condition from which the patient suffers. Therefore, we interviewed patients treated with AEDs for epilepsy, migraine, and both, in order to compare AEs distribution of frequency among the three groups.

Materials and methods: We collected AEs of some AEDs - valproic acid (VPA), topiramate (TPM), lamotrigine (LTG) - widely used in prophylactic therapy of migraine, in epilepsy as well as in epileptic migraineurs. All AEs were gathered through the Liverpool Adverse Events Profile (LAEP) [1].

Results: Three hundred and thirty-five patients were recruited: 142 suffered from epilepsy (group A), 131 from headache (group B), 62 from both (group C). Mean age was 44.5 in group A, 45.0 in B, 40.5 in C. AEs were significantly more reported in group B (69.5%) and under TPM treatment (71%). The most prescribed AED for group B was TPM, which was more commonly referred to cause paresthesias (68%) and language disorders (42%) among this group than in the other two. Complaints of weight gain were common with VPA in all three groups, with higher frequencies among group B and C. Memory impairment induced by AEDs was reported more frequently for TPM in all three groups, while maximal incidence was reported for VPA and TPM, respectively in group B (5%) and C (9%). Overall, migraineurs were more likely to drop out of treatment (46%) than epileptic patients (29.6%) and patients with epilepsy and migraine (41.9%).

Discussion and conclusions: Our data confirm the extensive safety and effectiveness of AEDs in clinical practice, and point to patient’s tolerability of AEs as pivotal for a successful treatment [2]. We emphasize the higher prevalence of AEs due to AEDs in migraineurs, suggesting a peculiar susceptibility of their condition to experience AEs. This finding, which emerges despite the average higher dosage of AED used for epilepsy, remains actually unexplained. Our results might be intriguingly considered as a clinical implication of central sensitization mechanisms or, not less intriguingly, they might represent the result of an abnormal network plasticity producing microstructural changes in migraine-affected brain [3].

Written informed consent to publication was obtained from the patient(s).

References

Table 1 (abstract A70) Migraine attack features and intrapatient variability

<table>
<thead>
<tr>
<th>Unilateral location</th>
<th>Pulsating quality</th>
<th>Pain intensity (4 point scale)</th>
<th>N</th>
<th>V</th>
<th>PT</th>
<th>PN</th>
<th>O</th>
<th>A</th>
<th>CAS</th>
<th>PS</th>
<th>Number (%) of patients with three identical attacks with respect to some of the features recorded at the moment of symptomatic medication intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (6%)</td>
</tr>
<tr>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9 (30%)</td>
</tr>
</tbody>
</table>

N: nausea, V: vomiting, PT: photophobia, PN: phonophobia, O: osmophobia, A: allodynia; CAS: cranial autonomic symptoms (at least one); PS: premonitory symptoms (at least one)
With respect to the response to frovatriptan, 39% of patients had the same outcome (positive or negative pain-free in 2 hours) on three consecutive attacks.

Conclusions: To the best of our knowledge this is the first study that systematically assessed the percentage of patients reporting migraine attacks with identical features in a given period. Our results demonstrate that migraine attacks show a high variability not just among patients, but also within the same patient. Our findings indicate that stereotype of attacks is uncommon, and reinforces the underlying logic of the current operational classification system.

Written informed consent to publication was obtained from the patient(s).

Conflict of interest: None.

Acknowledgements: This study was carried out in collaboration with UCADH (University Consortium for Adaptive Disorders and Head pain), University of Pavia, Italy. This work was supported by grants of the Italian Ministry of Health to RC 2013-2015

A71
O040. Migraineurs and self-consciousness of illness in a population of hospital workers
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The Journal of Headache and Pain 2015, 16(Suppl 1):A71

Background: The World Health Organization has classified headache as the 14th cause of disabling illnesses. Millions of people are affected by this pathology, especially during their working life. Surprisingly, subjects affected by headache, in particular by migraine, present a low degree of self-awareness of their pathology, and do not usually consult any headache center [1]. For this reason migraineurs often go towards serious complications, such as chronicization or drug abuse. We investigated, in a selected population of workers, employees of the Ospedali Riuniti in Ancona, the number of people affected by headache and their awareness. We also investigated the drugs used to verify the use of a specific therapy for such a diffused pathology.

Methods: We submitted all types of health workers (physicians, nurses, technicians, sanitary operators) to an anonymous questionnaire concerning the presence of headache and its characteristics. Particularly, we investigated if these subjects referred to their general practitioner or to a headache center for their symptoms. We also tried to understand the drugs employed by these people. The type of drugs and the category of the working activity were synthesized as two different ordinal variables. Difference in the distribution of the different drug categories was evaluated with $\chi^2$ test. Statistics was performed with SPSS 13.0 for Windows systems.

Results: We enrolled 1,700 consecutive subjects: 18.1% of the population (308 patients) resulted affected by migraine. Only a minimum part of these patients had consulted a headache center in their life. Subjects tended not to take any drugs for their acute attack of headache, or took significantly more non-steroidal anti-inflammatory drugs (NSAIDs) in respect to triptans. Distribution of the use of the drugs resulted significantly different ($p < 0.0001$) with $\chi^2$ test.

Conclusions: Migraineurs, also in presence of more than one attack in their life, typically showed low self-awareness about their condition and usually did not refer to a specialist headache center. Consequently, the use of specific molecules, such as triptans, presented a very low diffusion. These results reflect international literature, but on the other hand, underline a very unsatisfactory knowledge about migraine and its possible consequences [2,3]. Moreover, these data are especially worrisome because they are representative of a hospital population. Better education and awareness about such a prevalent and disabling pathology and its management should be favored.

Written informed consent to publication was obtained from the patient(s).

References

A72
O004. Improvement in clinical governance of chronic headache by an information network: HealthSOAF - Calabria Headache Network pilot study
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The Journal of Headache and Pain 2015, 16(Suppl 1):A72

Figure 1(abstract A72) Diagnostic and therapeutic paths per clinical scenarios managed by HealthSOAF in the Calabria Headache Network
Background: Good clinical governance of headache implies efficient and accessible diagnostic and therapeutic paths involving health care at different levels [1]. Often clinicians do not appropriately assess and treat headache. Information and communication technologies might play a key role in improving access, quality, efficiency and prevention in health care. HealthSOAF (Service-Oriented Architecture Framework) is a networking and interoperability technological platform aimed to assist multiple level health care access and decision making. Its first real testing scenario in Europe has been the Headache Network in the Italian Region of Calabria targeting to assist clinicians at different levels of health care to correctly diagnose, manage and refer headache patients (Figure 1).

Materials and methods: From November 2014 to March 2015, volunteer nodes in the Calabria Headache Network (10 primary care general practitioners in Catanzaro Lido, Borgia and Sorrento; 3 secondary care neurologists in Catanzaro Lido - spouses; 1 multidisciplinary team tertiary care at the regional Centre for Headache and Adaptive Disorders at the Pugliese-Ciaccio Hospital in Catanzaro - hub) shared the HealthSOAF software client and network access. We retrieved epidemiological and referral data and compared them with preexisting information and estimation about the area.

Results: One hundred and ninety-seven patients accessing the primary care units in the considered period obtained a diagnosis of headache. Nineteen (9.64%) were referred to the Emergency Rooms. Seventy-four patients (37.56%) were diagnosed as episodic primary headache. Sixty-eight patients (18.27%) were managed by an outpatient neurologist (episodic primary headache). Sixty-eight patients (34.52%) were referred to the Centre for Headache and Adaptive Disorders as chronic headache cases. Compared to preexisting data, this marked an improvement in access to headache care and reduction of inappropriate referrals to the Centre for Headache (pre: 15.42%; post: 7.35%).

Conclusions: The use of the HealthSOAF platform in this experimental pilot is associated with enhanced diagnostic correctness and access to tailored headache services in the considered area, suggesting that network-based clinical decision support informational tools can improve the clinical governance of headache.

Written informed consent to publication was obtained from the patient(s).

Reference

A74

P049. Migraine influence on female reproductive life and motherhood
Matteo Fuccaro1, Cristina Martin1, Martina Bruno2, Matteo Bellamio3, Federico Mainardi3, Carlo Lisotto2, Giorgio Zanchin3, Ferdinando Maggioni1
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The Journal of Headache and Pain 2015, 16(Suppl 1):A74

Introduction: Migraine (M) is one of the most frequent diseases recognized as a cause of disability, with a relevant influence on the quality of life, particularly in women.

Aim: Our study proposes to evaluate whether migraine affects reproductive choices and motherhood.

Methods: We interviewed 399 women affected by M without (93.5%) and with (6.5%) aura, aged 17-79 years, using a semi-structured questionnaire. We collected data about intensity of attacks and frequency, fertility, pregnancies, abortion/miscarriage, number of children, influence on decisions about pregnancy and perceived ability in motherhood. A control group of 400 non migrainean women was interviewed for comparable items.

Results: Among the 399 women interviewed, 94 (23.6%) were post-menopausal, while 305 (76.4%) had their menses; 155 (38.8%) were nulliparous while 244 (61.2%) had had at least one pregnancy; 224 (56.1%) were mothers while 175 (43.9%) did not have children; 86/244 (35.2%) experienced miscarriage or chose abortion at least once. Two hundred and twenty-three (55.9%) had less than 5 attacks/month, 130 (32.6%) had 5 to 14 attacks/month, 46 (11.5%) had 15 or more attacks/month. Pain intensity was low (NRS 1 to 4) in 18 (4.5%), moderate (NRS 5 to 7) in 108 (27.1%), high (NRS 8 to 10) in 273 (68.4%). Among the 399 women we interviewed, of those who wanted another child (184; 46.1%), 60/184 (32.6%) considered their headache a problem for a pregnancy. Two patients interrupted a sought-pregnancy because of the headache. Among patients who did not want (further) pregnancies (215; 53.9%), 20/215 (9.3%) listed headache among the causes for this choice. Few patients considered headache the only reason for their choice. Two hundred and twenty-seven of 399 women (56.9%) reputed headache an impediment to their being mothers. However, few women asked their doctor for information on the relationship between pregnancy and migraine.

A73

O063. Moyamoya disease and headache: case report
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The Journal of Headache and Pain 2015, 16(Suppl 1):A73

Background: Moyamoya disease is a vascular dysplasia clinically characterized by a combination of ischemic and hemorrhagic strokes. The Research Committee on Moyamoya disease in 1979 classified the initial attacks into 6 types; subsequently, the asymptomatic and the headache type were also added in 2003. In fact headache is common in Moyamoya disease and can be the first symptom especially in childhood; its characteristics and classification are largely unknown because of the uncertainty and probably multifactorial nature of the mechanism [1].

Case report: A seven-year-old Romanian girl, presented to the Emergency Department with a new headache. Headache is a well-known confounding factor in the clinical course of Moyamoya disease. Neurologic symptoms had appeared for four days and headache onset had started a year ago, with daily onset, especially in the evening, more pronounced in the frontal region, with oppressive and binding features, often triggered by physical exertion and requiring daily assumption of ketoprofen. The brain magnetic resonance imaging showed: bilateral cortical ischemic areas involving the fronto-mesial regions and the right periorbital region, complete occlusion of the medium and posterior cerebral arteries, and lenticulostriate and thalamostriate arteries dilated with a “puff of smoke” appearance. The patient was sent to the Pediatric Neurosurgery of the A. Gemelli Hospital in Rome where she underwent cerebral arteriography and surgical operation (121S). Indirect revascularization of the right (December 2014) and the left side (February 2015) was done by means of encephalo-myo-syngangiosis and accessory burr holes. At first follow-up: the drop attacks had disappeared, and there was significant improvement of the hemiparesis and the steppage. Current therapy is cardioaspirin 50 mg/die. The girl refers considerable improvement of the headache with weekly recurrence and mild intensity.

Discussion: Diagnostic classification of headache associated with Moyamoya disease is controversial: the characteristics of headache vary and may be migraine-like throbbing pain or the dull headache noted in tension-type headache. In most of the studies headache is suggested to be an important symptom of ischemic cerebrovascular diseases and surgery bypass seems to be an effective therapy in most patients. Other studies report that headache can persist or develop after indirect bypass surgery despite successful prevention of cerebral ischemia; thus, progressive recruitment and redistribution of blood flow should be considered another cause of headache. The efficacy of surgery revascularizations even on the headache symptom clarified that her headache was probably related to cerebral hyperperfusion.

Written informed consent to publication was obtained from the patient(s).

Reference

POSTER PRESENTATIONS

A74

P049. Migraine influence on female reproductive life and motherhood
Matteo Fuccaro1, Cristina Martin1, Martina Bruno2, Matteo Bellamio3, Federico Mainardi3, Carlo Lisotto2, Giorgio Zanchin3, Ferdinando Maggioni1
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The Journal of Headache and Pain 2015, 16(Suppl 1):A74

Introduction: Migraine (M) is one of the most frequent diseases recognized as a cause of disability, with a relevant influence on the quality of life, particularly in women.

Aim: Our study proposes to evaluate whether migraine affects reproductive choices and motherhood.

Methods: We interviewed 399 women affected by M without (93.5%) and with (6.5%) aura, aged 17-79 years, using a semi-structured questionnaire. We collected data about intensity of attacks and frequency, fertility, pregnancies, abortion/miscarriage, number of children, influence on decisions about pregnancy and perceived ability in motherhood. A control group of 400 non migrainean women was interviewed for comparable items.

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Conclusions: Our results seem to show a negative influence of M on decision of facing a pregnancy and self-perception as mothers, may be contributing in perceived disability.
Written informed consent to publication was obtained from the patient(s).

A75
P072. The visual cortical excitability in pediatric migraine as tested by sound-induced flash illusions
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The Journal of Headache and Pain 2015, 16(Suppl 1):A75

Objectives: Sound-induced flash illusions (SIFI) depend on visual cortex (V1) excitability [1]. In adults with migraine, in response to visual-acoustic illusions, V1 is hyperexcitable [2]. Susceptibility to SIFI is increased in children than adults. During childhood there is a change in sensory dominance: acoustic dominant switching to a visual [3]. Here we used SIFI to evaluate V1 excitability in children with migraine assessing also age-related differences in cross-modal audio-visual perception.

Materials: Twelve children (7 females) affected by migraine without aura: mean age: 10.17±2.76 years, disease duration: 2.91±2.34 years and frequency of attacks: 4.17±3.76/months. Fifteen healthy children (11 females), mean age 10.61±2.92 years and twenty-four healthy adults (12 females), mean age 25.12±5.74 years with no familiarity for migraine. All subjects were not taking any drugs known to affect cortical excitability. Migraineurs were examined interictally.

Methods: Visual (flash) and sound (beep) stimuli were presented with different combinations: multiple flash trials where a single beep caused the perception of less flashes, "fusion illusions" and trial where multiple beeps with single flash, induced perception of more flashes, "fission illusion". Each combination was randomly presented 10 times. At the end of each presentation the subject had to indicate the number of the flashes seen.

Results: Children saw more illusions than adults (fusions p < .005, fissions p < .0001). Children with migraine did not differ from age matched controls in the illusion percept of fusion or fusion, but they perceived more flashes (p < .05) in multiple flash trials with or without beep.

Conclusions: The increased number of SIFI seen by children is likely due to the higher propensity of visual stimulation driven by auditory stimulus, probably because of acoustic dominance typical for the age. Even if no differences in fusion or fusion illusion percept between controls and patients emerged, the increased ability of migraine children to perceive flashes, even outside migraine attack, reveals a hyper-functional visual cortex in migraine also in pediatric age. The sound-induced flash illusions proved to be a valid tool for testing the visual cortical responsiveness in pediatric migraine.

Written informed consent to publication was obtained from the patient(s).

References

A76
P069. Osmophobia in children with headache
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The Journal of Headache and Pain 2015, 16(Suppl 1):A76

Introduction: Osmophobia, or olfactory hypersensitivity, has variable prevalence in children with headache and was proposed as an additional criterion for the diagnosis of migraine in the appendix of the International Classification of Headache Disorders (ICHD)-III beta [1], showing low sensitivity and high specificity for this disturbance [2-4]. The aim of our retrospective study was to define the prevalence of osmophobia in a paediatric population with headache.

Methods: All the children admitted for headache to a Pediatric Headache Centre from 01/01/2013 to 31/12/2014 were included in the study. For children admitted in 2014, the diagnosis was carried out according to the ICHD-III beta criteria; for those admitted in 2013 the diagnosis was revised according to the same classification. We investigated the presence of osmophobia and type of offending smells reported by the patients.

Results: We included 482 subjects (259 females): mean age 10.2 years (range 2.5-17.5). Three hundred and forty-four patients (71.3%) had a diagnosis of migraine without aura, 25 migraine with aura (5.1%); 93 children (19.2%) showed tension-type headache; 17 children (3.5%) had an unspecified form of headache or headache not elsewhere classified; 3 patients (0.62%) presented episodic syndromes that may be associated with migraine. Out of 39 patients (8.1%) reporting osmophobia, almost all had migraine (36 without aura, 2 with aura) and only 1 was diagnosed as tension-type headache. Osmophobia was a symptom detected in 10.4% of patients with migraine without aura and in 8% with migraine with aura. The most frequent offending smells were: perfume in 12 cases (30%), 9 food (22.5%), 4 cigarette smoke (10%), 2 food plus perfume (5%), 1 perfume plus cigarette smoke (2.5%), 5 other odours (15%) and 6 undefined (15%).

Conclusions: Our study showed a lower prevalence of osmophobia in children with headache than that reported in the literature. However, we confirm that osmophobia is more specific for migraine without aura. As already demonstrated in adults and younger patients, osmophobia should be considered in clinical practice as a peculiar symptom useful in the differential diagnosis between migraine without aura and tension-type headache in childhood.

Written informed consent to publication was obtained from the patient(s).

References

A77
P061. Clinical characteristics of elderly with headache in an outpatient geriatric setting in Italy
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The Journal of Headache and Pain 2015, 16(Suppl 1):A77

Background: Multiple epidemiological studies show that headache is less prevalent in elderly people. Despite this, there is evidence that headache has a significant impact in elderly quality of life. There are few studies evaluating characteristics of elderly patients with headache. Aim of the present observational study was to evaluate the characteristics of elderly patients reporting headache in an outpatient geriatric service in Italy.

Methods: Data were collected from October 2014 to March 2015 in patients over 70 years of age. We used the Pain Detect Scale, a previous validated instrument, to investigate presence of any type of non cancer pain. The scale detected presence of pain, including headache, and assessed intensity of pain during the last month, using a numeric rating
Mean age of 94 participants was 81 years, 65 (69.1%) were women and 29 (30.8%) were men. Eight (8.5%) patients reported headache with significant pain intensity (VAS > 5). Patients with headache had high comorbidity (mean of 6 different diagnoses) and took multiple drugs (mean of 6 different drugs). Two of the 8 patients had a significant cognitive decline (MMSE < 23) (Table 1).

Conclusions: Among older adults assisted in outpatient setting, headache is not highly prevalent but when present, is a cause of significant chronic pain. Elderly persons with headache are a frail population with high comorbidity and multiple drug therapies that can represent a challenge for physicians involved in pain management.

Written informed consent to publication was obtained from the patient(s).

Table 1(abstract A77) Clinical characteristics of elderly with headache

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</table>

scale. We also collected data about comorbidity, number of drugs taken and cognitive status (using MMSE score).

Results: Mean age of 94 participants was 81 years, 65 (69.1%) were women and 29 (30.8%) were men. Eight (8.5%) patients reported headache with significant pain intensity (VAS > 5). Patients with headache had high comorbidity (mean of 6 different diagnoses) and took multiple drugs (mean of 6 different drugs). Two of the 8 patients had a significant cognitive decline (MMSE < 23) (Table 1).

Conclusions: Among older adults assisted in outpatient setting, headache is not highly prevalent but when present, is a cause of significant chronic pain. Elderly persons with headache are a frail population with high comorbidity and multiple drug therapies that can represent a challenge for physicians involved in pain management.

Written informed consent to publication was obtained from the patient(s).

A79

P033. Headache and commuting: preliminary data in a group of workers
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Introduction: The different forms of primary headache disorders are highly prevalent which, taken together, affect a greater extent of people of working age. Risk factors of headache triggers can be physical, psychosocial or organizational (work in shifts, night work, working conditions non-ergonomic, etc.). Commuting is a phenomenon which consists in the double daily shift of people moving, usually by public transport.

Objective: The aim of this study was to study the phenomenon of commuting, especially the prevalence, in a group of workers of a chemical industry.

Patients and methods: Health surveillance and medical history questionnaires focused on employment and on the presence of primary headache in 95 workers of a chemical industry (91 M, 4 F). Night shift work interested 52.6% of workers, while 47.4% worked during the day. The diagnosis of migraine was defined according to the criteria of the ICHD-III beta version.

Results: The analysis of the questionnaires and the processing of the results showed that the form of primary headache with higher prevalence, in both night shift workers and day workers, was represented by migraine without aura (51.5% of all headache workers) followed by tension-type headache (42.5%) and by migraine with aura (6%). The different prevalence of primary headaches in the two groups of workers (shift and day workers) did not reach statistical significance. We then decided to consider instead the commuting variable since 46% of night shift workers were also commuters. Processing of the data of the subgroup showed a statistically significant association between the prevalence of primary headache and commuting/night shift (p < 0.05).

Conclusions: The commuters/shift workers are more prone to develop a primary headache, especially migraine without aura. Further investigations are needed to better clarify the association between primary headache and commuting/shift working, and also, more generally, “unusual” rhythm of work.

Written informed consent to publication was obtained from the patient(s).

A80

P051. Olfactory migrainous hallucinations: a typical aura manifestation?
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Introduction: Although olfactory hallucination or phantosmia could occur in several neurological and non-neurological conditions, olfactory migrainous hallucination (OMH) is a rare and probably underestimated phenomenon, involving about 0.1% of migraine patients [1], and not considered among the migrainous aura manifestations according to the
International Classification of Headache Disorders, 3rd edition (ICHD-III beta version) [2]. Very few clinical studies on the topic have been published [3]; therefore, the clinical characterization of OMH is still lacking.

Materials and methods: We report the clinical features of OMH prospectively collected by a detailed and structured anamnesis obtained in 5 patients who spontaneously referred the presence of OMH associated to their headache attacks. Patients were subsequently followed with a diary for at least a year. Moreover, the efficacy of the prophylactic therapy, if suggested, has been recorded.

Results: Five patients (4 females, 1 male) presented a history of migraine without aura (MO) (n=4) and with aura (MA) (n=1) associated with OMH. Mean age at the first evaluation and at headache onset was respectively 42.2 years (range 25-51) and 17.0 years (range 5-28), while OMH appeared at a mean age of 34.6 years (range 5-54). In 4 cases, a comitant primary headache was diagnosed (MA, n=2; episodic tension-type headache, n=1; primary stabbing headache, n=1). Physical and neurological examinations, laboratory analyses, neuroimaging and EEG resulted unremarkable. OMH presented with an average frequency of once every 3 attacks. Onset and resolution of phantosmia were sudden in 3 cases and gradual in the remaining 2, with a mean duration of 10 min. The painful phase followed the disappearance of OMH in all the cases. The type of the perceived smell was invariably constant in 9 patients, whereas different odors were reported by different patients for every different attack.

Conclusions: When properly asked, patients are able to describe in detail the features of their olfactory hallucination. Their characteristics fulfilled the ICHD-III beta criteria for the aura symptoms [2]: if these features should find confirmation in further prospective studies, OMH could be considered similarly to the typical aura manifestations and included among them in the MA diagnostic criteria in the appendix of the next ICHD.

Written informed consent to publication was obtained from the patient(s).

References

A81
P055. Prevalence of migraine in subclinical hypothyroidism: a case-control study
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The Journal of Headache and Pain 2015, 16(Suppl 1):A81

Background: The existence of an association between migraine and thyroid diseases is still a matter of debate. Epidemiological studies have shown a potential association between plasma TSH concentrations and migraine but results are contradictory. Subclinical hypothyroidism (SCH) is a common clinical entity defined biochemically as a normal serum free thyroxine (FT4) concentration in the presence of an elevated serum thyroid-stimulating hormone (TSH) concentration. In population-based studies, the prevalence of SCH ranges from 4 to 15 percent, while in headache patients the incidence is lower. In a previous study the prevalence of SCH was 6% among migraineurs.

Purpose of the study: To evaluate the prevalence and clinical characteristics of migraine in patients with SCH.

Methods: A case-control clinical study was conducted to investigate the prevalence of migraine in 75 consecutive patients (66 females, 9 males; mean age ± SD: 52.8 ± 14.9 y) with SCH and in 120 matched healthy controls. Detailed information about migraine was obtained using a structured questionnaire at a face-to-face interview. Moreover, TSH, FT4, anti-thyroid peroxidase antibody (TPO-ab), and antithyroglobulin (TG-ab) antibodies were measured in SCH patients.

Results: The prevalence of lifetime migraine in SCH patients was statistically significantly higher than that in controls (62% vs 18%; p < 0.001; odds ratio = 7.43; 95% confidence interval = 3.88-14.25). Percentage of migraine with aura versus migraine without aura (MA/ MO) was statistically significantly higher in SCH patients than controls (p = 0.03). TSH, FT4, TPO-ab and TG-ab concentrations were not significantly different between SCH patients with and without migraine.

Conclusions: Our data suggest that patients with subclinical hypothyroidism have a higher risk of lifetime migraine than controls. Additional studies are needed in order to confirm this association and to investigate potential mechanisms of this comorbidity. Written informed consent to publication was obtained from the patient(s).

References
P037. Headache in multiple sclerosis: prevalence and clinical features in a case control-study

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The Journal of Headache and Pain 2015, 16(Suppl 1):A83

Background: Ten cross-sectional studies have examined a potential association between migraine and multiple sclerosis (MS); some of them found an association between the two conditions [1,2] while five studies did not [3]. The overall incidence of migraine in MS patients ranges from 4% to 64%, but very few controlled studies has been conducted [4,5].

Objective: The aim of the present study was to investigate the prevalence and the clinical features of different types of headaches in subjects affected from MS respect to a control group.

Methods: One hundred and fifty adults (F/M = 98/52; mean age 40 years) with a diagnosis of MS and 150 sex and age-matched controls (F/M = 101/49; mean age 40 years) from the general population were evaluated by means of an ad hoc semi-structured interview according to the International Classification Headache Disorders (ICHD-3-beta) criteria. All subjects filled out validated questionnaires about fatigue, Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS). The χ2 and Kruskal-Wallis tests were used when appropriate.

Results: The two groups differed significantly for education level and employment. Among the 150 patients with MS, 1 (0.7%) presented a radiologically isolated syndrome (RIS), 17 (11.3%) a clinically isolated syndrome (CIS), 20 (13.3%) a primary progressive form (PPMS), 96 (64%) a relapsing remitting form (RR), and 16 (10.7%) a secondary progressive form (SPMS). Headache was reported by 80 (53.3%) MS cases and 71 controls (47.3%), (p = 0.356); migraine was reported by 47 (31.33%) cases and 51 (34%) controls, tension-type headache was present in 21 (14%) MS affected vs 14 (9.33%) controls (p = 0.245). The simultaneous presence of migraine and tension-type headache was statistically higher (p = 0.002) in MS (28.8%) compared to controls (8.5%). Women with MS presented a low correlation between migraine and menstruation compared to controls while migraine normally improves during pregnancy as much as in controls (p = 0.65). The preliminary analysis of FSS and MFIS scores showed that fatigue resulted overall higher in MS patients with or without headache.

Conclusions: Although MS patients showed a high prevalence of headache, particularly migraine, the overall prevalence was not significantly different compared to the general population. Fatigue, a well-known symptom of MS, seems to be primarily correlated to disease and poorly influenced by the presence of headache. Moreover, women with MS and migraine should be reassured regarding the possibility that their headache could improve during pregnancy as in those without MS.

Written informed consent to publication was obtained from the patient(s).

References
patients present to the Emergency Department (ED) because their auras are different from usual. The more frequent causes are abnormal prolongation, increased frequency of recurrence or the developing of new symptoms, particularly in patients that presented in the past only visual auras. Generally these conditions are not dangerous, but ambiguous situations may occur, with the possibility of considering as trivial a potentially serious disorder, as in our patient.

Case report: A 41-year old male suffered since his youth of sporadic episodes of migrainous headache preceded, 3-6 times/year, by typical auras consisting of a spreading right-sided visual field associated, after about ten minutes from the onset, with paresthesias ascending along the right arm. In 2010 he referred a transitory increase in frequency of these episodes and the MRI performed was normal. In November 2012 he experienced a transitory increase in frequency of the episodes, but also noticed an extension of the ascending paresthesia to his right leg. Duration of aura slightly increased, and was followed by ‘usual’ headache. Evaluated in the ED, a brain-CT (b-CT) scan demonstrated the presence of a cortical-subcortical hemorrhage in the left posterior parietal lobe. During hospitalization, EEG and four vessel cerebral angiographies were normal. In May 2013 after a 6-month free-of-episodes period, he went again to the ED for several daily episodes of visual and paresthetic aura, involving the right arm; b-CT and MRI were negative for acute ischemia. Discharged with topiramate 50 mg/day, the patient presented in the following years only sporadic episodes of visual aura but in March 2015 he experienced again a recrudescence of daily episodes of aura. Admitted to our Neurology Ward, b-CT scan, EEG and MRI were unremarkable for new events.

Discussion: In the ICHD-III classification [2] we find a group of MA complications as persistent aura without infarction and migrainous infarction; we performed a literature research to find if there were other possible modifications in typical aura presentation that could represent a risk factor of a complication as in the case here reported. The data about this topic are lacking and we think that prospective studies on this matter are desirable.

Written informed consent to publication was obtained from the patient(s).

References

A86
P014. Migraine and hypnosis
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The Journal of Headache and Pain 2015, 16(Suppl 1):A86

Aims: Hypnosis is an alternative therapy treatment for those patients who do not want pharmacological therapy or for those who need more therapy to control pain due to migraine attacks. In our study, we evaluated 105 migraine patients randomly selected from those patients treated at the Headache Centre of the University Hospital City of Health and Sciences of Turin and who had shown interest in hypnotherapy, had been diagnosed according to the ICHD-3beta criteria, and had experienced headache days (HD) in the last three months.

Methods: We submitted a questionnaire reporting a brief description of hypnosis, proposing the possibility to try this therapy. We obtained informed consent from the patients interested in the study. At a later date, we gathered diagnosis and HD from the patients’ clinical records.

Results: Patients were divided by gender: 50% males and 55% females were responders with a mean of 53%. According to the ICHD diagnostic criteria: 42% of patients with migraine without aura were interested in hypnosis (HI) and 35% were not interested in hypnosis (NHI); migraine with aura: 1% (HI) and 2% (NHI); migraine without and with aura: 7% (HI) and 6% (NHI); chronic migraine: 4% (HI) and 4% (NHI). Analysing HD we found that: 65% of patients with < 3 HD were not interested in trying hypnotic therapy (HT) for migraine treatment; patients with > 30 HD, 78% were interested; patients with > 11 HD, 68% were interested in HT and 32% were not; in patients with < 11 HD, 61% were not interested in HT and 39% showed interested.

Conclusions: We have for the first time an estimate of migraine patients interested in HT regardless of headache diagnosis and gender. There is a 53% probability that a migraine subject could be interested in HT. Taking HD into account, we found a linear correlation between HD and treatment seeking. Patients with > 12 HD or < 12 HD have a 2/3 probability of being or not being interested in HT.

Written informed consent to publication was obtained from the patient(s).

ORAL PRESENTATIONS

A87
0066. Kynurenine pathway metabolites in cluster headache
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The Journal of Headache and Pain 2015, 16(Suppl 1):A87

Cluster headache is a severe, disabling disorder with pain that ranks among the most severe known to humans. It is associated with accompanying autonomic symptoms ipsilateral to the pain and a sense of restlessness or agitation. Patients with cluster headaches have few therapeutic options, and a further 10-20% develop drug-resistant attacks. The often brief duration of cluster attacks makes abortive therapy a challenge, and preventive medications are almost always provided to patients.

Although NMDA-R activation by glutamate has been hypothesized to play a role in the pathophysiology of primary headache disorders, its role is still not fully understood. In fact, the trigeminovascular nociceptive transmission from primary afferents through the trigeminal nucleus caudalis and on to other parts of the CNS involves both the NMDA and non-NMDA glutamate receptors. The kynurenine pathway (KP), accounting for more than 90% of the tryptophan metabolism, generates neuroactive compounds that are able to interact with glutamate receptors both in the central and in the peripheral nervous systems. Among the KP metabolites, Kynurenic Acid (KYNA) and Quinolinic Acid (QUINA) have been shown to interact with ionotropic glutamate receptors. QUINA acts as an orthosteric agonist at the GluN2 subunits of NMDA receptors and it might regulate endogenous glutamate release and uptake inhibition and lipid peroxidation. In contrast, KYNA acts as a competitive antagonist at the glycine site on the GluN2 subunits of NMDA receptors, thereby inhibiting NMDA receptor function. KYNA also inhibits the kainate and the amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptors, and has a non-competitive inhibitory action on the a7-nicotinic acetylcholine receptors [1].

In this preliminary study we enrolled 14 cluster headache patients (CH, 13 males) and 15 age-matched healthy controls (HC, 14 males). We developed a HPLC tandem mass spectrometry method to assess the serum concentrations of KYNA, QUINA, Anthranilic acid and Kynurenine. Kynurenine serum levels resulted not significantly different between the groups (HC 0.33±0.1 and CH 0.35±0.14; Z= -0.53, p = 0.597), while both QUINA, KYNA and Anthranilic Acid were significantly reduced in cluster headache patients with respect to healthy controls (QUINA: CH 18.94 ±5.24 and CH 3.14±4.87; Z= -4.38, p < 0.001; KYNA: HC 3.53±1.33 and CH 2.53±1.20; Z= -12.45, p = 0.041; Anthranilic Acid: HC 1.28±1.14 and CH 0.17±0.06; Z= -4.46, p < 0.001). These results highlight that the endogenous regulation of the glutamatergic transmission in cluster headache might play an important role in its pathophysiology.

Written informed consent to publication was obtained from the patient(s).

Reference
A88

0015. Evaluation of the genetic polymorphism of the α3 (CHRNA3) and α5 (CHRNAS) nicotinic receptor subunits, in patients with cluster headache
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The Journal of Headache and Pain 2015, 16(Suppl 1):A88

Introduction: About 80% of patients with cluster headache (CH) have a history of cigarette smoking [1]; a common genetic basis between CH and smoking has been suggested by the identification of a gene cluster on chromosome 15q25, encoding for neuronal acetylcholine receptor subunits α3, α5 and α4 (CHRNAS-CHRNA3-CHRNA4). Receptors containing the α5 subunit contribute to nicotine withdrawal symptoms and anxiety modulation [2,3].

Aim: To identify rare variants with a possible role in the etiology of CH and nicotine addiction, we investigated the genetic variants into the locus CHRNAS-CHRNA3 using the blood of CH patients and compared it with the control patients (case-control association study).

Materials and methods: We enrolled 65 patients with CH, of which 53 men and 12 women; male to female ratio=4:1. In the sample there were 48 active smokers, 12 former smokers and 5 patients whom had never smoked. CH patients were, respectively, divided into two groups: 54 with episodic and 11 with chronic form. We analyzed three single nucleotide polymorphisms (SNPs) known to be associated with nicotine addiction (rs16969968 and rs6495306 localized on CHRNAS gene; rs578776 localized on CHRNA3 gene) in CH patients and in a control group consisting of 263 individuals that were comparable for age, smoking status and geographic origin. The analysis of rare variants of the genes was performed by sequencing of the coding portion of the gene and 5’-untranslated region (5’UTR) with the Sanger method. The sequence and genomic organization were obtained from the University of California Santa Cruz (UCSC) genome browser (http://genome.ucsc.edu/). PLINK (http://pngu.mgh.harvard.edu/~purcell/plink/) was used for the statistical analysis of the data.

Results: The analysis of the sequences did not evidence new mutations with a functional effect on the development of disease. However, as regards the three polymorphisms selected, the comparison of the allelic frequencies in CH patients and in healthy smokers, highlighted a slight but statistically significant with regards to the SNP rs578776 localized on 3’-untranslated region (3’UTR). The A allele, protective in the risk of developing nicotine addiction and obtained by the replacement of the aspartic acid with asparagine in position 398, is less expressed (p = 0.038) in CH patients.

Discussion: CH patients seem to have a stronger genetic predisposition to develop smoke dependence. Probably, the excessive intake of nicotine could be associated with an up-regulation of pineal nicotinic receptor α2β4 [4], and could trigger a dysfunction of melatonin release linked to the CH’s chrono-biological profile.

Written informed consent to publication was obtained from the patient(s).

References

A89

0034. Type of pain and onabotulinumtoxin-A in chronic migraine: four years of follow-up
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The Journal of Headache and Pain 2015, 16(Suppl 1):A89

Background: Refractory chronic migraine (rCM) [1] is a debilitating neurological disorder, characterized by headache on ≥ 15 days per month for > 3 months, resistant to conventional symptomatic and/or prophylactic polytherapy. The effectiveness of the OnabotulinumtoxinA (OnabotA) was demonstrated in PREEMPT trials and approved in 2010 for rCM treatment [2,3]. The prophylactic pharmacological actions of OnabotA include: a direct antinociceptive-antialgesic effect for primary peripheral afferent terminals by inhibiting release of nociceptor mediators (glutamate, substance P, CGRP) [4] and an indirect effect presumed to involve inhibition of peripheral and central sensitization in trigeminovascular neurons. The purpose of this study was to evaluate the efficacy, safety and tolerability of OnabotA as a prophylactic therapy in patients with rCM and observe the influence of the type of pain on the effectiveness of the treatment itself.

Materials and methods: We analyzed 76 patients (64 F), mean age 52 years (23-82 yr) with rCM referred to the RRCCD of the Careggi Hospital, between 2011-2014. The patients were treated (after informed consent) with OnabotA injection in 31/39 sites at the total dosage of 155/195U every 3 months, according to the PREEMPT protocol. The frequency of headache days (F), intensity of pain (I) and the consumption of drugs (D) were measured using a Headache Diary. Two groups of patient were identified by the type of pain reported: type 1 (severe unilateral) and type 2 (moderate bilateral) [5]. For statistical analysis we used ANOVA for repeated measures and the T-test.

Results: All 76 patients received the toxin treatment at least four times (a one-year follow-up). Of these 44/76 responded to treatment (38 F). The parameters F, I, D showed a progressive and gradual decline with time (p < 0.001 for each variable), reaching the maximum effect from the fourth treatment. The F and D were statistically significantly reduced in both type groups. There were no changes for age, sex and menstrual cycle. Only one patient (1.3%) dropped out of the study because of neck pain.

Conclusions: In our four years of follow-up study a high percentage of rCM patients (58%) showed an improvement in the quality of life with a reduction of F, I and D. The kind of pain in migraine patients affects the efficacy of the treatment itself, and is more successful in patients with type 1 pain in respect to patients with type 2 pain. OnabotA is a safe treatment, well tolerated and effective as a prophylactic treatment in rCM.

Written informed consent to publication was obtained from the patient(s).

References
A90

O042. Phase-dependent defective functional activity of the default mode network and facilitated temporal processing of nociceptive stimuli in cluster headache

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Background: In cluster headache (CH) during the active period we described a facilitated temporal summation (TS) of nociceptive signals at spinal level linked to a defective supraspinal control of pain and followed by a normalization of the values during the remission period [1]. TS of sensory neuronal responses to nociceptive stimuli is a form of central plasticity that shifts the sensory information from tactile to nociceptive before transmitting the nociceptive information to brain areas mediating pain sensation. This feature of the sensory system results pivotal in physiological nociception, for discrimination between innocuous and potentially dangerous stimulation, as well as in pathological nociception, for induction and maintenance of the central sensitization, subsequently resulting in pain chronification [2]. In this study we sought to determine which brain sites are involved in the modulation of temporal processing of pain sensation in CH subjects during both the active and remission period. We utilized functional magnetic resonance imaging (fMRI) to compare the Blood Oxygenation Level Dependent (BOLD) signal changes related to the temporal summation threshold (TST) of the nociceptive withdrawal reflex (NWR). We used the single NWR response as control stimulus.

Methods: We studied 10 episodic CH patients during both active and remission period and 17 healthy subjects (HS). Two types of stimulation blocks were delivered during the fMRI scanning according to the stimulation paradigms previously determined to evoke both the TST of the NWR (SUMM) and the NWR single response (SING).

Results: The analysis of the hemodynamic signals showed a comparable activation of sensory and pain related areas in both CH (during active and remission period) and HS. The most relevant differences emerged in the deactivation of both posterior cingulate cortex (PCC) and bilateral angular gyrus (AG) and in the activation of the anterior cingulate cortex (ACC). CH during the active phase showed a lack of deactivation of PCC and AG and a more relevant activation of the ACC when compared to CH during the remission phase and HS.

Conclusions: PCC, AG and ACC are considered to be pivotal in default mode network (DMN), with a high activity correlated to the rest and reactive deactivation during most tasks where the attention is directed externally. Our data have demonstrated that in CH during the active phase of the disease, the facilitation in temporal processing of nociceptive stimuli is linked to a defective functioning of the DMN. Interestingly, both these abnormalities are dependent on the clinical activity of the disease.

Written informed consent to publication was obtained from the patient(s).

Reference

A91

O043. Frequency-dependent habituation deficit of the nociceptive blink reflex in cluster headache and paroxysmal hemicrania

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Background: The habituation phenomenon is a frequency-dependent form of non-associative learning which reflects the excitability level of both sensory and pain systems. We previously demonstrated a frequency-dependent deficit of habituation of the conventional blink reflex in cluster headache (CH) [1]. We investigated the habituation of the trigeminal nociceptive system by studying the habituation of the late component (R2) of the nociceptive blink reflex (nBR) in a wide range of stimulation frequencies in CH and paroxysmal hemicrania (PH).

Methods: We studied 12 episodic CH patients during both, active and remission period, 12 PH patients and 20 controls. We delivered a series of 26 electrical stimuli, at different and randomly chosen stimulation frequencies (0.05, 0.1, 0.2, 0.3, 0.5, and 1Hz), subsequently subdivided into five consecutive blocks of five averaged and rectified responses for each stimulation frequency. Habituation was measured as the percentage decrease of the mean area under the curve of the R2 component across the blocks.

Results: A significant habituation deficit of the nBR was found at higher (1Hz and 0.5Hz) and intermediate (0.5 and 0.3Hz) frequencies in CH during both active and remission phase, as well as in PH, when compared to controls. No differences in the habituation rate were found at lower (0.1 and 0.05Hz) frequencies between patients and controls.

Conclusions: A frequency-dependent habituation deficit in trigeminal nociception was clearly detected in CH and PH, indicating a common abnormal processing of trigeminal nociception in these two different TACs. In addition, in CH this abnormal pain processing at trigeminal level is independent of the clinical activity of the pathology.

Written informed consent to publication was obtained from the patient(s).

Reference
Materials and methods: SIFI were examined in ten untreated patients with episodic CH and in twelve age- and sex-matched healthy volunteers. Five out of the ten patients were evaluated both inside (in the interval between two pain attacks) and outside bout. Visual stimuli were accompanied by beeps in different combinations to evaluate both fusion illusion (one flash presented with a number of beeps varying between 0 and 4) and fusion illusion (2-4 flashes accompanied by only one beep).

Results: The fusion but not the illusion fusion was significantly reduced in CH patients with respect to healthy controls. No significant differences were observed between bout and outside bout phases in patients evaluated both in the ictal and interictal state.

Discussion: The present results provide evidence of increased visual cortical excitability in CH that is detectable not only during the bout, but also in the pain-free period. This is in agreement with previous findings by our group of increased motor cortex excitability in CH inside and outside bout.

Conclusions: These results strengthen the notion that an abnormal cortical excitability state exists in CH. Moreover, findings in CH patients are very similar to those observed in migraine with aura patients [3], thus supporting the idea that CH and migraine could share at least some common pathophysiological pathways.

On such bases, we suppose that visual cortex hyperexcitability could play a pathogenic role in CH as well as in migraine with aura. This suggestion may also be supported by the rather frequent occurrence of aura symptoms in CH sufferers.

Written informed consent to publication was obtained from the patient(s).

References

We found significant differences in CH time course: attack duration was longer among patients with MLF (89.0±88.9 minutes vs 76.3±68.3 minutes), while there was a lower number of attacks per day (1.5±0.9 vs 2.0±1.6) only among women. We did not find differences in cluster bout duration and frequency.

Patients with MLF had a higher number of cranial autonomic symptoms (3.2±1.5 vs 2.8±1.6), with a significantly higher proportion of lacrimation, conjunctival injection, rhinorhoea, facial sweating and miosis occurring in men only; ptosis was more frequent in both men and women with MLF. Other clinical features such as pain side, pain intensity and restlessness were similarly distributed.

Conclusions: Our study confirms the high proportion of CH patients with MLF which is reported in the literature [1-3]. The presence of MLF seems to relate to some peculiar demographic and clinical characteristics of CH sufferers. Whether these features influence the response to therapy remains to be determined.

Written informed consent to publication was obtained from the patient(s).

References
A95

OO13. Neuro-imaging and history of cases of refractory chronic cluster headache in young patients: a hint for reflections

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Background: Hypothalamus has been suggested to be the crucial area of the brain for the stemming off of cluster headache (CH) attacks [1-3].

Aim: To verify activation of brain areas during attacks in chronic, refractory young CH sufferers.

Materials and methods: The observation included 6 patients (6 males; aged 18-21 years). The observation started in February 2011. Inclusion criteria were: diagnosis of chronic CH according to the ICHD-II, and patient refractory to any prophylactic and acute abortive treatment. In all the patients vegetative signs, characteristic of CH attack, were not observed, whilst VAS and behaviour measures showed excruciating pain. Exclusion criteria were: psychiatric illness (DMIS IV parameters), epilepsy, CNS pathology evidenced with MRI. All the volunteers underwent both sumatriptan and fentanyl, when they presented to our structure. Fentanyl and sumatriptan gave very moderate benefits (mean 1.5, 05%±0.5 SD on 0-10 VAS). The abuse lasted over 1 year (mean 3.6 years±1.2 SD).

Nevertheless, it was impossible to obtain a real dis-habituation in these young sufferers. All patients, as well as one or both their parents, reported headache onset when the patient was 6 to 10 years old. Diagnosis of migraine without aura was made in accordance with the IHS criteria. It lasted for a period of 3-10 months (mean 4.1±4.7 SD). Furthermore, migraine switched to CH and became chronic in a very short period (mean 3.3±1.4 month SD). During the migraine period the 6 young patients underwent a SPECT observation during attack. In all the cases, thalamic hypoperfusion was evidenced at the centro-lateral side where CH manifested, another symptom was a moderate ipsilateral hypoperfusion at the frontal level. We performed (18) FDG-PET-CT, where CT implemented attenuation-corrected images and better defined hypoperfusion at the frontal level. We performed (18) FDG-PET-CT, where

Results: The PET-CT examination evidenced hypometabolism at the level of the thalamus on the same side of cluster pain. The datum, together with the previous SPECT outcomes, supports the suggestion that a thalamic genesis is a possible origin of refractory CH.

Conclusions: It seems that the use of imigran sumatriptan and fentanyl may have induced some variations in receptoral binding affinity which is not expected to dramatically change anatomic area of activation during the stemming off of CH attacks. This may suggest verifying the focus area in refractory CH, leading us to consider alternative therapy.

Written informed consent to publication was obtained from the patient(s).

References

A96

OO04. Refractory chronic cluster headache responding absolutely to indomethacin

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Background: Cluster Headache (CH) attacks typically respond to triptans, in particular to subcutaneous sumatriptan and/or to inhaled oxygen. These treatments are effective in most cases. Anecdotal evidence suggests that some CH patients may respond absolutely to indomethacin, as do patients with paroxysmal hemicrania (PH) and hemicrania continua (HC). We report the case of a male with refractory chronic CH, who responded both acutely and prophylactically to indomethacin.

Materials and methods: Following the International Classification of Headache Disorders (ICHD-3 beta) criteria, we diagnosed chronic CH in a 72-year-old male, whose headaches started when he was 56. For the first 4 years CH was episodic and later became chronic, with short remission periods lasting less than 1 month. The pain was strictly left-sided and was accompanied by conjunctival injection, lacrimation and nasal congestion. During most of the attacks the patient felt restless and had pacing activity. The mean frequency of headaches was two per day, one often occurring at night during sleep, and their duration was about 20-30 minutes. MRI and Angio-MRI of the brain were within normal limits.

Results: The patient’s attacks did not respond to subcutaneous sumatriptan and oxygen inhalation. Interestingly, the patient noticed that his headaches would promptly and completely subside by injecting 50 mg intramuscular indomethacin. The patient was previously treated prophylactically with verapamil, prednisone and lithium, reporting no benefit. Given the absolute response to acute parenteral indomethacin, the patient was commenced with preventive oral indomethacin at the dose of 50 mg, three times daily. He showed a complete response in 10 days after the start of treatment; a tapering of the dose consistently led to the relapse of headaches.

Conclusions: The clinical features and, to a certain extent, also the pathophysiology of both PH and HC, which respond in an absolute way to indomethacin, considerably overlap with those of CH. Indomethacin is largely considered to be ineffective in patients with CH, but a response to this drug is not contrary to the diagnostic criteria for CH [1]. Our case fulfills the ICHD-3 beta criteria for both chronic CH and also for probable chronic PH, lacking one criterion, i.e. frequency of attacks. The review of the literature suggests that indomethacin-responsive CH exists and that some cases may be misdiagnosed when one relies on therapeutic responsiveness to make a diagnosis. This seems to be particularly true for chronic CH, whose clinical characteristics may overlap with those of chronic PH [2].

Written informed consent to publication was obtained from the patient(s).

References
injection and tearing. Brain magnetic resonance imaging excluded any underlying lesions. Sumatriptan 6 mg i.m. maintained over time its efficacy, but during the last year the risk of serious cardiac side effects suggested to look for an alternative treatment to reduce its harmful overuse.

After careful psychological assessment, the patient was considered eligible for occipital nerve stimulation (ONS) trial. Three weeks later he was implanted with a >50%/<85% reduction of attack number and intensity of pain. Unfortunately, three months after surgery, the patient complained of a reappearance of his usual severe CH attack (VAS 10), periorbitally located. We decided to implant an additional electrocatheter stimulating bilaterally the supraorbital nerves (SON). At six-month follow-up the patient referred suffering of 1 attack a week, of mild/moderate intensity, not altering his overall improved quality of life.

ONS was efficient in most of the rCCH patients reported in the literature with low complication rates [2]. In our patient, the ONS was partially effective in relieving symptoms, achieving excellent pain relief only when supraorbital stimulation (SON) was associated (Fig. 1). Evidence from future RCTs should support this approach in order to give guidelines for a multimodal approach to similar rare/unusual case reports.

Written informed consent to publication was obtained from the patient(s).

Conflicts of interests: The authors state that there were no conflicts of interests in respect to the work reported in the paper. IPG and the electrocatheters were paid by the National Heath System as compassionate therapy.

References

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Background: Real clinical setting data about onabotulinumtoxinA treatment on chronic migraine are poor, especially in patients with medication-overuse headache (MOH) and ≥ 65 years old, as well as data on predictors of responsivity. We present results on chronic migraine patients treated at the Padua Headache Centre from April 2014 to March 2015.

Materials and methods: By compiling a headache diary, efficacy parameters (mean reduction of headache days and hours) were evaluated at 90 days after the first cycle. We analyzed also: 30% and 50% response rates and the percent of first-time responders to II cycle; association with headache related symptoms and comorbidities (depression/anxiety disorders, hypertension, sleep disturbances, caffeine intake, BMI ≥30).

Results: Forty patients were evaluated (35 F, 5 M; mean age, 53 ±12.8) of which 37/40 (93%) with MOH. At 90 days after the first cycle headache diary documented a significant mean reduction of headache days (56.2 vs 69.2, p < 0.005), of the total hours of headache (455.4 vs 601.6, p <0.005), of the hours of moderate pain (147.8 vs 263.5, p < 0.005) and severe pain (102.5 vs 131.2, p < 0.05), of the consumption of triptans (30.7 vs 46.5, p < 0.001) and associations (15.4 vs 22.7, p <0.05). The 8 patients ≥65 years old did not present a significant reduction of efficacy parameters vs younger patients. 50% and 30% response rate was respectively 22.5% and 38% for at least one efficacy parameter, 15% and 25% for headache days, of 20% and 35% for hours, 12.5 and 23% for both parameters. Percent of “first-time 50% responders” was 15.8% and 10.8% respectively for headache days and hours; percent of “first-time 30% responders” was 26.3% and 15.8%. Cluster analysis showed a higher severe headache share and a lower share of mild headache in responsive patients vs non-responsive: 146.7 (26.3%) vs 119.1 (17.6%) severe pain hours, 162.2 (29.1%) vs 287.1 (41.1%) mild pain hours. ANOVA analysis did not show significant association between responsivity and headache symptoms or related comorbidities, except for a lower response trend of depression/anxiety at limit of significance (p = 0.07).

Conclusions: OnabotulinumtoxinA treatment appears useful also in a clinical setting with high presence of MOH. Responsive patients are <65 years old and have a higher frequency of severe headache and a lower share of mild headache. Depression/anxiety disorders are associated also to a lower responsiveness trend at limit of significance.

Written informed consent to publication was obtained from the patient(s).

Conflict of interest: The principal author declares that there is no conflict of interest.
A99

0045. Cluster headache improvement during Ketogenic Diet

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Introduction: Ketogenic diet (KD) is a valid treatment for drug-resistant epilepsy, recently proposed as effective also in migraine. Hitherto, no data are available about KD effects on cluster headache (CH), a severe form of primary headache, characterized (similarly to migraine) by a trigemino-vascular activation. Prophylaxis drug-resistant patients have a great need for care and could seek help in invasive treatments and/or alternative drugs, such as illegal substances. Here we performed a prospective observational study of the potential beneficial ketogenesis-induced effects on CH, studying a group of consecutive drug-resistant CH patients.

Methods: We recruited 12 CH drug-resistant patients (7 chronic, CCH) that accepted to undergo a 3-month trial with KD in order to try to treat their headache. Patients received a ketogenic "modified Atkins diet" or "Classic Diet" characterized by a 3:1 ratio (75% fat, 25% non-fat macronutrients). During ketogenesis, patients underwent medical supervision and standard laboratory blood tests. At the end of the KD, patients were free to decide whether to prolong ketogenesis or revert to their standard diet (SD).

Results: Out of 5 episodic CH (ECH) patients, all fully responded to the diet at the end of the first month (three became headache free in a couple of weeks, the other two reported to have had "shadows" and mild attacks up to the end of first month). All of them, at the end of KD period reverted to a standard diet and, since out of active phase of disease, have not had bouts as yet. Out of 7 CCH patients, six reported a progressive reduction of bouts in terms of number and intensity (three during the first 4-week period, one during the second 4-week period, one during the third 4-week period). At the end of the 3-month KD period, four patients reported not yet having had attacks, one reported only 'shadows' and one reported having 2-3 attacks per week. One of patients that responded in the first month of diet decided to revert to SD and CH recurred after 7 weeks.

Discussion: Drug-resistant CH is one of the greatest challenges in headache medicine, and new therapeutic options are welcome. Our observation suggests that ketogenesis can also help CH patients other than migraineurs, maybe by modulation of cortical excitability, or by dampening neural-inflammation. It is interesting to note that both CH and migraine are headache forms that involve the trigeminovascular system, maybe the real target of ketogenesis in headache patients.

Written informed consent to publication was obtained from the patient(s).

A101

P065. Cluster headache: when to worry?

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Introduction: Cluster headache (CH) is a rare and disabling primary trigeminal autonomic cephalalgia which interests especially the male population with smoking and alcohol ingestion habits.

CH typically occurs at the same time of the day, once to eight times per day, and in the same period of the year. CH is featured by severe unilateral head pain associated with autonomic activation (eyelid oedema and nasal congestion), that usually rule out the diagnosis of migraine attacks. On the contrary, these features are thought to be specific of TACs. Furthermore, the clustering of attacks, more than one per day, the ineffectiveness of different prophylactic therapies, and the complete efficacy of therapeutic doses of indomethacin, support the diagnosis of paroxysmal episodic hemicrania in our patient.

Written informed consent to publication was obtained from the patient(s).

Reference

external jugular vein which climbed up to the distal portion of sigmoid sinus. Cerebrosplinal fluid (CSF) isoelectric focusing after lumbar puncture was positive for oligoclonal bands in the gamma regions, while cytological, biochemical, serological, and virological findings of the CSF and blood were normal.

Discussion: According to 2013 ICHD-III criteria, our patient suffered from episodic CH. In the literature we found data on cluster-like headache which can be the only manifestation of a secondary and more dangerous pathology. In our case both CH periods were not involved in the pathogenesis of thrombosis or CSF alterations. It is important to pay attention if there are any changes in headache in the patient’s history because they could be a warning of a secondary form.

Written informed consent to publication was obtained from the patient(s).

References

A102
P001. Trigeminal neuralgia-like symptoms: an unusual case
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Introduction: Lymphoma of the central nervous system [1] accounts for 2% of cerebral tumors; it is typically located in the supratentorial and periventricular white matter; extra-axial localization is rare. When found in the cerebellopontine angle or the Meckel cave [2], the differential diagnosis includes meningioma, trigeminal neurinoma or epidermoid carcinoma. Correlated painful symptoms are often atypical, mimicking trigeminal neuralgia, cluster headache or trigeminal autonomic cephalgias (TACs). Recommended therapy involves: chemotheraphy with cyclophosphamide, high dose cytarabine, steroid (dexamethasone), etoposide, and rituximab (CHASER) followed by whole-brain irradiation. We describe the case of a young man who came to our observation for excruciating headache related to mediastinal lymphoma with bilateral infiltration of the the ganglion of Gasser.

Case report: A 38-year-old man came to our attention suffering for the past 3 months of left fronto-orbital-zygomatic headache with intense pain, mainly nocturnal, subcontinuous, initially with nasal congestion and conjunctival injection, unresponsive to FANS, triptans and oxygen therapy. Brain MRI showed a lesion in the left Meckel cave suggestive of trigeminal neurona. The patient was treated with carabamazepine and steroids. Radiosurgical treatment was advised. Waiting for surgery, the patient was admitted to our department because of inadequate pain control. The neurological examination and serological tests were normal. Follow-up brain MRI (two months later) revealed the presence of pathologic tissue with homogeneous enhancement in both ganglia of Gasser cisterna along the course of the trigeminal nerve, associated with thickening of the dural surface and adjacent the temporal pole, suggesting granulomatus or lymphoproliferative disease. Cerebral spinal fluid (CSF) examination showed hyperproteinorachia and non-neoplastic cells. CT showed a mediastinal and intraabdominal mass, confirmed by PET total body. Histological examination of mediastinal lesion confirmed diffuse large B cell lymphoma. The patient is now in treatment with high-dose MTX infusion.

Discussion: Our case emphasises the need for proper and timely diagnosis of the “trigeminal neuralgia-like” symptoms. With a lesion in the Meckel cave, biopsy is mandatory for a more precise diagnosis and targeted therapy [3].

Written informed consent to publication was obtained from the patient(s).

A103
O038. I.V. methylprednisolone plus diazepam in medication-overuse headache
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Medication-overuse headache (MOH) is a secondary chronic headache developing as a consequence of prolonged overuse of symptomatic headache drugs for at least 3 consecutive months. It usually, but not invariably, resolves after the overuse is discontinued [1]. Benefit of acute withdrawal of the overused medication has been shown to be effective [2]; performing a transitional therapy (“bridge therapy”) during the days of withdrawal may ensure symptomatic relief from rebound headache and avoid withdrawal symptoms. In this setting, i.v. methylprednisolone may have a protective role [3].

This retrospective study aimed to evaluate the effectiveness of detoxification protocol applied in our Headache Centre, which consists in interruption of the abused drug and in the intravenous administration of methylprednisolone 125 mg plus diazepam 10 mg and esomeprazole 40 mg for 5 consecutive days. Depending on patients’ features, prophylactic therapy for chronic headache was either introduced or modified by the end of the wash-out. We enrolled 36 patients with MOH who underwent wash-out from baseline of 60% in the washout group and 50% in the control group and 11 in the control group (Mann-Whitney U test, p 0.012), with a statistical significance.

At T0, mean monthly days of headache was 25 in the washout group and 20 in the control group; at T1 means decreased to 8 in the washout group and 11 in the control group (Mann-Whitney U test, p 0.012), with a 68% reduction in the washout group and 40% reduction in the control group. At T3 means were 10 for both groups (p 0.103), with a reduction from baseline of 60% in the washout group and 50% in the control group. At T1 we found 54.4% of “responders” in the washout group, versus 22.8% of responders in the control group (Fisher’s exact test, p 0.04); “high responders” rates were 40.4% in the washout group versus 8.8% in the control group (p 0.004). At T3 differences in “responders” and “high responders” rate between the two groups were attenuated, losing statistical significance.

This retrospective study shows that a detoxification protocol with i.v. methylprednisolone and diazepam is widely effective and ensures an adequate reduction of headaches.

Written informed consent to publication was obtained from the patient(s).

References
A104

O067. Osmophobia in allodynic migraine: role of frequency of attacks and headache duration
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Background: Migraine is a primary headache with recurrent attacks of head pain with associated symptoms like nausea, phonophobia, and photophobia. Osmophobia, although not included in diagnostic criteria, seems to be a very migraine-specific symptom [1]. Cutaneous allodynia (CA) is also a common symptom in migraine, especially when frequency of attacks is high. CA is considered a clinical manifestation of central sensitization, a mechanism involved in migraine chronification [2]. Recent works put in evidence a relationship between the presence of osmophobia and CA in migraineurs [3]. This study was aimed to investigate possible clinical elements able to influence the relationship between osmophobia and allodynia in migraine.

Materials and methods: We enrolled 871 patients consecutively evaluated in our Headache Center. Chronic migraine was defined as a mean frequency of headache of at least 15 days per month. Two hundred and sixty-three patients had chronic migraine (63% with aura, CHMA, and 200 without aura, CHMO) and 608 were episodic (165 with aura, MA, and 443 without aura, MO).

Results: Osmophobia was significantly more frequent among patients with CA with respect to patients without CA (33.9% vs 26.7%; p = 0.016 at Chi square test). The association between these two symptoms was significant only in chronic migraineurs, among which osmophobia was present in 39.4% of allodynic patients and in 24.1% of non-allodynic patients (p = 0.008 at Chi square test). No difference was found in the distribution of osmophobia comparing chronic migraineurs with and without aura (44% of CHMA and 37% of CHMO). Both CA and osmophobia were significantly more frequent among women with respect to men: CA was found in 30% of men and 55% of women (p < 0.001) and osmophobia in 18.2% of men and 32.6% of women (p = 0.001). The relationship between CA and osmophobia was confirmed in both CHMA and CHMO among women. Even if the proportion was similar, significance was not found among men, probably because of the smaller sample size. Osmophobic episodic migraineurs, both with and without aura, had a longer migraine history. This evidence was not found among chronic patients.

Conclusions: The highlighted relationship between allodynia and osmophobia seems not to be influenced by gender nor by aura. The observation that it is related to a higher frequency of attacks and longer history of migraine may be interpreted as a common consequence of central sensitization, able to induce in parallel a distortion of both cutaneous sensitivity (CA) and olfaction (osmophobia).

Written informed consent to publication was obtained from the patient(s).

References

A105

O049. Psychodynamic functioning in chronic headache patients: a short term psychodynamic psychotherapy (STPP) study
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Background: Chronic headache (CM) occurs in 2–5% of the general population, often associated with medication-overuse headache (MOH), and comorbid psychiatric disorders [1,2]. Among therapeutic approaches, psychotherapeutic interventions may be effective, either alone or associated with pharmacological therapies. As we previously showed, the short-term psychodynamic psychotherapy (STPP), plus drug therapy, is more effective in patients with probable MOH to reduce headache symptoms and relapse rate than drug therapy alone [3]. Moreover, STPP alone is not inferior to valproate in CM, as preventive therapy [4]. According to psychodynamic diagnosis (BPI) some psychodynamic profiles with poor ability to process the emotional content or low mentalizing level (i.e., pre-psychosis, psychosis and borderline) could be at risk of developing chronic headaches. The aim of the present study was to identify the most frequent psychodynamic profiles in CM and test the effect of STPP in those patients with no record of psychiatric disorders.

Methods: We consecutively recruited all CM patients, with or without MOH, attending our Headache Clinic over two years, according to the ICHD-II criteria. The protocol of psychotherapy reckoned on a first evaluation with 4 Brief Psychodynamic Investigation (BPI) and then psychotherapy treatment over the subsequent 2 months. At baseline, all patients with MOH were instructed to withdraw from the abused drugs. Follow-ups were planned at 15, 30 and 60 days when headache clinical features were recorded. HIT6, MIDAS and Depression and Anxiety Hamilton scales were also acquired.

Results: We recruited 105 patients with chronic migraine (74% with MOH). Forty-eight patients (46%) did not complete the protocol. Fifty-seven patients (54%) actively participated in the study. According to BPI criterion, the patients were diagnosed as “psychotic” (44%), “pre-psychotic” (28%) and “borderline” type (28%). Clinically, 40% (n=23) of patients completed the full treatment period with a significant improvement of disease parameters (33% less attack duration, 17% less pain intensity, 41% lowering in MIDAS score, and 93% less medication overuse). However, we did not observe any correlation between headache characteristics and psychodynamic profiles.

Conclusions: This study suggested that CM, with or without MOH, is associated with a low mentalizing level, condition characterized by a poor ability to process the emotional content. We confirm that the short term psychodynamic psychotherapy is effective in the treatment of CM.

Written informed consent to publication was obtained from the patient(s).

References

A106

O060. Rotigotine improves drug-resistant cluster headache: a case series
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Introduction: Cluster headache (CH) is a severe form of primary headache, characterized by trigeminal-autonomic system activation.

Conclusions: The efficacy of intranasal rotigotine in CH has been reported previously. The present case series adds further support to this evidence.
Bouts, lasting 15-180 minutes, occur 1-8 times a day, for a period persisting for weeks or months, followed by a full remission. However, about 10-15% of patients have no remission periods and their CH is defined chronic (CCH). While symptomatic treatment is often effective, preventive treatments are limited. Our group has already reported the case of a patient affected by refractory CCH who underwent a complete and sustained response to rotigotine, a non-ergoline D3-like receptor agonist, also with a SHT1A effect, administrated by transdermal patches. Here we report a case series of patients that have tried transdermal rotigotine for their drug-resistant CH.

Methods: We recruited 14 CH drug-resistant patients (11 chronic) that accepted to try transdermal rotigotine to treat their CH, increasing dose weekly of 2 mg up to 6 mg, according to our previous report.

Results: Out of 3 episodic CH (ECH) patients, two had an improvement of bouts at 4 mg, but obtained a stable benefit at 6 mg; after the presumed end of their CH period they progressively discontinued the patches and the CH did not come back till the next cluster period. The other ECH patient did not respond at 6 mg, than the dose was further increased to 8 mg, without benefit thus the treatment was interrupted. Out of 11 CCH patients, 8 were considered responders since CH disappeared (5 cases) or significantly decreased (more than 50% of reduction in terms of bouts frequency and intensity, or somnolent consumption). Six patients had an early benefit at 4 mg but stable response at 6 mg. In two cases the dose was further increased to 8 mg since CH worsened. Two patients suddenly discontinued treatment by an ‘overnight-switch’ to promipexole due to late dermatological reactions; one of them remained CH free after the switch. Patients who did not respond at 6 mg continued to not respond at 8 mg and treatment was interrupted.

Discussion: This case series seems to confirm our early observation that transdermal rotigotine could act as preventive treatment in cluster headache. Further, this series gives us other information: 1) Rotigotine could be increased up to 8 mg if necessary; 2) If up to 6 mg it does not act, it will not act at 8; 3) Some late dermatological complications could occur during the treatment.

Written informed consent to publication was obtained from the patient(s).

References

Poster Presentations
A107
0048. Chronic migraine, cluster headache or both? The suggestion of botulinum toxin
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Introduction: Cluster headache (CH) is an uncommon primary headache that may be difficult to diagnose when comorbid with other headache disorders [1]. We describe two patients with a challenging diagnosis, emerging after treatment with botulinum toxin (BTX).

Case 1: A 58-year-old man presented with a three decades history of almost daily unilateral, not side-locked, pulsating head pain with severe exacerbations, lasting 4-72 hours, associated with photo-, phonophobia, and osmophobia, conjunctival injection, increasing with physical activity. Indomethacin overuse was present and the patient met diagnostic criteria for both chronic migraine (CM) and medication-overuse headache. He had tried, over the years, several drugs (anti-epileptics, such as, valproate and topiramate, antidepressants, calcium-channel blockers, and beta blockers) and non-pharmacological treatments (biofeedback, acupuncture) with only transient improvements. Treatment with BTX, according to the PREEMPT injection protocol [2], was started together with venlafaxine and steroids for two weeks with mild improvement of the headache. After two cycles of treatment with BTX, the patient developed attacks of stabbing pain localized behind his right eye, spreading to the right side of the head, with marked conjunctival injection. The pain recurred 8-10 times per day, usually lasting about 60 minutes, and was associated with restlessness. CH was diagnosed. Steroids and verapamil, as well as subcutaneous sumatriptan in acute attacks, were started with cessation of the CH attacks and persistence of migraine attacks. Four months later, CH attacks relapsed and were again successfully treated.

Case 2: A 41-year-old woman presented with a history of pulsating pain in the left, sometimes right, temporal region and behind the eye associated with ipsilateral lacrimation, photophobia, and vomiting occurring 15 times a month, lasting 12-24 hours and fulfilling diagnostic criteria for CM. Drug prophylaxis with amitrtryline and fluoxetine was initiated but stopped for ineffectiveness and side effects. Treatment with BTX, according to the PREEMPT [2] injection protocol was started with complete cessation of attacks. After three cycles of treatment, the patient developed stabbing pain localized behind her left eye with autonomic signs, spreading to the left side of the head, recurring 3-4 times per day and lasting 60-120 minutes, fulfilling diagnostic criteria for CH. BTX was stopped; treatment with steroids and topiramate was initiated with resolution of the attacks. Off the cluster, the patient autonomously withdrew all treatments with recurrence of migraine-type headache; BTX was restarted with good response.

Discussion: In our opinion, in both the cases there was a comorbidity between chronic migraine and CH. In the former case the presence of CH was covered up by the prominence of migraine features and by the effects of preventive and acute phase treatments used to treat migraine that may also have limited the disclosure of CH symptoms thus making its diagnosis more challenging. In the second case, CH developed during treatment with BTX and, although unlikely, we do not know if and how BTX could have trigger CH.

Written informed consent to publication was obtained from the patient(s).

References
papilledema. All displayed an OP lower than 250 mm H2O (range 102-245). Six patients (19%) had an OP greater than 200 mm H2O: three of them achieved an improvement of headache frequency or intensity after 8-18 ml CSF withdrawal. Fifteen patients (48%) had MRV evidence of TSS: bilateral in 4 and unilateral in 11. Using a Pearson’s correlation coefficient test, no significant correlation between CCS and OP was found. After CSF withdrawal, no changes of CCS were found in the six patients who repeated MRV.

Conclusions: In our series, all patients displayed normal OP values (< 250 mm H2O). Nineteen percent of patients had an OP greater than 200 mm H2O. Our results confirm a low prevalence of IIHWOP in chronic headache sufferers. Moreover, the prevalence of sinus venous stenosis (50%) was lower than previously described in unresponsive chronic headache patients (92.8%), but similar to a series of unselected chronic headache patients (50.6%) [1,5]. Transverse sinus stenosis seems not to correlate with CSF opening pressure, putting its role into question. Written informed consent to publication was obtained from the patient(s).

References

A109
P044. Anger expression in chronic daily headache patients with and without psychiatric comorbidity
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Background: Previous studies suggest the high prevalence of psychiatric comorbidity in chronic daily headache (CDH) patients. In particular, CDH patients showed higher frequency of anxiety and depressive disorders than episodic migraineurs [1,2]. However, negative affect emotions (like depression, anxiety and anger) influence the course and impact of headache within the normal range of affective experience, not simply when an Axis I disorder is present [3]. In the literature it is reported that individuals with headache are more likely to hold their anger-in than controls. Individuals who hold anger-in experience an increased pain severity, failure to express anger leads to more disability [4,5].

The aim of this study was to investigate if anger expression levels in CDH patients are related to psychiatric comorbidity.

Materials and methods: Eighty-five CDH patients (19 M, 72 F) with and without medication overuse were recruited and assessed by Mini International Neuropsychiatric Interview (M.I.N.I.), and State-Trait Anger Expression Inventory (STAXI). On the basis of M.I.N.I. results patients were divided into two groups: with psychiatric comorbidity (group A) and without (group B). STAXI scores were compared between the two groups. T-test was performed to compare continuous variable between groups.

Results: According to the ICHD-II revised criteria, 4% of subjects had a diagnosis of CM, 19% of CTH, and 77% of MOH. Psychiatric comorbidity was detected in 39 patients (45.8%) (group A) and was absent in the remaining 46 patients (54.1%) (group B). The disorders most frequently diagnosed were mood and anxiety disorders (43.6%). All STAXI scores were within the normative range, however the highest score was detected in the anger-in subscale, indicating a disposition to suppress rather than express angry feelings. No differences were found between patients with and without psychiatric comorbidity (p = 0.316).

Conclusions: STAXI results showed no differences in the experience of anger between patients with and without psychiatric comorbidity. Interestingly the highest mean score was in the anger-in subscale that indicates the tendency to suppress anger expression instead of directing it towards other people or objects. Patients with CDH appeared to have a tendency to control their anger expression and to hold their anger-in. The disposition to suppress anger detected in all CDH patients might play a role in the transformation from episodic to chronic headache.

Written informed consent to publication was obtained from the patient(s).

References

A110
P010. OnabotulinumtoxinA for treatment of chronic migraine: results after 1 year of treatment
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OnabotulinumtoxinA (OnabotA) was approved for treatment of chronic migraine (CM) following the PREEMPT trials [1,2], and was licensed in Italy in February 2013. Thus, in December 2013 we began to offer OnabotA to patients with CM who did not respond to other preventive therapy (mostly topiramate, beta blockers, amitriptyline and calcium channel antagonists). Demographic and migraine characteristics of patients were recorded, and changes in monthly migraine days and headache intensity (the latter variable was evaluated only after the first session of treatment), as well as, the number of symptomatic medications intake, were assessed. From December 2013, 40 patients (9 males, 31 females) were treated with at least one preventive session (median number of sessions was 13.5). The first session was given in February 2013. In 34 of these patients (85%) overuse of symptomatic medications was observed at the onset of treatment. After obtaining an informed consent, we administered OnabotA according to the PREEMPT protocol (155 UI for a total of 31 injections divided across 7 head/neck muscles), performing no
additional injections in the first session (from the second session we also adopted "follow the pain" protocol), and we gave the patients a paper diary to register the headache evolution. After one year of treatment we analyzed the data related to the 40 patients, observing positive results in all the variables considered. In particular, following 1-year treatment there was a reduction from 25.1±6.1 to 19.9±9.1 in the mean (± SD) number of monthly migraine days (reduction of 21%, p < 0.0001). The intake of symptomatic medications was reduced of about 12%, but the difference was not statistically significant. Most (78%) of the patients (n = 30) who had accurately registered the data reported that the greatest clinical benefit of OnabotA was the reduction in the headache intensity. Finally, no severe adverse event was observed, and no pain in the injection site was the most reported experience. No patient discontinued the treatment because of side effects. We can conclude that the use of OnabotA according to the PREEMPT paradigm is an effective and well-tolerated treatment in patients with chronic migraine in a real-life setting.

Written informed consent to publication was obtained from the patient(s).

References

A111
P012. Body image role in medication-overuse headache associated with persistent depressive disorder
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Background: Body image is a part of each person’s self-esteem. Some evidence suggests that body image perception may have direct effects on one’s feeling regarding quality of life [1,2]. Nonetheless, no research has examined the relationship of the impact of body image on medication-overuse headache (MOH) patients suffering also with persistent depressive disorder (PPD). Moreover, the role of body image is stressed in trials concerning mirror therapy [3,4].

Aim: We propose that body image improvement can influence both pain perception and PPD in MOH sufferers.

Materials and methods: The present observational study started in March 2014. Inclusion criteria: 165 women, mean age 43.05±6±3.1 SD diagnosed as MOH with the ICH-III criteria and fulfilling DSM-V criteria for PPD. Controls were 160 healthy women, (mean age 43.7±1.59 SD). Women completed affective/cognitive measures of body image (BSQ-track and field). Zung and Hamilton tests were used for scoring depression, MIDAS for perceived quality of life. Each patient was videotaped. Raters, blind to health status, independently rated the attractiveness of the patients. Headache patients with depression reported lower self-esteem, a more negative body image perception than controls; all of them were rated as less attractive by observers when compared to the control group. The multivariate and univariate analyses of variance indicated that MOH patients with depression were less satisfied than control subjects. Patients gave their formal consent and underwent aesthetic treatments which included peelings, fillers and polydioxanone stitches.

Results: Aesthetic medicine improved body image (BSQ - track and field: 0-3 changes from baseline 2 p < 0.0001), depression (self administered Zung and Hamilton tests decreased, respectively, from 46.2±5.2 SD to 30.2±2 SD, p = 0.002; and from 52.6±6.4 SD to 28.4±6.4 SD p > 0.0001), headache pain scores (mean monthly VAS from 8.18±0.5 SD to 4.7±0.7 SD, p<0.0001), and perceived quality of life (MIDAS 0-21, 15.6±2.4 SD versus 10±0.8 SD p = 0.00001) improved. The improvements were also matched with better rates from the raters (p > 0.01).

Conclusions: These findings suggest that medical care of body image may induce: A) relief of alteration of body image perceived as a discrepancy between the way sufferers formerly perceived themselves and how they see the changes of their body attributed to excruciating pain and treatments; B) Aesthetic medicine applied, wisely and knowledgeably, using the clinical pharmacology profile of available tools, results in a significant reduction of dissatisfaction, depression and pain perception, as shown by pain score and improvement of perceived condition of severely compromised quality of life.

Written informed consent to publication was obtained from the patient(s).

References

A112
P053. An Italian study on the actual cost/benefit of onabotulinumtoxinA (BT-A) in chronic migraine: preliminary results
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Background: In Italy, the estimated cost of chronic migraine (CM) is around six billion euros per year [Agenas, 2011] considering the health costs, the loss in working productivity and quality of life.

The efficacy of BT-A in the prophylactic treatment of CM has been demonstrated [1]. However, BT-A therapy is expensive and the limited health service resource may raise the question of the cost/benefit ratio. Ruggeri et al [1] carried out a study to provide an estimate of the incremental cost-effectiveness ratio of the treatment of CM with BT-A 2. They compared the benefit as extrapolated from the PREEMPT data with those of a population of CM patients using the METER study, as well as with those of an actual population of CM from a district of Rome [1]. In the present study we compared actual costs and benefit in a CM population before and after BT-A treatment.

Methods: We recruited CM patients with or without MOH, according to the ICHD-3-beta classification. All patients were injected using the standard protocol for CM. At follow-ups, planned every 12 weeks, headache clinical features (including quality of life scales), direct health costs and indirect costs due to loss of work productivity [1] supported within 3 months, were recorded.

Results: We consecutively enrolled 34 patients with CM, (19 with MOH). To date, we have considered the results at 24 weeks (T2). Nine patients (26%) dropped out because of side effects or poor compliance (3 at T1, 4 at T2). In the nineteen patients, who completed the T2 follow-up (56%), we observed a statistical clinical benefit (p < 0.001) in headache features (29% less in attack frequency, 39% less in attack duration, 21% less in pain intensity, 63% less in drug intake) and a significant reduction of pain-killer costs per month (-75%) and a decrease of working productivity loss (-28%). Moreover, MSQ and MIDAS were also significantly improved.

Conclusions: After the first 24 weeks, BT-A was effective in both clinical CM features, as well as the decrease of the amount of its direct and indirect costs. These preliminary data seem to confirm the findings from studies of probabilistic estimates although they will need to be confirmed in a larger population and a longer follow-up.

Written informed consent to publication was obtained from the patient(s).

References

A113

P058. Refractory chronic migraine, fatigue and OnabotulinumtoxinA: a clinic setting experience
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Objective: To assess OnabotulinumtoxinA safety and efficacy in prophylactic treatment for chronic refractory migraine (headache occurring at least 15 days per month with lack of responsiveness to at least two preventive medications with established efficacy) [1] with associated fatigue symptom.

Methods: From March 2014 to May 2015 patients meeting the clinical diagnostic criteria for chronic refractory migraine were enrolled. Patients were treated with OnabotulinumtoxinA every three months according to the standard procedure (155-195 units) [2]. At baseline (T0) and after 6 months, at the third treatment (T1), a structured questionnaire was administered, including: a) migraine features (frequency [headache days/month], pain severity [Verbal Numeric Scale, VNS]), acute medicines consumption/month, disability (Headache Impact Test, HIT-6), ictal cutaneous allodynia (Allodynia Symptoms Check-list 12, ASC-12)); b) associated symptoms [Fatigue (Fatigue Severity Scale, FSS), anxiety symptoms (Generalized Anxiety Disorder, GAD-7), depressive symptoms (Patient Health Questionnaire, PHQ-9)]. Wilcoxon test was performed for the T0-T1 comparisons.

Results: Twenty-one patients were enrolled (M:F=3:18; mean age: 52.6±9.71). A patient discontinued the study after the first treatment due to a adverse event (eyelid ptosis). Twenty patients were evaluated at T1, with migraine features changing as follow: T0 frequency Me=30 IQR=10, T1 frequency Me=13 IQR=13, T0 VNS Me=8 IQR=3, T1 VNS Me=8 IQR=4, T0 acute medicines consumption/month Me=20 IQR=15, T1 acute medicines consumption/month Me=7 IQR=13, T1 HIT-6 Me=66 IQR=7, T1 HIT-6 Me=63 IQR=13, T0 ASC-12 Me=8 IQR=5, T1 ASC-12 Me=6 IQR=7. Associated symptoms changed as follow: T0 FSS Me=48 IQR=19, T1 FSS Me=33 IQR=23, T0 GAD-7 Me=10 IQR=8, T1 GAD-7 Me=9 IQR=7, T0 PHQ-9 Me=10 IQR=11, T1 PHQ-9 Me=7 IQR=7. After two injection cycles with OnabotulinumtoxinA, a statistically significant reduction was found in: a) frequency (p = 0.001; r = 0.51); b) acute medicines consumption/month (p = 0.001; r = 0.54); c) FSS score (p = 0.009; r = 0.41).

Conclusions: OnabotulinumtoxinA resulted well tolerated and effective in reducing not only frequency and acute medicine use, but also fatigue in our population of chronic refractory migraineurs. Written informed consent to publication was obtained from the patient(s).

References

A114

P074. Almotriptan in the acute treatment of Vestibular migraine: a retrospective study
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Introduction: Vestibular migraine (VM) has become a well-defined diagnostic entity, based on recurrent vertigo attacks, unexplained by other central or peripheral otologic abnormalities, occurring in patients with a history of migraine headache. The duration of vertigo attacks varies from seconds to days, usually lasting minutes to hours, mostly occurring independently of headaches.

Background and objective: This was a retrospective, multicentric, open-label investigation with the aim to assess the efficacy of an oral dose of almotriptan (ALM) 12.5 mg in the treatment for acute vertigo attacks in VM, defined according to the ICHD criteria, 3rd edition, beta version (2013). This triptan, a selective 5-HT1B/1D receptor agonist, since its introduction in the market in 2001, has emerged as the one with the best efficacy and tolerability profile in acute migraine treatment.

Materials and methods: The study included 26 subjects with VM (25 F, 1 M), aged from 19 to 53 years (mean, 30.0 years), reporting vertigo in more than 50% of attacks, a history of migraine for at least one year, onset of migraine before the age of 50. Three (11%) of the 26 subjects were lost to follow up; five (19%) discontinued the ALM treatment due to adverse events or any other causes.

At the time of the prescription the patients were drug-free and did not receive any prophylactic therapy. The data were recorded in a headache diary: the intensity of vertigo attacks was assessed by a 3-score scale (with "1" indicating mild vertigo, "2" medium intensity and "3" the worst vertigo imaginable), while the therapeutic response to vertigo attacks by a 4-score scale (with "0" indicating any change, "1" under 50% reduction, "2" over 50% reduction and "3" the complete disappearance of vertigo). Almotriptan was administered as a single 12.5 mg tablet with the advise to take the drug within 1 h of onset of vertigo attack. Follow-up was performed every month for the following three months after the ALM treatment initiation and the response on vertigo attacks during the study were considered as the main and primary outcome, while secondary variable was the effect on pain relief at 2 and 4 hours. From the first visit onward, patients reported if they had experienced any adverse events.

Statistical analysis of data was carried out using student t-test.

Results: Eighteen patients were examined; they reported 27 vertigo attacks in the course of the three-month follow-up, with mean intensity scores ranging between "2" (24%) and "3" (76%). Among all the patients, 10 (55%) reported complete disappearance of vertigo, 5 (28%) over 50% reduction and 3 (16%) under 50% reduction. Also, the pain relief were significantly reduced since the first month and confirmed in the following two months (p < 0.001).

These data suggest a benefit from almotriptan at the oral dose of 12.5 mg in 83% of the patients with vestibular migraine attacks; good was the tolerability profile.

Conclusions: This study suggests that almotriptan is effective and safe in reducing both vertigo and headache among patients who suffer from Vestibular migraine. This will have to be reconfirmed in a large scale, randomized, controlled clinical trial.

Written informed consent to publication was obtained from the patient(s).

A115

P073. Impaired oxidative balance in migraine: an open study
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Introduction: Migraine is the most common neurological disorder, but the molecular basis is still not completely understood. An impairment of mitochondrial oxidative metabolism might play a role in the pathophysiology. Moreover there is strong evidence associating migraine with a variety of comorbid disorders, including cardiovascular disease and stroke, in which oxidative stress seems to be an important underlying mechanism. However, data are in part controversial and the possible underlying mechanism remains elusive to date. Also, the data regarding the intestinal state in migraineurs is limited.

Written informed consent to publication was obtained from the patient(s).
Aim of this study was to evaluate the oxidative balance in a sample of patients with migraine by means of routine specific serum tests, such as d-ROMs test and BAP test.

**Materials and methods:** One hundred outpatients, (74 F, 26 M), mean age 39.2 years (SD 13.2), range 18-62 years, suffering from migraine without aura (ICHD-II 2004 criteria) were enrolled. The mean duration of disease was 1.8 (SD 0.8) years, range 1-3 years. Serum total oxidant capacity was determined by performing the d-ROMs test, whose chemical principle is based on the ability of a biological sample to oxidize N,N-diethylparaphenylenediamine (normal range 250-300 CARR U, where 1 CARR U is equivalent to 0.8 mg/L H2O2), while serum total antioxidant capacity was assessed by means of BAP test, which measures the ability of a serum sample to reduce iron from the ferrous to the ferric ionic form (optimal value >2200 micromol/L reduced iron).

**Results:** Mean values of d-ROMs tests were 397.5 CARR U (SD 144.3) while mean values of BAP test were 1758.2 micromol/L reduced iron (SD 485.7).

According to the data, enrolled patients were found to be in a classical condition of oxidative stress. In fact, compared to the normal range, oxidant capacity, as measured by means of d-ROMs test, was increased (>300 CARR U) and biological antioxidant potential (as measured by means of BAP test) was decreased (<2200 micromol/L reduced iron).

**Conclusions:** Although preliminary, our study confirms that oxidative stress may represent a key event in the clinical routine of patients suffering from this frequent disease. Our data suggest that oxidative stress may represent a key event in the pathophysiology of migraine and a suitable therapeutic target. Further knowledge about this issue may contribute to understanding the cause and complications of migraine and may be essential for development of treatment approaches.

Written informed consent to publication was obtained from the patient(s).

**A117**

**P054.** Chronic migraine and onabotulinumtoxinA: results from clinical practice

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**The Journal of Headache and Pain 2015, 16(Suppl 1):A117**

**Background:** OnabotulinumtoxinA injection according to PREEMPT protocol is a second-line therapy for chronic migraine (CM) [1]. While its efficacy on frequency of headache has been demonstrated [2], our current clinical experience indicates that patients report benefits regardless of reduction of frequency of attacks, as Lipton et al previously showed [3]. The present study aimed at assessing the impact of botulin injection on intensity, quality and perception of pain in patients with CM.

**Materials and methods:** We enrolled 25 patients who underwent botulin injections from April 2014 to June 2015. We evaluated patients at baseline (T0, the day of the first botulin injection) and every three months, along with a new injection session. Evaluation consisted in a multiparametric self-assessment questionnaire: pain intensity through 11 point Box Scale (BS-11) and Present Pain Intensity (PPI), changes in functioning through 6-point Behavioral Rating Scale (BRS-6), quality of pain through Short-form McGill Pain Assessment Questionnaire (SF-MPQ) and disability through Migraine Disability Assessment (MIDAS) questionnaire and HIT-6.

At the present time, we have follow-up data for 57% of patients at three months (T1) and for 38% of patients at six months (T2).

**Results:** We found a global reduction in the intensity of perceived pain and in restriction of activities due to headache: Wilcoxon signed-rank test showed significant reduction in median values of BS-11 at T1 (p = 0.026) and T3 (p = 0.017), of PPI at T1 (p = 0.02) and T3 (p = 0.046), of BRS-6 at T1 (p = 0.008) and T3 (0.026). Analysis of SF-MPQ showed a significant reduction in median values of the descriptors "throbbling" at T1 (p = 0.041) and "stinging-exhausting" at T1 (p = 0.011). We did not find significant difference in MIDAS score at T1 and T3 and in frequency of headache in the past three months.

**Conclusions:** Our preliminary results show that the OnabotulinumtoxinA usefulness is primarily improving the quality of life more than in reducing the frequency of headache.

Written informed consent to publication was obtained from the patient(s).

**References**


**A116**

**P030.** Global postural rehabilitation and migraine: a pilot-study

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**The Journal of Headache and Pain 2015, 16(Suppl 1):A116**

**Introduction:** Global postural rehabilitation (GPR) is a method of physical therapy, designed by Professor Souchard, for the treatment of osteo-neuro-muscular pathologies. The correction of oculo-motor, cranio-cervical and tempo-mandibular joint dysfunctions inside “postural globality” can lead to the elimination of muscle tension that is one of the most important triggers and, at the same time, complications of headaches. The present study aimed at evaluating whether this method could be useful in reducing the number, intensity and duration of attacks and also the use of painkillers in patients with migraine without aura.

**Methods:** We recruited a sample of 16 female patients, aged between 25 and 65 years, affected by migraine without aura. Following a randomized criterion, 8 patients were included in the “Control Group” and the other 8 patients in the “Control Group”. Both groups were evaluated before starting treatment (T0), after 3 (T1) and 7 weeks (T2). Intensity and quality of pain were evaluated by BS-11, PPI and SF-MPQ, while disability was assessed by BRS-6 and HIT-6. Experimental Group patients received a “Postural and Morphological Assessment” plus a particular evaluation of Oculo-Motor System, upper cervical district (C0-C2) and tempo-mandibular joint. This group underwent both additional pharmacological treatment and 10 GPR sessions. Control Group received only pharmacological treatment. Each patient filled out a migraine diary: particular attention was paid to the number of painkillers taken.

**Results:** Friedman test for non parametric data showed an improvement of all rating scales values in the Experimental Group. In particular, at T1 there was a decrease of all the considered parameters (pain intensity and quality, attacks duration, frequency and disability) compared to T0 (p < 0.05). Improvement trend resulted also at T2, except for two subjects (p < 0.05).

In the Control Group, after an initial partial improvement at T1 compared to T0, most of the values remained unchanged or worsened; few patients improved at T2 compared to T0.

**Conclusions:** Pain intensity and quality, attacks duration, frequency and disability improved in patients undergoing GPR. Furthermore, 80% of patients in the Experimental group replaced the anti-migraine medication, i.e., triptans, with NSAIDS, while the other 20% reduced the number of painkillers. Our study shows the efficacy of GPR treatment in patients affected by migraine without aura.

Written informed consent to publication was obtained from the patient(s).
Objectives: To evaluate the effectiveness, safety, and tolerability of a 12-month treatment with low doses of methadone (MT) (mean MT dosage 12.3 mg ± SD 7.3) as prophylaxis in patients affected by daily refractory headache and medication-overuse headache.

Methods: Prospective cohort study (METACEF study).

Results: Since May 3rd, 2012 up to January 8th, 2015, we enrolled 24 patients (18 females, 6 males; average age, 48 years) who were considered eligible to be treated with methadone. Nine patients dropped out because of adverse drug reactions (n=4, mean time of drop-out 7 days) or treatment ineffectiveness (n=5, mean time of drop-out 6 months). Six patients completed the 12-month treatment. After 1-year follow-up they still reported daily headache, however, they showed an impressive decrease of analgesic and/or antimigraine drug consumption (from 147.7 medications per month ± SD 124 to 8.5 medications per month ± SD 61) and a significant decrease of visual analog scale (VAS) pain intensity (from 5.8 ± SD 2.6 to 2.8 ± SD 2.1). These patients were treated with daily methadone dosages ranging from 5 mg to 60 mg; methadone dosages were safe and well tolerated.

Conclusions: In patients affected by daily refractory headache and medication-overuse headache, who are exposed to the risk of serious side effects due to prolonged analgesic and/or antimigraine treatment, prophylaxis with low-dose methadone therapy seems to represent an effective therapeutic option.

Written informed consent to publication was obtained from the patient(s).

Reference

ORAL PRESENTATIONS

A118
P057. Prophylaxis with low-dose methadone in patients affected by daily refractory headache and medication-overuse headache: a prospective cohort study (METACEF study)
Chiara Lupi1, Chiara Pracucci2, Francesco De Cesare1, Eleonora Rossi1, Pierangelo Gepetti1, Silvia Benemeril, Valentina Galli2, Brunella Occupati2, Viola Mazzucco2, Guido Mannion2
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The Journal of Headache and Pain 2015, 16(Suppl 1):A118

Objective: To evaluate the effectiveness, safety, and tolerability of a 12-month treatment with low doses of methadone (MT) (mean MT dosage 12.3 mg ± SD 7.3) as prophylaxis in patients affected by daily refractory headache and medication-overuse headache.

Methods: Prospective cohort study.

Results: Since May 3rd, 2012 up to January 8th, 2015, we enrolled 24 patients (18 females, 6 males; average age, 48 years) who were considered eligible to be treated with methadone. Nine patients dropped out because of adverse drug reactions (n=4, mean time of drop-out 7 days) or treatment ineffectiveness (n=5, mean time of drop-out 6 months). Six patients completed the 12-month treatment. After 1-year follow-up they still reported daily headache, however, they showed an impressive decrease of analgesic and/or antimigraine drug consumption (from 147.7 medications per month ± SD 124 to 8.5 medications per month ± SD 61) and a significant decrease of visual analog scale (VAS) pain intensity (from 5.8 ± SD 2.6 to 2.8 ± SD 2.1). These patients were treated with daily methadone dosages ranging from 5 mg to 60 mg; methadone dosages were safe and well tolerated.

Conclusions: In patients affected by daily refractory headache and medication-overuse headache, who are exposed to the risk of serious side effects due to prolonged analgesic and/or antimigraine treatment, prophylaxis with low-dose methadone therapy seems to represent an effective therapeutic option.

Written informed consent to publication was obtained from the patient(s).

Reference

A119
P009. A case of new daily persistent headache treated with botulinum toxin type A
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The Journal of Headache and Pain 2015, 16(Suppl 1):A119

Background: New daily persistent headache (NDPH) is a primary headache disorder, characterized by chronic and unremitting daily headache with abrupt onset and more than three months in duration. It lacks typical clinical features, the pain being suggestive of chronic migraine without aura or tension-type headache. It may be self-limiting within months or years without therapy, or be refractory to most treatments.

Case report: M.L., female, 19 years old, first seen in August 2013, with left tension-type headache. It may be self-limiting within months or years without therapy, or be refractory to most treatments.

She was treated with botulinum toxin type A 195 U s.c. since January 2014, with cycles every three months. The pain partly relieved after the first cycle and subsided almost completely after the third cycle, becoming tolerable although the patient never became headache free. She is still regularly in treatment, and consistently experienced relief of headache immediately after each cycle, with subsequent worsening of pain, without side effects.

Discussion: The clinical characteristics of the headache, normality of examinations and refractoriness to most therapies were in accordance with NDPH. Other cases of responsiveness of this headache entity to botulinum toxin have been described [1], but the therapy has still not been approved in Italy for NDPH, due to the lack of controlled studies. In this case we can reasonably exclude a spontaneous remission of the headache because of the persistence of less severe pain, clearly relieved by the therapy. Botulinum toxin type A was the only effective treatment in this case, and strongly contributed to the improvement of the quality of life of the patient.

Conclusions: We present this case report as a stimulus to perform more observations to test the validity of botulinum toxin in chronic refractory primary headaches, including NDPH. Written informed consent to publication was obtained from the patient(s).

Reference

A120
O039. Case-control genetic association studies in migraine: a 7-year experience at the Interinstitutional Multidisciplinary Biobank (BioBIM) of IRCCS San Raffaele Pisana
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The Journal of Headache and Pain 2015, 16(Suppl 1):A120

Background: Current advances in molecular biology, together with the development of Biobanks as stable sources of biologic material, are enhancing the possibility of detecting genetic factors involved in the molecular pathogenic mechanisms of migraine, a complex neurological disorder classified as the seventh most disabling disease worldwide.

Results: To date, the migraine section of the Interinstitutional Multidisciplinary Biobank (BioBIM) of IRCCS San Raffaele Pisana has recruited 863 migraine patients and 400 healthy individuals as controls. Each biological sample has been associated with extremely detailed socio-demographic and clinical features of the donor [1]. Thanks to this extended sampling, our group was able to identify significant correlations between several genetic variants and specific migraine features. In a study carried out on the V129M polymorphism of the prion protein gene (PRNP), we showed an association between the 129V genotype and an earlier age at migraine onset [2]. By investigating the common I/D polymorphism of the angiotensin I-converting enzyme (ACE) gene we found that the I/I genotype (associated with reduced ACE and angiotensin II serum levels, hence to reduced gluamatergic and increased GABAergic neurotransmission) seems to confer a milder migraine phenotype in patients with migraine with aura and chronic migraine [3]. Focusing on the role played by factors controlling oxidative mechanisms in the pathophysiology of migraine we described a striking correlation between the rs4880 variant of the superoxide-dismutase 2 (SOD2) gene (associated with reduced antioxidant activity) and the presence of unilateral cranial autonomic symptoms in patients affected by migraine with aura [4]. Given the strong influence of female gender and sex female hormones on migraine susceptibility, we also investigated the possible association of the rs10422838 polymorphism of Progesterone...
receptor gene (PGR) with this disease. Indeed, our data highlighted a linear relationship between the copy number of the T allele and the age of migraine onset [5]. Finally, we excluded any correlation between polymorphisms rs4818 and rs4680 of Catechol-O-Methyltransferase (COMT) gene and migraine, suggesting to look over COMT to explain catecholamine derangement in migraine, exploring enzymes involved in catecholamines synthesis and catabolism such as monoamine-oxidase, dopamine beta hydroxylase, tyrosine hydroxylase or tyrosine decarboxylase [6].

Conclusions: Our Biobank dedicated to migraine has proven to be a valuable resource to conduct molecular studies on this disease, allowing the identification of a new potential biomarker for detection of asymptomatic individuals at increased risk for migraine development, in addition to providing the basis for the design of more tailored and effective therapies.

Conflicting interests: None.

Acknowledgements: These studies were partially supported by the grant PO FESR 2007/2013 (Linea di Intervento 4.1.1.-SIASOP).

References

A121
0056. Migraine as presenting symptom of SLC20A2 gene mutations
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The Journal of Headache and Pain 2015, 16(Suppl 1):A121

Background: Idiopathic basal ganglia calcifications (IBGC), also known as Fahr’s disease, are neurological diseases characterized by symmetric calcium deposits in basal ganglia and other brain regions. Clinically, IBGC patients show high phenotypic heterogeneity, both in the clinical manifestations and neuroradiological findings. Recently, PDGFBR, PDGFB, XPR1 and SLC20A2 have been identified as causative genes for IBGC [1].

The aim of this study was to report on two Italian patients with idiopathic basal ganglia calcifications associated with novel mutations in the SLC20A2 gene who both presented with episodic migraine.

Materials and methods: Two 48-year-old unrelated women presented to the Headache Center, Department of Neuroscience “Rita Levi Montalcini”, University of Turin, with a long-lasting history of headache. The reported symptoms fulfilled ICHD-III beta version criteria for episodic migraine without aura (code 1.1). Computed tomography scans showed in both cases severe calcifications at the bilateral globus pallidus, caudate nuclei, putamen, and dentate nucleus. On the basis of neuroradiological findings, SLC20A2 gene was sequenced.

Results: A novel missense mutation Gly63Asp (exon 1) and a frameshift mutation p.Val507Glufs*2 (c.1520_1521delTG, exon 8) in the isoform 1 of the SLC20A2 gene were identified. In silico analysis showed that the first substitution was predicted to have a damaging role. For the frameshift mutation, the genetic variant was found to change an aminoacid and insert a stop codon, likely leading to a degradation of the mutated messenger RNA.

Discussion and conclusions: The clinical manifestations in patients with IBGC range widely from neurological and psychiatric symptoms to asymptomatic status [2]. We suggest that migraine should be considered when evaluating patients with IBGC and first-degree relatives, in particular in young age, when other neurological symptoms are absent. The identification of new genetic variants further enlarge the spectrum of mutations in SLC20A2, helping to better elucidate the worldwide distribution and the different clinical features.

Written informed consent to publication was obtained from the patient(s).

References

A122
0061. Frontal thermography in healthy individuals and headache patients: reliability of the method
ristina Vitalicovichios-Losito1,2, Fabio Antonaci3, Elena Rossi4, Alfredo Costa5, Ennio Pucci2, Grazi Sances3, Giorgio Dalla Volta4
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The Journal of Headache and Pain 2015, 16(Suppl 1):A122

Introduction: Infrared Thermography detects infrared lights emitted by the body to visualize changes in temperature due to abnormalities in the surface blood flow of affected areas. This method may aid in the diagnostic process in pain medicine.

Objective: To assess the reliability of human body temperature measurement by means of Frontal Infrared Thermography (FIT).

Methods: Thirty-five volunteers with a mean age of 35±11.6 years were evaluated. Fifteen of the 35 subjects were headache patients. FIT was assessed with an infrared thermal camera (model LT3, Zhejiang Dali Technology Co. Ltd) with a thermal sensitivity inferior than 0.08°C at 30°C. FIT measures the spatial distribution of the heat over the face and the image analysis evaluates the temperature in two target points (left and right side) in the frontal polar sites, equidistant 17 mm from inion (fig. 1). The image analysis evaluated the temperature in two target points in the frontal polar sites. The measurements were performed in two separate sessions (T1 and T2), each session being the mean of three separate measurements. The Asymmetry Index, ANOVA 1 way, intra-class correlation coefficient and Pearson’s correlation coefficient for the T1 were calculated. ANOVA 2 way compared the measurements between T1 and T2.

Results: The analysis of variance did not show statistically significant difference between the three consecutive measurements during the first session (p = 0.21 right side; p = 0.35 left side) and the second session (p = 0.07 right side; p = 0.074 left side). Considering the excellent reliability threshold (Fleiss), the measurements of both sides revealed a good reliability. The ICC values for right and left side were: 0.75 and 0.79 respectively during T1, and 0.72 and 0.74 respectively during T2. The best reliability was found between the second and the third measurement. The statistical test ANOVA 2 way did not reveal intra-individual test-reatest variations. A low correlation (r = 0.38) was found between FIT and external
factors (room temperature, age and sex of subjects) while no correlation was found between FIT and pain side or VAS score.

**Conclusions:** FIT can be an effective method for the temperature evaluation in humans. FIT measurements were symmetrical on both sides and were not influenced by room temperature, sex or age of the individuals. The Asymmetry Index was reliable in control subjects to describe the absence of lateralization of FIT and may be used as clinical control limits.

Written informed consent to publication was obtained from the patient(s).

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**A062. Post ambulatory surgery headache in patients affected from primary headaches: a comparison with the general population**

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The Journal of Headache and Pain 2015, Volume 16 Suppl 1

**Background:** Primary headaches, such as tension-type headache and migraine, are very common. Migraine is one of the most weakening diseases, especially in women [1]. Ambulatory surgery consists in performing some surgical procedures, in selected patients, with discharge from the hospital the same working day [2]. After discharge, some complications may occur at home, above all, pain, nausea, vomiting and headache. We detected the predominance of headache at home in women affected from

**Table 1 (abstract A123)**

<table>
<thead>
<tr>
<th>Features</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>64</td>
</tr>
<tr>
<td>Age 48.2 (±8)</td>
<td></td>
</tr>
<tr>
<td><strong>Type of Headache</strong> (ICHD-3)[4]</td>
<td></td>
</tr>
<tr>
<td>Tension-type headache</td>
<td>6</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>5</td>
</tr>
<tr>
<td>Migraine without aura</td>
<td>52</td>
</tr>
<tr>
<td>Cluster headache</td>
<td>1</td>
</tr>
</tbody>
</table>

**Symptomatic Medications**

| Triptans                       | 15       |
| NSAIDs                          | 23       |
| Acetaminophen                   | 8        |
| Combinations                    | 7        |
| O2 therapy                      | 1        |
| None                            | 10       |

**Preventive Medications**

| ß-blockers                      | 8        |
| Amitriptyline                   | 5        |
| Topiramate                      | 3        |
| Vitamins and Supplements        | 6        |
| None                            | 42       |

---

**Figure 1 (abstract A122):** Standard evaluation obtained with infrared frontal thermography.
primary headaches compared to the general population, and its correlation with both anesthetics, the medications usually taken for headache and the drugs given during the intraoperative period.

Methods: Previously we analyzed data collected within an interval of four months, regarding 1,479 patients (Group A) whom had undergone ambulatory surgery and discharged following the criteria of Post anesthetic discharge score system (PADSS) [3]. At a later stage, we decided to study, in the same way, 64 patients with history of primary headache (Group B - Table 1), treated with a different type of anesthetics (Table 2). Nurses questioned all the patients, during two phone calls at home, both in the evening and in the morning following their discharge from the hospital, concerning the presence of headache and its intensity measured with the Numerical Rating Scale (NRS).

We also analyzed data about the personal medications taken for headache, the type of anesthetics, the drugs received during operations for nausea and vomiting such as ondansetron and/or dexamethasone [5] and for postoperative pain, such as acetaminophen, tramadol or ketorolac, individually or combined.

Results: One hundred and ninety-six patients (13.27%) of Group A and 11 patients (17.19%) of Group B had been suffering from headache at home (Table 3). In Group B, no correlation was shown with usual assumption of headache treatments, the technique of anesthesia, the administration of either prophylaxis for nausea and vomiting (OR: 1.006; 50% CI: 0.52-1.93), or analgesics for the treatment of the postoperative pain (OR: 1.77; 50% CI: 0.54 -7.42). Nevertheless, we noted a higher incidence of headache after the administration of acetaminophen alone (OR: 4.32, 50% IC: 1.36-17.15) but lower incidence with ketorolac alone or in combination (OR: 0.48, 50% IC: 0.24-1.00), and with dexamethasone (OR: 0.125, 50% IC: 0.02-0.49).

Conclusions: The study showed that headache is a very frequent complication at home, after ambulatory surgery. A higher incidence of headache in the patients already affected from primary headaches was observed. Few correlations, only with some single drug administered during the intraoperative period, were found.

Written informed consent to publication was obtained from the patient(s).

References

A124
O009. Early pain relief from orthostatic headache and hearing changes, assessed with the visual analogue scale, in spontaneous intracranial hypotension after epidural blood patch in Trendelenburg position: 28 case reports
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The Journal of Headache and Pain 2015, 16(Suppl 1):A124

Background: Spontaneous intracranial hypotension (SIH) is characterized by orthostatic headache (OH), diffuse pachymeningeal enhancement on brain MRI and low CSF pressure. Hearing change (HC) is a frequent finding. Epidural blood patch (EBP) is now the most recommended available treatment. Our study aimed at investigating the EBP efficacy on OH and HC by asking patients to rate their OH and HC at different time intervals with a visual analogue scale (VAS).

Materials and methods: Twenty-eight consecutive patients with SIH were treated with EBP in Trendelenburg position. Two Psychologists asked them to rate, on a VAS, the intensity of their OH and HC before, 24 hours after, and two months after treatment.

Results: A significant improvement in OH and HC was found (p < .001) 24/48 hours after EBP. When followed-up, all patients showed complete relief from OH. Four patients out of 16 reported very mild HC.

Discussion and conclusions: To the best of our knowledge, this is the first time a specific pain assessment with VAS was conducted before and after EBP, showing a fast improvement of OH and HC in a large group of SIH patients. Importantly, patients have been followed up for two months and 13-25 months after discharge, which confirmed the effect to be complete and long-lasting. In a future work, it may be worth monitoring patients’ changes over time with multiple follow-ups, also involving larger patients sample in a multicentric study.

Written informed consent to publication was obtained from the patient(s).

References

A125
O030. Treatment of orthostatic headache from spontaneous intracranial hypotension syndrome: single institutional experience of 326 cases
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The Journal of Headache and Pain 2015, 16(Suppl 1):A125
Background: Spontaneous intracranial hypotension (SIH) is characterized by orthostatic headache (OH), diffuse pachymeningeal enhancement on brain MRI and low CSF pressure. Treatment is usually conservative, but autologous epidural blood patch (EBP) has emerged as the most important non-surgical management.

Materials and methods: From 1992 to 2015 we observed 326 patients (169 females and 157 males; age range 15-84; mean, 47 years) with OH from SIH according to the ICHD 2004 criteria. One hundred and sixteen performed a conservative treatment, while 210 underwent lumbar EBP with 15-50 ml (mean 28 ml) autologous blood. In 203 cases blood was mixed with contrast medium (1 ml of gadolinium (12 pts) and 5 ml of iopamidol (191 pts)), because about 30 after EBP they underwent a spinal MRI or CT to document the blood spread into the epidural space. All patients were kept in a 30° Trendelenburg position for an hour before the procedure, during and for 24 h (52 pts) or 16 h (158 pts) after the procedure. Fifty-two patients were pre-medicated with acetazolamide (500 mg). The follow-up ranged from 6 months to 8 years.

Results: OH disappeared after about 4-24 weeks in patients treated with conservative treatment and more quickly, in 16/24 hours, after EBP when the pts assumed an upright position. Twelve patients had a recurrence of OH, 6 after a short period of time (1-4 week) and 6 after a long period of time (1-4 years). One pt had 3 relapses and another 2. Two patients did not recover after four EBP. Severe SIH complications were: cerebral venous sinus thrombosis: n. 4 pts (2 treated with EBP); coma (GCS: 5); 4 pts (3 treated with one EBP and 1 with three EBP); subdural hematoma: 48 pts (12 women, 36 men) with a thickness of the hematoma varying from 4 to 18 mm. Twenty pts performed hematoma evacuation (in 16 pts because of intracranial hypertension). EBP complications were in 90% of cases low back pain for 2-7 days, and in 5% of cases (10 patients) pneumocephalus, by use of air to locate the epidural space, as a result of accidental dural puncture or pressure gradient between the extra dural/subdural space, which resolved after a few days with symptomatic treatment.

Discussion and conclusions: The lumbar EBP in Trendelenburg position appears to be safe and quickly effective in 99% of cases of OH from SIH, and in these, 94% after just a single treatment. While the conservative treatment seems to be effective in the longer period and sometimes with risk of severe complications.

Written informed consent to publication was obtained from the patient(s).

References
The red ear syndrome.

A previously healthy 37-year-old nurse was admitted and she was given, steroids and "Low heat pain thresholds in

8(2)
To investigate perception intensity of trigeminal heat

14(1)
stimulation (THS) [2] in patients with migraine without (MwoA CA-) and

THS - Heat Pain Thresholds

Different intensities: a low-innocuous and a high-


POSTER PRESENTATIONS

A129

P075. Secondary headache due to bilateral dissection of vertebral arteries

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The Journal of Headache and Pain 2015, 16(Suppl 1):A129

Introduction: Headache with or without neck pain can be the only manifestation of cerebral arterial dissection. Headache is the most common and the most frequent onset symptom in cervical arterial dissection. Section 6.5.1 of the International Classification of Headache describes facial or neck pain imputable to arterial dissection. The described diagnostic criteria are: acute onset of facial or neck pain with or without other neurological signs or symptoms, developing in close temporal relationship and on the same side of the dissection and disappearing within 1 month. In addition, the dissection must be diagnosed by appropriate vascular/ neuroimaging investigations. Post-traumatic and spontaneous dissection occurrence is described in the literature; these occurrences although rare should be considered and promptly investigated in order to begin an effective treatment.

Case presentation: A previously healthy 37-year-old nurse was admitted in our department for acute onset of headache with vertigo and nausea. In her past medical history there were post-partum onset of major depression and anorexia nervosa. At the Emergency Department she underwent a brain-CT and lumbar puncture which showed no significant alterations. Once she was transferred to our department we required an MR of the brain that showed no pathological signs. We considered the diagnosis of tension-type headache and she was given, steroids and benzodiazepine treatment. Two days after starting the therapy no improvement of the pain was observed. She reported persistence of headache worsening during orthostatic position; neurological examination revealed nistagmoid movements at the higher quadrants. The worsening headache with bilateral continuous occipital and posterior cephalgia, associated with nausea and persisting after two weeks from the established therapy led us to perform a TSA echo-color-doppler followed by angi-TC. These exams showed alterations suspected for vertebral dissection, and a diagnostic angiography confirmed bilateral dissection of vertebral arteries.

Discussion: Headache and migraine are the presenting symptoms in 57-92% of the carotid artery dissections and in 69-72% of vertebral artery dissections. Pain localization is not specific for the dissected artery; however, carotid dissections tend to present with frontal pain, while pain resulting from the dissection of the vertebral artery is easier to posterior or occipital. Pain localized in the eye, ear or face more easily indicates involvement of the carotid artery. Cervical artery dissection occurs when the tonaca intima is damaged due to direct trauma or an anomaly. Thus, blood can fill the space created between the layers of the artery wall forming clots, potential cause of stroke, pseudo aneurysms and occlusions of vessels. Intracranial dissections can cause a subarachnoid hemorrhage. Considering that cervical artery dissections may present with common signs or symptoms such as headaches, neck pain, neurological deficits and stroke, it is important to consider and rule out the possibility of a dissection. CT angiography, angiography, aneurysm-MR and digital subtraction angiography are useful for diagnosis. The first-line therapy for the treatment of spontaneous or traumatic dissection is an anticoagulant or antiplatelet therapy to reduce the risk of stroke. There may be an indication for endovascular treatment or surgery. There is a significant risk of recurrence or re-bleeding that must be taken into account. In particular, the recurrence occurs in 10-28% of cervical artery dissections.

References


A 44-year-old woman with unremarkable medical history was treated with indomethacin 50 mg daily for 4 days and then 50 mg twice a day for 2 months. The headache gradually disappeared after 5 days of therapy.

After 12 months of follow-up the patient is in good health.

### Discussion and conclusions:

The pathophysiology of headache triggered by VM is unknown. The most reasonable hypothesis is a sudden increase in intracranial pressure secondary to sudden coughing or straining in the absence of any systemic or intracranial disorder. The clinical features of the pain are characterized by sudden onset, lasting from 1 s to 2 hours, and brought on by and occurring only in association with coughing, straining, and/or VM. Neuroimaging plays an important role in differentiating secondary forms.

**Case report:** A 71-year-old woman with obesity, high blood pressure, type 2 diabetes, hypothyroidism and glaucoma was admitted because for the past 18 months she had headache attacks with stabbing severe pain (N9R 10/10), on the right fronto-temporal side with parietal-occipital diffusion. The pain lasted from 30 to 360 minutes with and without intake of analgesic, respectively. For the first 6 months, the headache was triggered only when bending over. Subsequently, also other activities that required the execution of a Valsalva maneuver (coughing, sneezing, laughing) caused the same headache attacks. Neurological examination and hematologic work up were normal. MRI of the brain, angiography and CSF circulation study were normal. The patient was treated with indomethacin 50 mg daily for 4 days and then 50 mg twice a day for two months. The headache gradually disappeared after 5 days of therapy. After 12 months of follow-up the patient is in good health.

**Discussion and conclusions:** The pathophysiology of headache triggered by VM is unknown. The most reasonable hypothesis is a sudden increase in intracranial pressure secondary to sudden coughing or straining, such as during coughing; other reported contributing factors are transient post-infective hypersensitivity of pressure receptors localized in venous vessels, reduction of the posterior fossa volume with consequent crowding of its structures, incompetence of the valves of the internal jugular veins, venous stenosis, and intermittent intracranial pressure elevation. The initial history of our case and some cases reported in the literature suggest that the headache caused by maneuvers related to increased intrathoracic pressure (Valsalva’s maneuver like stimuli) may not be triggered by coughing. In these cases, when structural lesions are excluded by MRI or similar tests, we propose the eponym, “primary Valsalva maneuver headache” (which is more appropriate than the equivalent “PCH”). In these patients it is possible that the Valsalva maneuver provoked by the cough did not reach the pain threshold to cause headache. Written informed consent to publication was obtained from the patient(s).

### Background:

Colloid cysts are rare congenital benign tumors accounting for 0.2-2% of all intracranial neoplasms. They usually occur in the front part of the third ventricle. The clinical presentation is related to the increased intracranial pressure and is widely variable; sudden death associated with acute hydrocephalus can occur, therefore recognition of this rare condition is important in order to select an appropriate surgical treatment. We report a case of new onset headache secondary to a colloid cyst of the third ventricle.

**Case report:** A 44-year-old woman with unremarkable medical history was admitted to our clinic for recurrent attacks of pressing headache, with abrupt onset and brief duration, accompanied by nausea, transient hearing loss and tinnitus. These symptoms were relieved by supine position. The clinical picture progressively worsened, with episodes of vomiting during headache. Neurological examination was negative. A magnetic resonance imaging (MRI) scan showed a spherical mass lesion with lipid signal at the intraventricular foramina of Monro causing compression of the third ventricle and expansion of the ventricular system, suggestive of hydrocephalus. After neurosurgical evaluation the patient underwent an endoscopic removal of the lesion. Histological findings were compatible with colloid cyst of the third ventricle. After surgical treatment the patient recovered completely from symptoms and the follow-up MRI demonstrated the complete excision of the lesion.

**Conclusions:** Colloid cysts are congenital, slow growing, benign intraventricular lesions usually arising in the third ventricle. They may cause obstruction of the foramen of Monro with blockage of cerebrospinal fluid (CSF) flow, producing progressive or intermittent elevated intracranial pressure with chronic or acute hydrocephalus [1]. The onset of symptoms is usually between 20 to 50 years of age, often with paroxysmal attacks of severe headache associated with nausea and vomiting [2]. Presentations with thunderclap headache have also been described [3]. Headache can resolve or reduce in supine position, suggesting that the colloid cyst moves in and out the foramen of Monro with intermittent obstruction of CSF. Colloid cysts, if left untreated, may lead to serious complications such as visual loss, memory difficulties, acute disturbances of consciousness and even sudden death as a consequence of acute obstructive hydrocephalus with brain herniation or cardiovascular failure due to abrupt disturbance of hypothalamic function. The risk of sudden neurologic deterioration cannot be predicted, therefore surgical treatment is recommended [1,2].

Our case highlights the importance of early detection and prompt treatment of this potentially life-threatening cause of headache.

Written informed consent to publish was obtained from the patient(s).

### References

Headaches and other cranio-orofacial pains are widely distributed in the general population. Unfortunately, there is very little evidence regarding the impact of these conditions in patients admitted to rehabilitation units, regardless of the disease or syndrome requiring rehabilitation. The availability of diagnostic and therapeutic guidelines, as well as the increasing number of data coming from controlled clinical trials, should be implemented in these patients to reduce the burden of pain and improve their global outcome.

The Italian Society for Neurorehabilitation, in collaboration with the Italian Society of Physical Medicine and Rehabilitation, has promoted the Consensus Conference on Pain with the aim to foster attention on pain also in the rehabilitative field (http://www.doloreinneuroriabilitazione.it/).

The working group has proposed the following recommendations:

- Standard methods or criteria exist to evaluate head and cranio-facial pain in terms of intensity (B);
- Standard methods exist to evaluate migraine in terms of disability (A);
- It is important to evaluate the impact of cephalic and cranio-facial pain in neurorehabilitation (D);
- Standard methods or criteria exist to diagnose head and cranio-facial pain (GL);
- It is important to identify predictive factors associated with the development of cephalic and cranio-facial pain in association with a condition requiring neurorehabilitation (D);
- Effective pharmacological treatment exists for primary headaches and for trigeminal neuralgia (GL);
- Manual therapy is indicated in the management of migraine and tension-type headache (GL);
- Manual therapy may be effective in TMD-associated pain (D);
- Botulinum toxin A is effective in the treatment of idiopathic trigeminal neuralgia (B);
- Botulinum toxin A is effective in the treatment of hemifacial spasm (B);
- Topical capsaicin is effective in chronic neuropathic pain (B);
- Evidence is needed to evaluate the impact of treating cephalic and cranio-facial pain on the outcome of patients undergoing neurorehabilitation (D).

The recommendations are presently under evaluation by the Consensus Conference panel.

Introduction: We conducted an observational study of patients attending our outpatient headache clinic, suffering from episodic tension-type headache (ETTH) and migraine without aura (MO). The purpose of the study was to compare the efficacy of magnesium bisglycinate, L-tryptophan, niacin, vitamin B2 and vitamin D, pineal tens (PT) and amitriptyline (A) in the prophylaxis [1-4] of these primary headaches using as outcomes: pain modification with visual analogue scale (VAS); the change in the number of attacks/month; the change in the consumption of analgesics/month.

Patients and methods: ETTH and MO were diagnosed according to the International Classification ICHD-II criteria. We studied a total of 200 patients: 100 patients were diagnosed with ETTH and 100 with MO. Of these patients, 50 with a diagnosis of ETTH (15 M, 35 F; mean age: 34 years) were treated with PT (1 sachet morning and evening) and were compared with 50 patients (17 M, 33 F; mean age: 39 years) undergoing amitriptyline therapy (20 mg in the evening). Fifty patients with MO (15 M, 35 F; mean age: 37 years) were treated with PT (1 sachet morning and evening), and compared with 50 patients (8 M, 42 F; mean age: 40 years) taking A (20 mg in the evening).

Results: The VAS modifications, the number of attacks and the number of analgesics taken during the study are shown in Figure 1 for the patients diagnosed with ETTH. The group treated with PT clearly showed a reduction in all treatment outcomes during the study compared to the group taking A. VAS modification, the number of attacks and the number of analgesics taken during the study are shown in Figure 2 for the patients diagnosed with MO. The group treated with PT clearly showed a reduction in all treatment outcomes during the study compared to the group taking A.

Conclusions: Our clinical observation of an improvement in headache in patients receiving PT led us to conduct this cohort study comparing PT with A therapy. Although this study is obviously limited because of the absence of patient randomization, its results confirm the clinical impression of an improvement in the primary headache in patients with PT in terms of improvement in VAS, reduction in the number of attacks/month, and the consumption of analgesics/month. In fact, PT treatment was found to be more efficacious when compared to A treatment in many outcome measures.

Written informed consent to publish was obtained from the patient(s).

References

Figure 1 (abstract A133) Patients with ETTH
Efficacy of prophylactic therapy in chronic primary headache with use of biofeedback

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Introduction: Retrospective study of patients with chronic tension headache (CTH) and chronic migraine (CM).

Objective: To compare the efficacy of biofeedback (BFB) compared to only prophylactic therapy in these primary headaches [1-4].

Materials and methods: We evaluated a total of 8 patients with CTH and 8 patients with CM. All patients had a history of primary headache and had never undergone prophylactic therapy. The observation period lasted 90 days. Four CTH patients and 4 CM patients underwent only prophylactic therapy (amitriptyline 20 mg daily), the remaining 4 CTH and 4 CM prophylactic therapy and BFB training sessions. Assessment tools outcome measures were:

- Headache diary to assess days per month with headache;
- Analgesic consumption and/or triptans;
- Score of the visual analogue pain scale (VAS);
- SEMG parameter for patients who carried out BFB training.

Results: At the end of the 90 day observational period there was a significant improvement (reduction in headache days per month, in VAS score, in analgesic consumption and in SEMG parameter) in CTH and CM patients that had undergone both BFB training and prophylactic therapy when compared to the group of patients treated only with prophylactic therapy drug.

Discussion and conclusions: The overall data confirmed the efficacy of the BFB training in the prophylaxis of primary headaches, further supporting the benefits already possible with the therapy of only pharmacological prophylaxis (Table 1). The data also showed a clear dominance of efficacy, especially in the forms of chronic tension headache (Table 2).

Written informed consent to publication was obtained from the patient(s).

References


Table 1(abstract A134) Overall differences between the two groups after 90 days of therapy

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>VAS</th>
<th>Analgesic consumption</th>
<th>Triptan consumption</th>
<th>SEMG</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTH</td>
<td>-58%</td>
<td>-37%</td>
<td>-62%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTH BFB</td>
<td>-75%</td>
<td>-67%</td>
<td>-86%</td>
<td></td>
<td>-54%</td>
</tr>
<tr>
<td>CM</td>
<td>-53%</td>
<td>-34%</td>
<td>-60%</td>
<td></td>
<td>-50%</td>
</tr>
<tr>
<td>CM BFB</td>
<td>-61%</td>
<td>-43%</td>
<td>-75%</td>
<td></td>
<td>-63%</td>
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</table>

POSTER PRESENTATIONS

A135
P067. Multimodal therapy in the management of MOH: a 3-year experience

Valerio De Angelis¹*, Francesca Cherubini², Gaia Nigrelli², Denise Erbuto², Paolo Martelletti³

¹Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy; ²Department of Neurosciences, Mental Health and...
The relationship between migraine and psychopathology has been clinically discussed in various studies. Medication-overuse headache (MOH) has been often found comorbid with emotional disturbances and disordered personality traits [1,2]. This might play a role in the evolution of migraine to MOH and might be associated with higher risks of chronicization and/or relapses in drug abuse. Psychological disturbances may also be risk factors for a later development of MOH [3]. Since 2012 the Psychology Service of Sant’Andrea Regional Referral Headache Centre has offered short cycles of psychological interviews mostly oriented towards the support of MOH patients during the post-rehabilitation infusional phase in order to prevent relapses.

In these past 3 years 106 MOH patients afferent to the Headache Centre underwent the infusional therapy and were eligible for psychological support. Patients’ profiles highlighted avoidant and dependent personality traits together with a high level of anxiety and depressive mood. Patients showed a low perception of their personal skill, resources and a perception of their body mostly related to the head pain. The psychological intervention has been cognitive-behavioral and has improved patients’ perception of self relative to their body, their personal skills and resources.

Psychological support together with prophylaxis therapy with OnabotulinumtoxinA produced in patients a reduction of relapses in drug abuse of 38% compared to a sample of 108 patients age and gender matched that was not eligible for psychological support but received the detoxification and prophylaxis therapy. This means that in some selected cases a multimodal therapy, consisting in a program of pharmacotherapy and psychological support, is necessary for the treatment of MOH patients in order to reduce the risks of relapses into drug abuse.

Written informed consent to publish was obtained from the patient(s).

References

A136
P019. Transcutaneous supraorbital neurostimulation in “de novo” patients with migraine without aura: the first Italian experience
Antonio Russo 1,2,*, Francesca Conte 1, Laura Marcuccio 1, Alfonso Giordano 1,2, Giacchino Tedeschi 1,2, Alessandro Tessitore 1,2
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Background: Pharmacological anti-migraine preventive therapies are widely used to reduce the impact of migraine on quality of life; nevertheless, they may exhibit incomplete efficacy and significant side effects. Transcutaneous supraorbital neurostimulation (tSNS) has been recently proposed for the treatment of migraine. Moreover, tSNS has been recently found superior to sham stimulation for episodic migraine prevention in a randomized trial [1].

Objective: To evaluate both the safety and efficacy of a brief period of tSNS treatment in a group of patients with migraine without aura (MwoA). To this end, we used a tSNS medical device, called Cefaly® (CEFALY Technology, Herstal, Belgium), approved for use in migraine prevention by the Food and Drug Administration (FDA) and for sale in Europe.

Methods: We enrolled 24 consecutive patients with MwoA experiencing a low frequency of attacks (≤5 attacks/month), whom had never taken migraine preventive drugs in the course of their life. Patients performed a daily supraorbital high frequency tSNS, for 20 minutes, for two months. Primary outcome measures were the reduction in migraine attacks and migraine days per month (p < 0.01). Secondary outcome measures were the reduction of headache severity during migraine attacks (by means of visual analog scale) and HIT-6 (Headache Impact Test) rating, as well as in monthly intake of rescue medication (p < 0.05). Finally, compliance, treatment satisfaction, and potential adverse effects related to tSNS were evaluated.

Results: Between run-in and second month of tSNS treatment, both primary and secondary endpoints were met. Indeed, we observed a statistically significant decrease in the frequency of migraine attacks (p < 0.001) and migraine days (p < 0.001) per month, as well as a reduction in average pain intensity during migraine attacks (p = 0.002), HIT-6 rating (p < 0.001), and intake of rescue medication (p < 0.001). All patients showed good compliance levels and no relevant adverse events occurred during the tSNS period.

Conclusions: In patients with MwoA experiencing a low frequency of attacks, significant improvements in multiple migraine severity parameters were observed following a brief period of high frequency tSNS [2]. Therefore, tSNS may be considered a valid option for the preventive treatment of migraine attacks in patients who cannot or are not willing to take daily medications, or in which low migraine frequency and/or intensity would not require pharmacological preventive therapies.

Written informed consent to publish was obtained from the patient(s).

References

A137
P070. A 2-year prospective evaluation study on onabotulinumtoxinA 155 U in chronic migraine
Andrea Negro 1, Lidia D’Alonzo, Noemi Lala, Paolo Martelletti
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The Journal of Headache and Pain 2015, 16(Suppl 1):A137

Background: OnabotulinumtoxinA (Botox®) is the first and so far the only treatment to receive a specific license for prevention of chronic migraine (CM). In our Headache Clinic the therapy with onabotulinumtoxinA is routinely administered to CM patients on a daily basis since 2001. Preventive treatment with onabotulinumtoxinA was offered to all patients...
To prospectively evaluate the variations in terms of headache "Ou rr e s u p p o rt f i n d i n g s P R E E M P T s t u d yi nal a r g e injection paradigm e Among all the patients that from 2011 to 2012 underwent 16(Suppl 1): 2010, suggests a possible systemic pain effects on pericranial muscle Coenzyme Q-10 (ubiquinone) is a small hydrophobic starting the therapy. oral medication during treatment with onabotulinumtoxinA. underwent withdrawal and detoxification therapeutic regimen before (± one week) [1]. Patients with criteria for medication-overuse headache PREEMPT 2 years. OnabotulinumtoxinA 155 U was injected in 31 sites following the treatment with onabotulinumtoxinA we randomly selected 100 CM patients the fourth, and remains stable until the last injection at 24 months. Patients were not allowed to continue preventive oral medication during treatment with onabotulinumtoxinA. Results: The efficacy results for each timeline are reported in Table 1. The reduction in terms of headache and m

<table>
<thead>
<tr>
<th>Table 1(abstract A137) Efficacy of onabotulinumtoxinA 155 U</th>
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<tr>
<td>Headache days</td>
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<tr>
<td>----------------</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Migraine days</td>
</tr>
<tr>
<td>Acute pain medication intake days</td>
</tr>
<tr>
<td>HIT-6 score</td>
</tr>
</tbody>
</table>

that were 1) adults; 2) fulfilling the ICHD-II criteria for CM with or without analgesic overuse; and 3) with contraindications or lack of efficacy or tolerability to other preventive drugs. Exclusion criteria were coexistent neuromuscular disorders, psychiatric diseases considered incompatible with this kind of treatment, pregnancy and breast-feeding.

Objectives: To prospectively evaluate the variations in terms of headache days, migraine days, acute pain medication intake days through a period of 24 months in comparison to a one-month baseline period before starting the therapy.

Methods: Among all the patients that from 2011 to 2012 underwent treatment with onabotulinumtoxinA we randomly selected 100 CM patients (F 88 / M 12; mean age 43.2, range 18-80 years; 96% drugs overusers) that were 1) adults; 2) fulfilling the ICHD-II criteria for CM with or without analgesic overuse; and 3) with contraindications or lack of efficacy or tolerability to other preventive drugs. Exclusion criteria were coexistent neuromuscular disorders, psychiatric diseases considered incompatible with this kind of treatment, pregnancy and breast-feeding.

Results: The efficacy results for each timeline are reported in Table 1. The reduction in terms of headache and migraine days, acute pain medication intake days and HIT-6 score increases strongly from the first injection to the fourth, and remains stable until the last injection at 24 months.

Conclusions: Our results support findings of PREEMPT study in a large cohort of patients and are representative of the patients observed in a tertiary headache centre. Written informed consent to publish was obtained from the patient(s).

Reference

A139
P032. Coenzyme Q-10 and migraine: a lovable relationship. The experience of a tertiary headache center
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E-mail: ennio.pucci@mondino.it
The Journal of Headache and Pain 2015, 16(Suppl 1):A139

Background: Coenzyme Q-10 (ubiquinone) is a small hydrophobic substance that acts as an electron carrier in the mitochondrial respiratory chain. Its main activity is to protect DNA, proteins and lipids from oxidative stress. In the literature, a role of brain oxidative metabolism in the pathogenesis of migraine has been hypothesized [1]. Few clinical trials are described using coenzyme Q-10 in migraine prophylaxis, even in pediatrics [2-4]. The aim of this work was to present our experience of migraine prevention, prescribing coenzyme Q-10 to 20 adult patients with migraine without aura.

Materials and methods: Patients were enrolled in a tertiary headache center and followed for a period of 60 days (visit 1 and visit 2). The dose of coenzyme Q-10 was 200 mg/day. Visual analogue scale (VAS) was used to measure pain.

Results: In our cohort, male/female ratio was 1:5, while the mean age was 32.1 years (range, 22-49 years). Patients had a relatively short history of disease (mean 5.6 years; range 2-18), indeed only 2 of them were on a first-line treatment whereas coenzyme Q-10 was the starting therapy for others. We noticed a significant reduction of the number of crises at visit 2 (mean 3.15 vs 0.9, p < 0.05), as well as VAS score (mean 6.65 vs 1.45, p < 0.05) and monthly days of headache (mean 6.3 vs 1.5, p < 0.05). No one showed side effects, body weight did not vary (mean 56.55 vs mean 56.65) and patients did not even experience drastic weight loss or gain. The drug was well tolerated with a mean satisfaction score of 7.65 (range, 0-10). Moreover, patients reported positive effects on fatigue.

A138
P042. Mechanism of action and clinical evidence of botulinum toxin in chronic migraine
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The Journal of Headache and Pain 2015, 16(Suppl 1):A138

Considerable evidence exists supporting the notion that botulinum toxin type A (BoNT/A) can exert a direct analgesic effect in addition to its myorelaxant effect. It is likely that the benefit of using BoNT/A as prophylactic treatment for chronic migraine is due to its ability to inhibit overactivity of motor neurons and hyperexcitability of sensory neurons, by involving the suppression of peripheral and central sensitization. In this study we aimed to evaluate the effects of BoNT/A on amplitude, latency and habituation of laser evoked potentials (LEPs) in patients with chronic migraine. We recruited 20 patients with a diagnosis of chronic migraine treated with type A botulinum toxin every 3 months. LEPs were recorded in basal, two hours and ten days after both BoNT/A and placebo injection. Headache frequency, allodynia and total tenderness score (TTS) were evaluated at basal condition and after one-year of treatment. We found N2 and P2 latency increased 10 days after toxin injection, while LEPs amplitude was not modified. Compared to placebo injection, the habituation of N2/P2 LEPs component obtained by stimulating supraorbital zone was significantly increased after BoNT/A infiltration. After ten days, habituation pattern in migraine patients was similar to that of normal subjects. In the one-year follow-up we observed a significant migraine frequency and allodynia improvement, but no effect on total tenderness score. Furthermore the habituation change correlated with the clinical effectiveness.

Study results suggest a toxin modulating action on nociceptive afferents in patients with chronic migraine. The N2 and P2 latency increase obtained from hand laser stimulation suggests a possible systemic pain inhibiting effect. Although the botulinum toxin did not show an inhibitory effect on trigeminal nociceptive system, it seems to improve the reduced habituation pattern which promotes the central sensitization. The therapeutic effect of BoNT/A seemed to be related to the effect on trigeminal habituation obtained after 10 days from the first infiltration, which could be considered as a potential neurophysiological pattern to predict the non-responders. Results of this study confirm that the effect of botulinum toxin on chronic migraine may be related to a modulation and normalization of central sensitization mechanisms. The lack of effects on pericranial muscle tension precludes to suppose a modulating effect on trigeminal nociception by the inhibition of the neuromuscular synapse. Written informed consent to publish was obtained from the patient(s).
Conclusions: Coenzyme Q-10 is a safe and effective therapy for migraine prophylaxis. Written informed consent to publish was obtained from the patient(s).

Conflict of interest: None. This study did not receive any industry funding.

References:

ORAL PRESENTATIONS

A140

O055. Headache and psychopathological aspects in Gilles de la Tourette Syndrome: a comparison between paediatric and adult patients

Valentina Bandera, Beatrice Bartoli, Chiara Luoni, Lucilla Selvini, Giorgio Rossì, Umberto Balottin, Andrea Cavanu, Cristiano Termine, Giuseppe Cosentino, Filippo Brighina.

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The Journal of Headache and Pain 2015, 16(Suppl 1):A140

Background: Only few studies have analyzed the occurrence of headache in patients with Gilles de la Tourette syndrome (GTS) [1-3]. The aim of this study was to compare the prevalence and characteristics of headache in paediatric and adult patients with GTS and the relationship of headache with tic severity, psychiatric comorbidities and quality of life.

Materials and methods: One hundred and nine children and adolescents with GTS (age range, 6-17 years) were screened for the occurrence of headache between April and December 2014 and twenty-five GTS patients (23%) showed headache. Sixteen of these have been compared with eighteen randomly selected GTS patients without headache with reference to severity of tics, psychiatric comorbidities (OCD, ADHD, anxiety, depression) and quality of life, using specific rating scales and questionnaires. Thirty-one adult GTS patients, randomly recruited from a group of 200 patients, were screened for the presence of headache and underwent the same clinical assessment.

Results: Adults with GTS, compared with children and adolescents, showed a higher prevalence of headache (48.4% vs 23%, p < 0.05), higher tic severity, lower quality of life and higher prevalence of associated comorbidities: OCD (77.4% vs 52.9%), anxiety (77.4% vs 32.4%), depression (64.5% vs 26.5%). Children and adolescent GTS patients with headache showed a lower severity and frequency of tics compared with GTS patients without headache.

Conclusions: Adult patients with GTS show a higher prevalence of headache and a more severe clinical phenotype compared to younger patients. Among children and adolescents, those with headache showed a lower severity and frequency of tics, thus supporting the hypothesis that in young GTS patients, headache and tics could be considered different phenotypic expressions of a common etiopathogenetic mechanism (e.g., psychosomatic symptoms of poor anger and aggression management) [4,5]. Written informed consent to publish was obtained from the patient(s).

References:
our findings suggest that migraine follows BPT in pediatric conditions which often require immediate medical care among the wide spectrum of headache diagnoses. The diagnostic approach starts with a thorough history followed by a complete physical and neurologic examination. The temporal features may be useful to classify headaches into four temporal patterns (acute, recurrent acute, chronic progressive, chronic non-progressive) that aid in reaching the etiological diagnosis. A normal neurological examination has been demonstrated to highly correlate with the absence of relevant intracranial processes in several pediatric studies. Neuroimaging should be considered in patients with recent-onset severe headache or change in the type of headache or with associated signs or symptoms suggestive for intracranial diseases. The therapeutic management of headache in ED depends on general clinical conditions of the patients and the presumable etiology of headache [1].

**References**


**Table 1 (abstract A142)** Comparison of the studies about etiology of headache in ED * only patients with focal neurological signs at admission to ED

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>130</td>
<td>150</td>
<td>185</td>
<td>432</td>
<td>288</td>
<td>550</td>
<td>101</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&gt;18</td>
<td>&gt;18</td>
<td>2-15</td>
<td>2-18</td>
<td>2-18</td>
<td>0-16</td>
<td>6-18</td>
</tr>
<tr>
<td>Secondary benign headaches (%)</td>
<td>63.2</td>
<td>59.6</td>
<td>60.5</td>
<td>35.4</td>
<td>63.2</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>Secondary life-threatening headaches (%)</td>
<td>15.3</td>
<td>14.9</td>
<td>4.3</td>
<td>4.1</td>
<td>2</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Primary headaches (%)</td>
<td>10</td>
<td>18</td>
<td>24.3</td>
<td>24.5</td>
<td>21.8</td>
<td>56.7</td>
<td>66.3</td>
</tr>
<tr>
<td>Unclassified (%)</td>
<td>11.5</td>
<td>7</td>
<td>10.8</td>
<td>36</td>
<td>13</td>
<td>1.3</td>
<td>23.7</td>
</tr>
</tbody>
</table>

**Background:** Migraine equivalents are clinical conditions which often involve children who do not complain of headache. They include abdominal migraine, motion sickness, limb pain, cyclical vomiting, benign paroxysmal vertigo, and benign paroxysmal torticollis (BPT). The aim of our study was to investigate whether children referred to us for BPT have developed migraine at a distance from our first observation.

**Methods:** Forty-one children were included in the study. Only 36 families could be contacted by phone, but 2 of them refused to answer our questionnaire. Therefore, the present results were obtained from 34 children (22 girls and 12 boys).

**Results:** Migraine could be diagnosed in 14 children (41%), while the remaining 20 patients (59%) did not complain of headache. At the moment of our interview, children who had developed migraine had a mean age of 5 years, while the mean age of non-migrainous children was 3.5 years. Among migraine children, 43% developed it when they were 4 years, 21% at the age of 3, and 14% when they were 7 years old. The last three migraineurs developed migraine at the age of 5 years, 13 years and 18 months, respectively. Moreover, 55% of patients had developed other migraine equivalents. In particular, 73% children had abdominal migraine, 55% vertigo, 45% limb pain, 27% motion sickness, 27% cyclical vomiting. As for the paroxysmal torticollis time course, two children had had only one event, one child had been still presenting episodes of torticollis, while in the remaining patients the torticollis events had not occurred for some years.

**Conclusions:** Our findings suggest that migraine follows BPT in approximately half of the children within the age of 13 years. Moreover, BPT is often associated to other migraine equivalents. Considered all together, all these periodic syndromes increase the risk of developing migraine. Written informed consent to publish was obtained from the patient(s).
second was composed of 100 children with epilepsy divided into rolandic, absence, grand-mal, and temporal lobe. The last group had 200 children without any disease. Behavioural problems were screened with the Aggression Questionnaire [3], a standardized and validated instrument. 

Results: Statistical analysis showed relevant differences between the groups. Children with headache had lower scores in all scales compared to the control sample and the epilepsy group (p < 0.05). Children with epilepsy obtained higher scores in physical aggression (p < 0.05) than children without any disease. Moreover, girls, considering the whole sample, had higher scores (p < 0.05) in the hostility scale, while boys had higher scores in physical aggression.

Conclusions: Results suggest that children with headache tend to inhibit their aggressive behaviours compared to children with epilepsy. On the contrary, children with epilepsy express their anger, hostility, physical and verbal aggression compared to children with headache and without any disease.

Written informed consent to publish was obtained from the patient(s).

References

A145
P046. ADHD and headache: observational study of case series
Debora De Carlo¹, Guido de Rênoche², Massimo Ronchese³, Luigi Bianchin⁴, Barbara Bolzonella, Pier Antonio Battistella
¹Juvenile Headache Centre, Department of Woman and Child Health, University of Padua, Padua, Italy; ²Children and Adolescents Neuropsychiatry Unit ULSS 16, Padua, Italy
E-mail: pierantonio.battistella@unipd.it
The Journal of Headache and Pain 2015, 16(Suppl 1):A145

Background: Attention deficit and hyperactivity disorder (ADHD) and headache are two very common diseases in childhood and both of them have an important impact on quality of life and academic performance [1]. In the literature there are many studies on psychopathology in headache, but the relationship between headache and ADHD is considered in few of them [2]. Recent studies have reported possible neural pathways and pathophysiological mechanisms that may underlie this relationship [3].

Aim: Analysis of comorbility between ADHD and headache and headache searching for the presence of ADHD trait in a population of headache patients.

Subjects and methods: Observational study of case series based on collection of clinical-anamnetic data and on the administering of a standardized questionnaire (Strengths and Difficulties Questionnaire, SDQ) to evaluate the presence of ADHD traits in all the patients consecutively referred to the Juvenile Headache Centre of Padua (December 2014-May 2015). Inclusion criteria: age 5-18 years; diagnosis of primary headache, using the International Classification of Headache Disorders III, 2013 [4]: migraine without aura (MO) or with aura (MA), chronic migraine (CM), episodic (ETTH) or chronic tension-type headache (CTTH).

Results: Total sample of 180 cases (61 M, 99 F) with mean age at interview of 11.8 years (8-18 years). Headache types: 120 migraine (M) (66.7%), 49 tension-type headache (TTH) (27.2%), 5 headaches with mixed pattern (M + TTH) (2.8%) and 6 other headaches (3.3%). M patients were divided into 107 MO (89.2%), 13 MA (10.8%); TTH were divided into 45 ETTH (91.8%) and 4 CTTH (8.2%). Family history for headache was present in 122/180 patients (71.8%), family history for M in 50/122 (41.0%). Prevalence of ADHD traits was 19.4% in SDQ questionnaires completed by parents and 21.3% in self-assessment SDQ questionnaires from children/adolescents. There was a low level of agreement between parents and children, reflecting heterogeneity symmetrical judgment between the two groups (p 0.53, K 0.53). There were no correlations with the diagnosis of headache or with other clinical features (sex, age of patients, age of onset, duration of illness, family history for headache); statistically significant relationships were found with the worsening of academic performance (p 0.001) and marginally with school absences (p 0.08).

Conclusions: This study confirms most literature studies on the possible relationship between headache and ADHD, especially concerning the important impact on quality of life and academic performance [1-3]. It confirms the remarkable role of ADHD traits in the personal and family history of the juvenile patients affected by primary headaches.

Written informed consent to publish was obtained from the patient(s).

References

A146
P016. Congenital ataxia, hemiplegic migraine due to a novel mutation of CACNA1A: a case report
Roberto Frusciante1, Alessandro Capuano1, Lorena Travaglini2, Ginevra Zanni2, Frederico Vegrevans1, Enrico Bertins3, Massimiliano Valeriani1, M°
1Headache Center, Neurology Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Italy; 2Unit of Molecular Medicine for Neuromuscular and Neurodegenerative Disorders, Bambino Gesù Children's Hospital IRCCS, Rome, Italy; 3Center for Sensory-Motor Interaction, Aalborg University, Aalborg, Denmark
E-mail: m.valeriani@tiscali.it
The Journal of Headache and Pain 2015, 16(Suppl 1):A146

Background: The CACNA1A gene encodes the pore forming alpha-1A subunit of neuronal voltage-dependent P/Q-type Ca (2+)+ channels. Mutations in this gene result in clinical heterogeneity, including hemiplegic migraine, episodic ataxia, or progressive chronic conditions.

Case report: An 8-year-old boy was admitted to our neurological unit due to an acute onset of left hemiparesis developed after a febrile episode. He also complained of headache with migraine characteristics. Brain MRI showed right hemispheric oedema. The hemiparesis disappeared completely after 1 week, and after steroid treatment. The patient was already known to our clinic since he was 2 years old when he was referred to us for a motor and cognitive developmental delay and for a cerebellar syndrome diagnosed as congenital ataxia. In the past all metabolic, biochemical and genetical analyses resulted negative. Serial brain MRI showed a progressive cerebellar atrophy. A CACNA1A gene mutation was hypothesised and sequence analysis revealed a heterozygous mutation c.4013C>T (p.I1338T) affecting the S4 segment and potentially damaging to the protein. This was a de novo mutation because it was not found in either parent.

Conclusions: To the best of our knowledge this mutation of the CACNA1A gene has not been reported in the literature. Similar cases of a relatively long history of cerebellar ataxia, cognitive impairment and paroxysmal episodes are reported in the literature due to CACNA1A mutations. CACNA1A mutations present with a wide clinical spectrum. Congenital ataxia, mental retardation, and hemiplegic migraine can be the presenting signs of CACNA1A mutations.

Written informed consent to publish was obtained from the patient(s).

References

A147
P034. Technostress and primary headache: psychosocial risk
Ennio Pucci1, Alfredo Costa1, Guido de Rénoche2, Massimo Ronchese3, Luigi Bianchin4, Federico Vegrevans1, Enrico Bertins3, Massimiliano Valeriani1, M°
1Headache Science Center, University Consortium for the Study of Adaptive Disorders and Headache (UCADH), Department of Brain and Behavioral Sciences, University of Pavia, IRCCS “C. Mondino”; Pavia, Italy; 2Department of
Introduction: Work and the working environment could have a decisive role in the development of symptoms which, in turn, may determine the onset of some forms of headache, as well as increase the frequency and/or intensity of pre-existing forms. Technostress is one of the new occupational diseases under the ruling of Judge Guariniello (2007) and has been included in the obligations of risk assessment in accordance with T.U. 81/2008 and Legislative Decree 106/2009. Under this term various addictions are covered: video addiction, internet addiction disorder, social network craze, information overload, multitasking, cybersex addiction, and email addiction. The psychologist Craig Brod was the first to coin this term, which can manifest itself with many symptoms: headache, hypertension, anxiety, panic attacks, loss of concentration, gastrointestinal and cardiovascular disorders, depression, loss of libido and even behavioral changes and relational isolation. In the past, this condition mostly affected the manager, it is now widespread among workers of other at-risk groups, such as, call center operators, accountants, networkers, journalists, advertisers and financial analysts. Training for stress prevention (art. 37, TU 81/208) and the evaluation of work-related stress are legal requirements for Italian companies, which would otherwise incur in breach of paragraph 1, article 29 of Law no. 81/2008. Nomophobia is the uncontrolled fear of remaining disconnected from the mobile phone network. The symptoms range from simple anxiety (e.g., low battery or credit, lack of coverage, mobile forgotten) to panic attacks: shortness of breath, dizziness, tremors, sweating, fast heartbeat, chest pain and nausea.

Conclusions: The technology dependency of labor today is still an underestimated phenomenon and not fully recognised within the psychological discomforts. Thus, it is diagnosed only when associated with other mental or physical problems, a state of affairs that currently is often diagnosed at an advanced stage, perhaps after a heart attack or other serious diseases, for which complete rest from working is prescribed. Technostress, bullying, burn-out, and work-addiction are not diseases but serious diseases, for which complete rest from working is prescribed. Technostress, bullying, burn-out, and work-addiction are not diseases but serious diseases, for which complete rest from working is prescribed. Technostress, bullying, burn-out, and work-addiction are not diseases but serious diseases, for which complete rest from working is prescribed. Technostress, bullying, burn-out, and work-addiction are not diseases but serious diseases, for which complete rest from working is prescribed. Technostress, bullying, burn-out, and work-addiction are not diseases but serious diseases, for which complete rest from working is prescribed.

Table 1(abstract A148) Prevalence of ICDH-3 Beta headache disorders for the total sample and by sex

<table>
<thead>
<tr>
<th>Category</th>
<th>Total number of adolescents with headache (first diagnosis)</th>
<th>Girls</th>
<th>Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any headache</td>
<td>91 (24.2% of 376)</td>
<td>55 (60.44%)</td>
<td>36 (39.56%)</td>
</tr>
<tr>
<td>Migraine without aura</td>
<td>10 (11% of 91)</td>
<td>2 (3.6% of 55)</td>
<td>8 (22.2% of 36)</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>2 (2.2%)</td>
<td>1 (1.8%)</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Probable migraine without aura</td>
<td>7 (7.7%)</td>
<td>5 (9%)</td>
<td>2 (5.5%)</td>
</tr>
<tr>
<td>Probable migraine with aura</td>
<td>3 (3.3%)</td>
<td>1 (1.8%)</td>
<td>2 (5.5%)</td>
</tr>
<tr>
<td>Chronic migraine</td>
<td>3 (3.3%)</td>
<td>3 (5.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Probable chronic migraine</td>
<td>1 (1.1%)</td>
<td>1 (1.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Infrequent TTH</td>
<td>4 (4.4%)</td>
<td>1 (1.8%)</td>
<td>3 (8.3%)</td>
</tr>
<tr>
<td>Frequent TTH</td>
<td>29 (31.8%)</td>
<td>22 (40%)</td>
<td>7 (19.4%)</td>
</tr>
<tr>
<td>Probable infrequent TTH</td>
<td>3 (3.3%)</td>
<td>2 (3.6%)</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Probable frequent TTH</td>
<td>5 (5.5%)</td>
<td>3 (5.4%)</td>
<td>2 (5.5%)</td>
</tr>
<tr>
<td>Chronic TTH</td>
<td>10 (11%)</td>
<td>7 (12.7%)</td>
<td>3 (8.3%)</td>
</tr>
<tr>
<td>Probable chronic TTH</td>
<td>4 (4.4%)</td>
<td>1 (1.8%)</td>
<td>3 (8.3%)</td>
</tr>
<tr>
<td>Medication-overuse headache</td>
<td>3 (3.3%)</td>
<td>2 (3.6%)</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>7 (7.7%)</td>
<td>4 (7.3%)</td>
<td>3 (8.3%)</td>
</tr>
</tbody>
</table>
Conclusions: Headache is common in adolescents and can affect schoolwork and social activity. Thus, it is important to raise the awareness among general practitioners, families and teachers, so that they can identify headache in adolescents in its early stages and refer them for appropriate treatment.

Written informed consent to publish was obtained from the patient(s).

Conflict of interest: None declared.

Acknowledgments: The authors express their gratitude to participating students, their directors and all the staff of the participating schools (Scuola Media c/o Comprensivo di Via Dante Alighieri, Voghera; Scuola Media “Robecchi”, Vigevano; Scuola Media Giovanni XXIII, Vidigulfo), for their cooperation and contribution to this study.

Reference

ORAL PRESENTATIONS

A149
0007. Self-referred cognitive impairment in migraine patients
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1Centre for Headache and Adaptive Disorders, Unit of Neurology, Department of Neuroscience and Sense Organs, Azienda Ospedaliera "Pugliese-Ciaccio", Catanza, Italy; 2Department of Health Science, Magna Graecia University, Catanzaro, Italy
E-mail: centrocefaleaopa@gmail.com

Background: Migraine patients often report cognitive impairment, especially regarding memory and attention. There is no consensus about the relationship between migraine and cognitive problems [1]. Aim of our open cross-sectional study was to explore the cognitive performance of migraine patients accessing our Headache Centre and its relationship with demographic, clinical and psychopathological measures.

Materials and methods: We assigned 30 migraine patients (25 females; 36.63±9.13 mean age) accessing to our Centre from November 2014 to May 2015 to one of three groups according to migraine frequency. Group A patients had no or little chronicity (< 5 headache days/month; n=9); Group B patients had moderate chronicity (> 5 < 10 headache days/month; n=10); Group C patients had severe chronicity (> 10 headache days/month; n=11) [2]. All patients had completed a headache diary, pain Numeric Rating Scale (NRS) and Migraine Disability Assessment (MIDAS) during headache assessment. We measured affective dimensions using Zung Self-Rating Anxiety Scale (SAS), Zung Self-Rating Depression Scale (SDS) and Hypomania Checklist (HCL-32) and we used the Cognitive Failures Questionnaire (CFQ) to quantify cognitive impairment. CFQ measures individual differences in daily cognitive errors, with 25 questions on a Likert-scale relating to everyday mistakes such as the probability of failing to keep a task objective in mind. Higher CFQ scores correspond to a higher cognitive impairment [3]. Using SOFA Statistics 1.4.4 software, we calculated descriptive indicators and Pearson’s correlation coefficient (r) between all measures. We compared groups on demographic, clinical, affective and cognitive variables by One-Way analysis of variance (ANOVA). We set p < 0.05 as threshold of statistical significance.

Table 2(abstract A148) Prevalence of ICDH-3 Beta headache disorders for the total sample: other types of headache

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total number of adolescents with more than one type of headache</th>
<th>First Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine without aura</td>
<td>2 Chronic TTH (n=1) Frequent TTH (n=1)</td>
<td></td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>8 Chronic TTH (n=2) Frequent TTH (n=5) Migraine with aura (n=1)</td>
<td></td>
</tr>
<tr>
<td>Probable migraine with aura</td>
<td>2 Chronic TTH (n=1) Frequent TTH (n=1)</td>
<td></td>
</tr>
<tr>
<td>Medication-overuse headache</td>
<td>1 Chronic Migraine (n=1)</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>13 (14.3% of 91) Chronic TTH (n=4) Frequent TTH (n=7) Migraine with aura (n=1), Chronic Migraine (n=1)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3(abstract A148) Headache-related disability (PedMIDAS Score) by diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Range</th>
<th>Grade I (0-10)</th>
<th>Grade II (11-30)</th>
<th>Grade III (31-50)</th>
<th>Grade IV (&gt;51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Headache (n=91)</td>
<td>0-176</td>
<td>49</td>
<td>23</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Migraine without aura</td>
<td>0-33</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>6-8</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Probable migraine without aura</td>
<td>2-18</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Probable migraine with aura</td>
<td>4-12</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chronic Migraine</td>
<td>13-176</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Probable Chronic Migraine</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infrequent TTH</td>
<td>1-5</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Frequent TTH</td>
<td>0-69</td>
<td>15</td>
<td>12</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Probable infrequent TTH</td>
<td>0-1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Probable frequent TTH</td>
<td>3-33</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chronic TTH</td>
<td>5-120</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Probable Chronic TTH</td>
<td>15-130</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Medication-overuse Headache</td>
<td>13-94</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>0-5</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
CFQ scores were highest (M±SD) among Group C patients (50.27 ± 13.65) followed by Group B (37.83±12.23) and Group A patients (23.63 ±7.00). ANOVA showed statistically significant difference between groups on CFQ scores (p < 0.01; F = 13.357). CFQ scores positively correlated with migraine frequency (p < 0.001; r = 0.573; fig. 1), MIDAS scores (p < 0.001; r = 0.614), SAS scores (p < 0.001; r = 0.743) and SDS scores (p < 0.05; r = 0.556).

Conclusions: Migraine patients accessing our Centre report cognitive issues that increase with headache frequency. Such impairment is associated with anxiety and depression levels and contributes to headache-induced disability. Further developments of our study should involve larger groups, include healthy controls and could also investigate the role of medical and psychological headache management in patients' cognitive performance.

Written informed consent to publish was obtained from the patient(s).

References

A150

Alexithymia and chronic migraine with medication overuse: what relationship?
Sara Bottiroli1, Federica Galli1, Michele Viana1, Grazia Sances1, Marta Allena1, Natascia Ghiotto1, Elena Guaschino1, Giorgio Sandrini1, Cristina Tassorelli1, Giuseppe Nappi1
1Headache Science Centre (HSC), C. Mondino National Neurological Institute, Pavia, Italy; 2Department of Health Sciences, University of Pavia, Pavia, Italy

Background: Alexithymia is a personality trait characterized by the inability to identify and express emotions. Neuroimaging studies showed specific neural correlates in alexithymics subjects (1) and pathological scores of alexithymia in several chronic pain populations and in episodic migraine (2,3). There is also evidence of a positive association between alexithymia, depression, and anxiety in migraine patients. So far, no study has evaluated alexithymia in medication-overuse headache patients (MOH) (progressed by migraine) versus episodic migraine patients (MIG).

The present study was aimed to evaluate whether MOH individuals differ from MIG as regards alexithymia scores and to investigate the association of alexithymia with headache characteristics.

Materials and methods: We recruited 99 patients suffering from MOH (n=54; 81.5% female; age: 41.6±10.9) evolved from migraine (chronic migraine + MOH) or MIG (n=45; 71.6% female; age: 41.0±9.3) at the Headache Centre of the "Mondino" Institute of Pavia. Diagnosis in the 2 groups was operationally defined according to the ICHD-III-b criteria. Patients were evaluated using the Toronto Alexithymia Scale (TAS-20), which uses a five-point Likert response scale and has a three-factor structure consisting of: (1) Difficulty in identifying feelings, (2) Difficulty in describing feeling, and (3) Externally oriented thinking. Demographic and clinical information were collected as well.

Results: According to multiple binary logistic regression analysis, MIG and MOH patients were comparable in terms of demographic characteristics, whereas they differed for some characteristics of illness (age of migraine onset, duration of illness, frequency of headache), disability and QoL, as well as for depression levels. MOH patients scored higher than MIG on two of the three alexithymia facets, which were those concerning difficulties in identifying (MOH = 19.1±6.7, MIG = 13.8±5.7, p < 0.001) and describing feelings (MOH = 14.4±4.5, MIG = 11.6±4.8, p = 0.003). Groups were instead comparable in terms of externally oriented thinking (MOH = 18.6±4.2, MIG = 18.0±4.1, p = 0.50). Significant correlations resulted between alexithymia and illness characteristics (e.g., headache frequency, perceived disability, and QoL).

Conclusions: Our results show a specific alexithymic profile in our MOH population. These findings suggest that alexithymia could represent a risk factor in the transformation from episodic migraine into the chronic subtype with medication overuse. Early and appropriate interventions aimed at improving emotional awareness and expression could then represent a further preventive measure to avoid drug-induced headache. Written informed consent to publish was obtained from the patient(s).

Conflicts of interests: None.

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References
non-randomized studies and identified works involving psychotherapeutic approaches showing evidence of efficacy. We performed descriptive statistics over quantitative and qualitative data.

Results: Concerning neuropathic pain conditions, we found evidence for Cognitive-Behavioral Therapy (CBT) (2 studies), Psycho-education (PE) (2 studies) and Neuropsychological Rehabilitation (1 study). Regarding fibromyalgia, we found evidence for CBT (3 studies), PE (3 studies), Guided Imagery (GI) (3 studies), Strategic-Systems Therapy (Ericksonian) (2 studies), Brief Psychodynamic Therapy (1 study), Relaxation Training (RT) (1 study), Acceptance and Commitment Therapy (ACT) (1 study), Biofeedback (1 study), Mindfulness (1 study). We found evidence for CBT (4 studies), RT (3 studies), GI (2 studies), Biofeedback (1 study), ACT (1 study) in the treatment of chronic headache (Figure 1). It is noteworthy that CBT studies often involved informational group meetings; brief psychodynamic therapy was always carried out as a group intervention rather than individual sessions; strategic-systems therapy always involved hypnosis as elaborated in the Milton H. Erickson model of brief therapy.

Conclusions: There is considerable terminological overlap between psychological approaches used in pain management. Many of the above-mentioned methods refer to similar practices under different names and therapists use them under different theoretical models. Our review supports the hypothesis that informative (psycho-education) and psycho-physiological interventions (biofeedback; relaxation training; guided imagery; mindfulness; ACT; neuropsychological rehabilitation) integrated with psychotherapy models (CBT; psychodynamic therapy; strategic-systems therapy) are useful in managing the considered forms of chronic pain.

Reference


A152

P028. Childhood migraine, epilepsy and tics: Are there similarities in the psychological profile?

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Background: Migraine, epilepsy and tics are common neurological disorders in children and adolescents. They can affect a patient’s life in a number of ways such as their school, sport and relationships. Although they are clearly different conditions, several studies have stressed the co-occurrence of migraine with both epilepsy and tic disorders. However, no study has compared the psychological/behavioral profile of children/adolescents with migraine, RAP or tics. The main aim of the present study was to compare the occurrence of internalizing and externalizing disorders between migraine, epilepsy and tics patients.

Methods: We studied 32 migraine patients (m.a. 11.8 years; s.d. 2.6; F: 19; M: 13), 25 epilepsy-normal IQ outcome (m.a. 15 years; s.d 2.6; F: 15; M: 10) and 29 tics (simple and multiple) (m.a. 8.8 years; s.d 2.6; F: 8; M: 21). The psychological profile was evaluated by the Child Behaviour Checklist 6-18 (CBCL). ANOVA one-way analysis was used to compare CBCL scales and subcales between groups.

Results: Migraine, epilepsy and tics showed a very similar trend in the Internalizing scale (p = 0.12). Tics had higher scores in Externalizing (p = 0.00) and Total scores (p = 0.00). While “Anxiety/depression” and “Withdrawn” scores did not show any significant difference among the three groups (respectively, p = 0.06 and p = 0.72), migraineurs had a significant higher score in “Somatic complaints” subscale, compared with epilepsy (p = 0.00).

Conclusions: Anxiety and depression are common psychological issues among children with migraine, epilepsy and tics. Moreover, our results suggest that although the three conditions did not show differences in internalizing symptoms, migraine tends to report higher levels of somatic complaints. On the other hand,tics are more prone to behavioural problems. Written informed consent to publish was obtained from the patient(s).

A153

P029. Migraine, body weight and psychological factors in children and adolescents

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Background: Several studies have assessed the associations between adult migraine and overweight, pre-obesity or obesity. Prevalence, frequency, and severity of migraine appear to increase in relation to the
body mass index, although this evidence is not supported by all the studies examined. The link between body weight and headache has hardly been examined in children. Data on the possible association between the body mass index (BMI) and the psychological profile in migraine children are sparse.

Objectives: Aims of the present study were: 1) to study the prevalence of pre-obesity and obesity in migraineur children/adolescents; 2) to analyze the possible relationship between frequency and severity of migraine and overweight; 3) to explore the role of anxiety and somatization on BMI in migraine patients.

Methods: We studied 92 migraineurs (mean age 11.3±2.3 years; 43 M and 49 F). Patients were divided into 2 groups according to headache attack frequency: 1) high frequency (HF) patients, having from weekly to daily episodes, and 2) low frequency (LF) patients, showing ≤ 3 episodes per month. Pain intensity was rated on a 3-level graduated scale (mild, moderate and severe pain). Given the low frequencies, the “moderate” and the “mild” intensity were collapsed into the same category. The psychological profile was assessed by SAFA Anxiety and Somatization scales. BMI was calculated as the weight in kilograms divided by the height in meters squared.

Results: Among our patients, fifty-seven (62.0%) were classified as “normal weight”, 15.2% were obese and 17.4% pre-obese (both collapsed into the “overweight” group). Due to their low frequencies, “underweight” children/adolescents (5.4%) were eliminated from our subsequent analysis. The weight (“normal weight” or “overweight”) did not correlate with migraine frequency and intensity (respectively: $\chi^2 = 0.6853$, $p = 0.41$; $\chi^2 = 0.0058$, $p = 0.94$). Compared to normal weight children, overweight patients showed a significant higher score in “Separation anxiety” subscale. In the “overweight” patients, the BMI showed a positive and significant correlation with Anxiety (SAFA-A Total, $p = 0.000$) and with Somatization (SAFA-S Total, $p = 0.000$).

Conclusions: Our results suggest that, in young patients, there is an association between migraine, weight and psychological symptoms. Overweight migraineur patients are more prone to “separation anxiety”. In particular, we can hypothesize that overweight in migraine children may be related to anxiety and somatization symptoms. Written informed consent to publish was obtained from the patient(s).

References
results, examined each patient and formulated diagnosis according to the ICHD-III beta criteria. HD and ID-Migraine were compared to clinical assessment considered as the reference standard.

**Results:** Sixty-two patients received the diagnosis of migraine by the headache specialist. HD showed a sensitivity of 0.98 (95% CI 0.91-0.99) and a specificity of 0.66 (95% CI 0.63-0.84) and a specificity of 0.66 (95% CI 0.3-0.90). ID-Migraine showed a sensitivity of 0.75 (95% CI 0.63-0.84) and a specificity of 0.66 (95% CI 0.3-0.90). Seventeen patients (27%) received the diagnosis of migraine with aura by the clinician. HD and clinical evaluation agreed upon headache onset, frequency and symptomatic therapy. Aura was overestimated by HD (4%).

**Discussion:** According to this pilot study, Headache Digest is more sensitive than ID-Migraine whereas both tools showed the same specificity. The former also gave clinical details pivotal for diagnosis. The study limitations include small sample size and the aura overestimation. A larger study is in progress based on a revised form of the Headache Digest aimed to improve the diagnostic power of this test. Written informed consent to publish was obtained from the patient(s).

**References**

**ORAL PRESENTATIONS**

**A156**

**O021. Abnormal connectivity within executive resting-state network in migraine with aura**

Antonio Russo1,2,3, Francesca Conte1, Laura Marcuccio1, Fabrizio Esposito4, Alfonso Giordano1,2,3, Manuela De Stefano1, Mario Cirillo4, Alessandro Testore1, and Gioacchino Tedeschi1.

**Background:** Despite the fact that the clinical features of migraine are well described, the relationship between migraine and cognitive performance is still poorly understood. Indeed, some authors have reported the presence of cognitive deficits in patients with migraine without aura (MwoA) and with aura (MwoA) whereas others have not confirmed these findings. Although neuropsychological studies in migraine are not conclusive, the most likely pattern of neuropsychological impairment would relate to the cognitive domain of executive functions (EF) [1]. Recent imaging studies have shown a significant functional connectivity decrease within the fronto-parietal networks (FPN), known to be associated with EF, in patients with MwoA in absence of significant executive dysfunction [2].

**Objective:** To further explore FPN functional connectivity in patients with MwoA and patients with MwoA, in the interictal period.

**Methods:** Using resting-state functional magnetic resonance imaging (RS-fMRI), we compared functional connectivity within the FPN in 20 patients with MwoA, versus 20 sex- and age-matched healthy controls (HC). To examine the specificity of any observed differences in FPN functional connectivity between patients and HC, we further studied 20 age- and sex-matched patients with MwoA. Furthermore, we assessed the correlation between functional connectivity within FPN and EF in both migraine groups. Finally, we used voxel-based morphometry to assess whether between-group differences in functional connectivity were dependent on structural differences.

**Results:** Neuropsychological data revealed no significant executive dysfunction in both migraine groups compared to HC. RS-fMRI showed that both MwoA and MwoA patients, compared to HC, had a significant functional connectivity decrease within the right FPN and specifically in the middle frontal gyrus and the dorsal anterior cingulate cortex. There were no structural differences between the three groups.

**Conclusion:** Our data demonstrate that, even in the absence of clinically evident EF deficits, MwoA and MwoA are associated with reduced FPN functional connectivity. We suggest that disrupted FPN functional connectivity might be only a part of a complex cascade that terminates in a migraine attack. In this context, FPN abnormalities may be the neuronal substrate on which biological, genetic and environmental factors could induce, and in turn correlate with, migraine attacks mostly characterized by high pain intensity in patients with MwoA and aura phenomenon in patients with MwoA. In other terms, observed FPN connectivity changes may represent a migraine biomarker, probably related to well-known maladaptive stress response in migraine patients. Written informed consent to publish was obtained from the patient(s).

**References**

**A157**

0020. Dysfunctional analgesic mechanisms in migraine patients with ictal cutaneous allodynia

Antonio Russo1,2,3, Fabrizio Esposito4, Francesca Conte1, Laura Marcuccio1, Michele Fratello1,2, Giusenpina Ciazzo2, Alfonso Giordano1,2, Renata Conforti5, Alessandro Testore1, Gioacchino Tedeschi1,2,3*

**Background:** Approximately two thirds of migraine patients complain of cutaneous allodynia (CA) which is defined as a pain perception evoked by ordinary non-nociceptive skin stimulation in cephalic regions during migraine attacks. CA may be underly by the sensitization of second-order trigemino-vascular neurons, belonging to the trigeminal-thalamo-cortical pathway. In this context, a crucial role seems to be played by supraspinal mechanisms related to the descending pain modulatory system [1].

**Objective:** To investigate the functional pattern of pain processing pathways during trigeminal heat stimulation (THS) in migraine patients with MwoA and patients without aura, experiencing ictal cutaneous allodynia (CA) (MwoA CA+).

**Methods:** Using whole-brain BOLD-fMRI, functional response to THS at three intensities (41°, 51° and 53°C) [3] was investigated in MwoA CA+ patients compared with MwoA patients without ictal CA (MwoA CA-), in interictal period, and healthy controls (HC). Voxel-based morphometry and diffusion tensor imaging were used to explore structural or microstructural changes. Secondary analyses evaluated associations between BOLD signal change and clinical features of migraine.

**Results:** During moderate-noxious THS (51°C), we observed a significantly greater activation in a) the anterior cingulate cortex in MwoA CA+ patients compared to HC and b) the middle frontal gyrus in MwoA CA+ patients compared to both MwoA CA- patients and HC. Furthermore, during high-noxious THS (53°C) a significantly decreased activation in the secondary somatosensory cortices was observed in a) MwoA CA- patients compared to both MwoA CA+ patients and HC and b) MwoA CA+ patients compared to HC. There were no structural or microstructural abnormalities between the three experimental groups. During high-noxious THS (53°C), a significant negative correlation was found between BOLD signal change in SSC and VAS scores in both MwoA CA+ patients and MwoA CA- patients. Furthermore, a significant positive correlation was found between BOLD signal change in SSC and CA severity in MwoA CA+ patients.
Conclusions: Our findings suggest that an imbalance between the inhibition and the facilitation of pain dynamics might contribute to dysfunctional analgesic mechanisms in migraine leading to ictal CA in the course of attacks in patients with MwoA CA+. This hypothesis is further corroborated by our correlation analyses revealing that the SSC functional activity, during high-noxious THS, was positively correlated with CA in MwoA CA+ patients.

Written informed consent to publish was obtained from the patient(s).

Funding: The study has been conducted with a grant from the Italian Foundation of Headaches (Fondazione Italiana Cefalea FLICEF).

References

A158
O025. Excitability of the motor cortex in migraine changes with the distance from the last attack
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A160
O024. Transcutaneous supraorbital nerve stimulation enhances somatosensory thalamic activity in migraine between attacks: a central mechanism of clinical efficacy?
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A159
O053. Intercital cerebral posterior circulation in migraineurs with aura: a transectional color-coded duplexsonography pilot study
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Background: Vascular cerebral dysfunction restricted to the posterior circulation in migraineurs has been reported. In this preliminary study we compared mean flow diastolic velocity in the posterior cerebral artery during visual stimulation in interictal state headache-free subjects and migraineurs with aura.

Materials and methods: Trancranial color-coded duplexsonography was used to assess mean flow diastolic and systolic velocity changes in the posterior cerebral artery, in particular P2, during visual stimulation.

Results: An increase in vascular reactivity of mean flow diastolic velocity was observed during visual stimulation in headache-free subjects (Group 1, 10 patients) and in the patients affected by migraine with aura (Group 2, 7 patients), without any differences between right and left sides. Reactivity of mean flow diastolic velocity to visual stimulation was found significantly higher in Group 2 (mean ±SD, 42±6%±2.6%) vs Group 2 (mean SD, 33.6%±1.8%) (p < 0.001). In contrast, no differences in flow systolic velocity between the two groups were observed.

Conclusions: These results indicate that occipital cortex is involved in migraine patients with aura. Moreover, these patients exhibit a larger cerebrovascular response during visual stimulation compared to headache-free subjects.

Written informed consent to publish was obtained from the patient(s).
Background: Vestibular migraine (VM) has been increasingly recognized as a possible cause of episodic vertigo [1], but its pathophysiology is still unclear. In our previous fMRI study, we had observed a significantly increased thalamic activation in patients with vestibular migraine (VM) during vestibular stimulation in comparison with patients with migraine without aura (MwoA) and healthy controls (HC) [2]. Recently, a voxel based morphometry (VBM) study has shown gray matter volume reduction in brain areas involved in pain and vestibular processing [3]. However, no studies have yet investigated white matter (WM) microstructural abnormalities in patients with VM.

Objective: To investigate whole-brain and thalamic WM microstructural changes in patients with VM, compared with patients with MwoA and HC.

Methods: By using magnetic resonance imaging and diffusion tensor imaging (DTI) with tract-based spatial statistic (TBSS) analysis [4], we analyzed WM integrity in twenty patients with VM, compared to twenty patients with MwoA and twenty HC. We performed a TBSS analysis generating fractional anisotropy (FA), mean diffusivity (MD) and radial diffusivity (RD) and axial diffusivity (AD) maps. TBSS was run with FA maps to create the “skeleton”, which represents the center of all fiber bundles in common to all subjects. The resulting statistical maps were thresholded at p < 0.05 corrected for multiple comparisons at a cluster level. Besides whole brain analyses, a region of interest (ROI) analysis was also performed to correlate the TBSS results with both thalamic standard anatomic ROI data and functional regions that were based on the results of our previous fMRI study.

Results: Between-groups analyses did not reveal statistically significant differences in both whole-brain and bilateral thalamic ROI FA, MD, RD and AD values between patients with VM compared with patients with MwoA and HC (p < 0.05 corrected).

Conclusions: Recent studies have demonstrated that the thalamus may play a major role in an abnormal information processing during ictal and interictal migraineineous periods. Our previous fMRI study has clearly demonstrated an abnormal thalamic activation during vestibular processing in patients with VM. However, this functional phenomenon seems not to be correlated to any structural connectivity changes since both whole-brain and thalamic ROI DTI analyses have not demonstrated significant differences between VM, MwoA and HC. Our preliminary data may support the hypothesis that thalamic functional changes may not be linked to, or alternatively, may precede structural abnormalities in patients with VM.

Written informed consent to publish was obtained from the patient(s).

References
Background: Migraine arises from a primary brain dysfunction that leads to episodic activation and sensitization of the trigeminovascular pain pathway. About one third of patients with migraine experiences transient neurological symptoms during attacks, so-called “aura”, among which the most common is visual aura [1]. In our previous fMRI study, we had observed a significantly increased resting-state visual network (RS-VN) functional connectivity in patients with migraine with aura (MwA) compared to patients with migraine without aura (MwoA) during the interictal period [2]. Nevertheless, both whole-brain and visual pathways microstructural white matter (WM) abnormalities in patients with MwA and MwoA is still under debate.

Objective: To investigate both whole-brain and visual pathways WM microstructural changes in MwA patients, compared to MwoA patients and HC during the interictal period.

Methods: By using magnetic resonance imaging and diffusion tensor imaging (DTI) with tract-based spatial statistic (TBSS) analysis, we analyzed WM integrity in twenty patients with MwA, compared to twenty patients with MwoA and twenty HC. We performed a TBSS analysis generating fractional anisotropy (FA), mean diffusivity (MD) and radial diffusivity (RD) and axial diffusivity (AD) maps. TBSS was run with FA maps to create the skeleton, which represents the center of all fiber bundles in common to all subjects [3]. The resulting statistical maps were thresholded at p < 0.05 corrected for multiple comparisons at a cluster level. Besides whole brain analyses, a region of interest (ROI) analysis was also performed to correlate the TBSS results with both visual pathways standard anatomic ROI data and functional regions that were based on the results of our previous fMRI study.

Results: Between-groups analyses did not reveal statistically significant differences in both whole-brain and bilateral visual pathways ROIs FA, MD, RD and AD values between patients with MwA compared with patients with MwoA and HC’s (p < 0.05 corrected).

Conclusions: Our preliminary data may support the hypothesis that visual pathways functional changes may not be linked to, or alternatively, may precede structural abnormalities in patients with MwA. Furthermore, MwA does not seem to be a risk factor for progressive microstructural WM changes in diffusion tensor tract-based spatial statistic (TBSS) analysis.

Written informed consent to publish was obtained from the patient(s).

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References

Table 1(abstract A164)

<table>
<thead>
<tr>
<th>Ease of use</th>
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<th>Tolerability</th>
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Most frequent provided reasons

- No need for vessel and water
- Time to attack reduction lower
- 1 Better working ability
- 2 Lower # second drug dose
- 3 Light and noise sensitivity reduced
- No adverse reaction
Conclusions: Patients consistently expressed a clear preference for DF HP (25 mg s.c.) over DF potassium (50 mg os). Since patients are treated on an individual basis, the more important question is not only which drug is best in relation to the other but, whether the chosen one has a route of administration that better fits the outcome desired by the patient, encompassing also ease of use and feelings of well-being on an individual basis and by the healthcare provider. Compared with the DF potassium (50 mg os) reference therapy, DF HP (25 mg s.c.) presents interesting advantages in terms of ease of use, onset of analgesic effect and tolerability profile. Further studies are needed to confirm the data obtained from this preliminary investigation.

Written informed consent to publish was obtained from the patient(s).

A165
P007. Inhibition of monoacylglycerol lipase activity modulates the activation of brain structures relevant for migraine pathogenesis
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Background: Experimental evidence shows that the anti-nociceptive action of endocannabinoids, related to the modulation of the trigeminovascular system activity, may be helpful for promoting new targets for the treatment of migraine. URB602 is an inhibitor of monoacylglycerol lipase (MAGL), a key enzyme in the hydrolysis of the endocannabinoid 2-arachidonoylglycerol (2-AG). URB602 induces analgesia in animal pain models not related to migraine, but there is no pre-clinical information as regards to its potential effect in migraine pain.

 Aim: To evaluate whether URB602 administration interferes with the level of activation of brain structures involved in migraine.

 Methods: Nitroglycerin (NTG) induces neuronal activation in a specific subset of brain nuclei that are considered relevant for the development of migraine attacks. In this study we evaluated the changes caused by URB602 in NTG-induced neuronal activation. Male Sprague Dawley rats were treated with NTG (10mg/kg, i.p.) followed by URB602 (2mg/kg, i.p.) or vehicle (DMSO, 1ml/kg, i.p.). Their brains were processed for the detection of c-Fos protein, used as an indicator of brain activation.

 Results: URB602 alone did not change Fos expression in the brain nuclei under evaluation. When administered 3 hours after NTG, URB602 reduced NTG-induced Fos expression in all the cerebral areas that were examined, with a significant effect in nucleus trigeminalis caudalis and ventrolateral column of periaqueductal grey.

 Conclusions: The inhibition of MAGL activity, with the theoretical increase of central content of 2-AG, may modulate the activation of structures involved in pain perception and pain integration in an animal model specific for migraine.

Competing interests: The authors declare to have no competing interests.

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ORAL PRESENTATIONS

A166
O037. Should aircrafts never land? Headache attributed to aeroplane travel: a new series of 140 patients
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The Journal of Headache and Pain 2015, 16(Suppl 1):A166

Background: Following our previously published paper on 75 cases [1], a new form of headache, Headache attributed to aeroplane travel (AH), has been recently codified in the ICHD-3beta classification [2].

Materials and methods: Since our publication, we continued to receive worldwide filled-in questionnaires.

Results: Up to now, 140 cases (males: 59%) were studied. A strictly unilateral side was reported in 85% of patients; side-shift in different attacks was observed in 21%. The pain site was mainly frontal-orbital (n=110) or frontal-parietal (n=9). The mean age at onset was 35.9 years (range 7-63). AH attacks occurred during landing (in nine patients also during take-off), lasted less than 30 minutes and remitted spontaneously. Its intensity was very severe or severe. Only in 16 cases the first attack occurred during the first flight. The attacks presented in more than 50% of flights in 38 patients; 24 reported its occurrence during every flight. AH negatively affected the propensity to air travel in more than 75% of the sufferers. Prophylactic use of NSAIDs prevented or effectively relieved the attacks in more than 50% of cases.

Conclusions: Considering the impact of AH, passengers should be appropriately informed about the existence of this severe headache, on its benign nature and its potential prevention. These new data confirm the stereotyped features of this specific headache, in keeping with the ICHD criteria.

Written informed consent to publish was obtained from the patient(s).

References

A167
O036. Cocaine and headache: a 2-year follow-up study in chronic cocaine users and literature review
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As many as 14-21 million people worldwide (0.3-0.5% of the population, aged 15-65 years) use cocaine [1]. In Europe, cocaine consumption has shown a 2- to 3-fold increase during the last 2 decades [2,3]; in Italy, lifetime cocaine experience among adults corresponds to 6.6% [4]. Cocaine use and headache share some common characteristics: present heavy global burden, prevail among young individuals, cause more severe consequences in females, may lead to emergency department access and progress to chronicisation. The study of headache in chronic cocaine users (CCU) is of interest also from a pathophysiological point of view, given that chronic cocaine use causes decreased dopamine and serotonin synaptic levels, a typical migraine biochemical feature (“empty neuron” condition) [5,6]. In a previous study we encouraged clinicians to carry out a more in-depth investigation on cocaine use in all headache sufferers, especially those with migraine, as headache occurs in a very high proportion of CCU (90%), mostly showing migraine or migraine-like characteristics, while cocaine-induced headache, as classified by the ICHD criteria [7], seems exceedingly rare (2.2%). Moreover, we pointed out that CCU sometimes use cocaine as an acute remedy for the headache attack, even though improvement occurs very rarely (17.2% of cases) [8]. Recently, it has been described that patients with intractable cluster headache who tried cocaine, being dissatisfied with conventional treatments in terms of efficacy and/or tolerability, referred a full or partial improvement in 30.8% of cases [9]. The present study was aimed to evaluate the modification of the clinical characteristics of headache in CCU after a 2-year follow-up period. We contacted by phone the 80 patients previously enrolled [8] attending the Cocaine Addiction
Service of the Drug Addiction Service, 20th District, Rome. Of these 80 patients, 60 (still followed by the Drug Addiction Service) were enrolled and interviewed by the same physicians of the previous study. We studied the modifications of headache pattern and characteristics relative to their actual cocaine consumption in CCU patients previously subdivided into 3 groups: neither lifetime nor current headache (group 0); lifetime and current headache (group 1); and de novo headache, i.e. individuals in whom headache developed only after cocaine use began (group 2). The correlation between headache and cocaine is controversial and still understimated.

Written informed consent to publish was obtained from the patient(s).

Conflict of interest: None.

Acknowledgment: No funding

References

A168

O04. The diagnostic mistake: when the patient reports pain affecting eyes and benzodiazepines abuse without any glaucoma or any apparent organic cause

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Background: It is not so infrequent that a patient reports severe pain with a clear focus in/around the eye that looks like an atypical facial pain/persistent idiopathic facial pain. All the patients fulfilled DMS-IV criteria for depression or bipolar disorder-I and sleep and benzodiazepines overuse were reported as the only escape and cure treatment. This may or may not appear as a psychological flight reaction characterized by vegetative signs [1], or a medication-overuse headache. The diagnosis could be wrong even though the IHS/IASP and psychological criteria were respected. What could be the problem? We did not take into account that demodex is present even in those patients, except one, achieved pain relief, i.e. decrease vs baseline 17% on VAS 0-10. Only narcotics induced a benefit, which vanished when treatment was discontinued. Magnifiers observation cilia showed that all non-responder patients were affected by demodex as evidenced with the use of a magnifying glass. The specific treatment for curing demodex completely relieved non-responders’ pain. Later (i.e., 3-25 years; mean 19.3 years+10.9 SD), episodic migraine without aura appeared in 25 patients.

Conclusions: a) When a headache is rare it does not mean it can be neglected; b) an inherited abnormality of the central nervous system, namely inherited hyperalgesia pattern seemingly provokes a redundancy of painful expression that may lead to diagnostic mistakes.

Written informed consent to publish was obtained from the patient(s).

References

POSTER PRESENTATIONS

A169
P066. Migraine with aura in the locker room: 4 case reports
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We describe four cases of young men 19, 21, 23 and 25 years old with recurrent episodes of migraine with aura occurring shortly after the end of physical activities (football match, swimming, gym training, physical education activities at school), when they were in the locker room. Since these types of symptoms could mime some important pathologies (approximately 10% of these headaches, it is mandatory, in this kind of patient, to exclude a form of secondary headache [1]. No other subtypes of headache, or head trauma were reported by the patients. It is well known that physical activity can lead to an aggravation of the intensity of the headache, but the pathophysiological relationship between exertion and aura is unknown and still debated. There are anecdotal reports of episodes of migraine preceded by head trauma and visual symptoms (with a past history of non-sports-related migraine) [2,3], migraine prodrome symptoms after unusually strenuous running with no following head pain [4] or recurrent attacks of hemiplegic migraine induced only by exertion [5].

According to the present version of the International Classification of Headache Disorders, (ICHD-III beta), the headache subtype presented by the four patients fulfilled criteria for “migraine with aura” (ICHD-III beta code: 1.2) and for “primary exertional headache” (pulsating headache,
lasting from 5 minutes to 48 hours, brought on by and occurring only during or after physical exertion; ICHD-III beta code: 4.2) [6]. To date, in the IHS Classification (ICHD-III beta), there is no mention of sport/exercise-induced migraine with aura episodes as primary headache, and there is the need of a double diagnosis, although there are anecdotal reports of attacks of migraine with aura shortly after sports. Written informed consent to publish was obtained from the patient(s).

References

A170
P006. Clinical management of migraine attributed to cerebral venous sinus thrombosis
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Background: Cerebral venous sinus thrombosis (CVST) is the presence of a blood clot in the dural venous sinuses. Symptoms include migraine, abnormal vision, stroke-like signs, seizures, and abnormalities of consciousness and mental status. CVST incidence is 3-4 cases per million adults with a higher frequency among younger people < 40 years old, thrombophilia patients, women who were pregnant and using hormonal contraceptives. Other risk factors are chronic inflammatory diseases, blood disorders, meningitis, ear, nose and throat infections, venous sinuses injuries, surgical procedures in the head and neck area, homocystinuria. Diagnosis requires neuroimaging. Recommended treatment is with anticoagulants [1]. The aims of our retrospective study were to detect CVST incidence among patients accessing our outpatient headache day service (DS) programme, whose main symptom was headache, to compare data with pre-existing estimation, and to identify diagnostic and therapeutic procedures in clinical management of CVST.

Materials and methods: We reviewed records of patients accessing our day service from September 2013 to April 2015 and selected cases that had prompted CVST assessment. We collected demographic information, medical history, clinical, psychosocial and neurocognitive assessments data, neuroimaging, referrals and therapy. We performed descriptive statistics for all data.

Results: In the population accessing our DS in the considered period (n=320), 13 patients (4.06%; 38.34±7.08 mean age; 4 males; 9 females) underwent a venous magnetic resonance angiography and findings were compatible with CVST. They were referred to the Unit of Hemophilia and Coagulation Disorders to be assessed for thrombophilia. Five headache presentations included as secondary migraine pattern associated with CVST being unresponsive to treatment and steadily worsening. Other clinical signs, symptoms, and medical history cues that prompted CVST assessment were stroke-like indicators (n=3); use of hormonal contraceptives (n=2); homocystinuria (n=1); blood disorder (n=1); chronic inflammatory disease (n=1); surgical procedure in the head area (n=1); cognitive and behavioral abnormal state (n=1). Prothrombin mutation was found in 8 patients. Four patients examined with venous angio-CT received anticoagulant treatment in addition to headache management.

Written informed consent to publish was obtained from the patient(s).

Conclusions: Our diagnostic and therapeutic headache programme is able to detect and appropriately refer CVST secondary migraine. The incidence of diagnosed CVST is higher than expected by population estimation and we could explain this with the overlap between headache and CVST demographics and risk factors.

Reference

A171
P024. Features of headache attributed to carotid and vertebral arteries dissection
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Headache and cervical pain are common but not specific symptoms of carotid and vertebral arteries dissection. It is difficult to identify a specific pattern of pain due to dissection, useful to correctly address the diagnosis of dissection at first clinical evaluation, if other neurological signs (e.g., cranial nerves deficit, Horner’s syndrome and other signs of cerebral ischemia) are not present. Recently, in the third edition of the International Classification of Headache Disorders (ICHD-III beta) diagnostic criteria for headache attributed to arterial dissection have been modified. Some Authors have suggested that this new classification is more reliable to detect carotid or vertebral arteries dissection at first clinical evaluation. Some headache features, such as, acute onset, continuous lasting and time-persistence, are currently emphasized. We have retrospectively investigated 34 patients diagnosed from January 2012 to March 2015 with cervical artery dissection. Our aim was to identify the main features of headache attributed to arterial dissection, in our cohort of patients, according to the new ICHD-III beta. We enrolled 34 patients (20 females; mean age 56 ± 11; age range 31-83), 20 of them with headache. In 10 of these 20 patients, headache was the unique symptom.

Methods: According to ICHD-III beta, we analysed headache features in our cohort of patients. We observed that item C 3a (pain is severe and continuous for days or less) was the most recurrent in our group of patients. The other common characteristic was the recent onset. Further studies are requested to individuate a typical clinical feature associated with headache secondary to artery dissection. We suggest that neurologists, when evaluating a recent-onset headache with a continuous and time-persistent pain, should also consider in the differential diagnosis (beyond other more common causes of secondary headache) carotid and vertebral arteries dissection.

Written informed consent to publish was obtained from the patient(s).

Reference

A172
P021. Investigation on occipital headache associated with vertigo and vomiting discovers a familial clustering of Chiari I malformation and a “puzzle”
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A 16-year-old male (patient 4) experienced an episode of bilateral parietal headache, preceded by vertigo and associated with vomiting, lasting about two weeks. An MRI scan performed for a subsequent episode of occipital
and neck pain with vomiting and vertigo showed an imaging to the limit of Chiari I malformation (CMI): cerebellar tonsils below the foramen magnum, not reaching posterior arch of C1, but with obliteration of peribulbar posterior liquoral space, cyst septum pellucidum and cavum vergae. Left facial nerve palsy at the age of 12, frequent alimentary vomiting and abdominal pain, episodes of exercise-induced asthma although not confirmed through respiratory tests, were found in the patient's history. An MRI was performed on his father for otonuereological symptoms characterized by a recurrent sensation of disequilibrium when suddenly changing position, on one occasion preceded by a sensation of right ear pressure (diagnosed as sudden hearing loss). Two years ago he experienced an episode of stabbing occipital headache with shoulder pain irradiation, nausea and phonophobia. The MRI revealed cerebellar tonsils slightly below the foramen magnum, to the limit of CMI. MRI was performed also on his mother (patient 1), who suffers from tension-type headache even for long periods of time (months), showing no alterations, and on his 21-year-old brother (patient 5) suffering from episodic tension-type headache, showing slight tonsillar descent diagnostic or to the limit of CMI, ? = MRI not performed.

Figure 1(abstract A172) oval = female, rectangle = male, shaded = tonsillar descent diagnostic or to the limit of CMI, ? = MRI not performed

Introduction: We describe the case of a man who presented with an episode fulfilling the ICHD-III criteria for thunderclap headache (TH), whose diagnostic work-up led to an unexpected diagnosis.

Case report: A 49-year-old man presented after the onset of a sudden throbbing laterocervical right pain, rapidly spreading bilaterally to his head, reaching the maximum of its intensity in 1 minute. Headache was associated with nausea, dizziness, blurred vision and bilateral tinnitus. Patient’s past medical history was significant for hypertension, hypercholesterolemia and obstructive sleep apnoea syndrome. He did not report any recent head traumas, physical efforts or consumption of vasoactive drugs. He had recently undergone chiropractor procedures. At arrival to our institution, nausea and blurred vision had resolved, a mild headache remained for days, without alteration, and neck pain with vomiting and vertigo showed an imaging to the limit of CMI. His mother’s interview revealed that her sister (patient 3) has five sons, two of them with CMI: 1) a 13-year-old male (patient 7), suffering from West syndrome, who at 3 years of age had an MRI that showed approximately 10 mm caudal descent of cerebellar tonsils with a reduction of the liquoral flow at the craniocevical junction and associated syringomyelia extending from C6 to D2 vertebral body; 2) a 26-year-old female (patient 11) with a cerebellar tonsils extending 11 mm below the foramen magnum, associated with posterior fossa hypoplasia. The “puzzle” comes from the fact that both the husbands of the two sisters (patients 1, 3) have the same surname but with no recognized relationship. The doubt seems to be resolved by the MRI performed on the 34-year-old daughter (patient 6) of the third sister (patient 2) showing slight tonsillar descent but without obstacle to liquoral flow (Figure 1).

This report adds to other descriptions of familial clustering of CMI malformations, which suggest an underlying genetic basis.

Written informed consent to publish was obtained from the patient(s).

A173

P048. Thunderclap headache as presentation of ischemic posterior circulation stroke

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Discussion: There have been an expanding number of conditions associated to TH, including cerebral venous sinus thrombosis, cervical artery dissection, and reversible vasocostruction syndrome [1]. Approximately 25% of patients with stroke develop an associated headache, but is often overshadowed by the abrupt neurological deficits. In these cases the pathophysiology for headache is multifactorial and involves the direct activation of nociceptive sensory afferents innervating the intracranial
vasculature, the release of vasoactive neuropeptides from sensory afferents and of inflammatory cytokines from damaged tissue. This is one of the rare reports of a TH as the presenting and primary clinical feature in an ischemic cerebellar stroke, in the absence of neurological findings [2]. The addition of ischemic stroke expands the differential diagnosis of TH and reinforces the need for MR imaging, even when the initial neurological examination, brain CT, are unrevealing.

Written informed consent to publish was obtained from the patient(s).

References

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**A174**

**P036. Headache attributed to non-traumatic intracranial bleeding**

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**Classification:** Headache attributed to non-traumatic intracranial bleeding is classified by the ICHD-2 and the ICHD-3 Beta criteria at code 6.2.1. In the ICHD-2 classification at code 6.3.4 is classified headache attributed to cavernous angioma as a result of intracerebral bleeding, while in the ICHD-3 beta version at the same code, the headache is closely linked to vascular malformation and not bleeding [1,2].

**Case report:** A male patient, 37 years old, married with 2 children, came to our observation with a history of 7 days of headache. Seven days before, at 3:30 am, he experienced a sudden onset of headache which in 2-3 minutes became severe, accompanied by paresthesia of the left upper limb, chest, right upper limb, lower limb, with tightness of the throat, unconsciousness and spreading of tremors. The patient was taken with an ambulance to the nearest Spoke Center, where a Stress Syndrome was diagnosed and treated with BDZ and discharged at 12.00 am.

In the following three days the patient reported a state of drowsiness and headache lasting for 6-7 hours daily, bilateral, at the temporal level, of pulsating nature, accompanied by sweating, photophobia, and phonophobia. Physical effort was a trigger factor. Given the brief medical history and absence of diseases worthy of note, the patient underwent imaging techniques: first CT and CT angiography, which excluded pathologies, then MRN and AngioRMN with and without contrast medium which showed a cavernous angioma in the left juxtaocular occipital, with signs of intraluesional bleeding.

**Conclusions:** The patient bearer of cavernous angioma had never previously suffered from headaches, and current symptoms are closely related to intracranial bleeding.

Written informed consent to publish was obtained from the patient(s).

References

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**ORAL PRESENTATIONS**

**A175**

**O031. Physiotherapy treatment in chronic tension-type headache: an ongoing study**

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**Objective:** Aim of the study was to verify the efficacy of an individualized physiotherapy treatment based on a protocol assessment of cervical spine disorders in patients with chronic tension-type headache (CTTH).

**Methods:** We enrolled patients with CTTH (ICHD-3-beta criteria) attending the Headache Centre of Trieste who preferred not to take pharmacological treatment. Patients were prophylaxis free in the last 3 months and were asked to fill in an ad hoc diary in a three-month baseline period. The physiotherapy group (PhG) underwent a three-month combined protocol of postural advice, exercises and manual therapy. Intensity (NRS), frequency and duration of pain were analysed with GraphPad InStat 3.06. Cervical range of motion (CROM) was evaluated with a headgear provided with goniometer and spirit level. Neck pain was studied with the Neck Pain and Disability Scale I (NPD’s) Questionnaire. A control group (CG) treated with amitriptyline for three months was compared with PhG.

**Results:** We enrolled 8 PhG patients (5 M, 3 F; mean age, 58±16 years) and 8 CG patients (4 M, 4 F; mean age, 49±21 years). Six of the 8 PhG patients improved, in 2 patients headache was eliminated, none worsened. All headache patterns were statistically reduced (pain intensity from NRS 5.7±1.6 to 2.2±2 [p = 0.007]; frequency from 26±5 to 15±13 days per month [p = 0.03]; duration of attacks from 14±7 to 5±7 hours [p = 0.01]). The patients who were headache-free had the most significant clinical improvement in the NPD’s I Questionnaire, while the 2 patients without improvement had null score. The NPD’s score improved statistically after the treatment (p = 0.03). Most CROM improvement were Flexion 44% and Rotations (right: 75%; left: 48%). In the CG, duration (from 24 to 1 hour per crisis [p = 0.0001]) and frequency (from 23±3 to 7±6 days per month [p = 0.0005]) were significantly reduced, but no reduction in intensity (NRS from 3.25±0.7 to 2.5±0.9 [p = NS]) was noted.

**Conclusions:** An individualized physiotherapy treatment based on combined exercises, manual therapy and postural advice, is efficient in improving headache, cervical motion and disability in CTTH. Individualized physiotherapy may represent an effective alternative option in treating patients with cTTH who prefer not to take prophylactic drugs. Written informed consent to publish was obtained from the patient(s).

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**POSTER PRESENTATIONS**

**A176**

**P031. An observational study on chronic tension-type headache treatment with Quantum Molecular Resonance according to I.A.R.A. model**

Francesca Gulotta1, Licia Grazzi2, Giovanni B Allias3, Sara Roland3, Maria G Saracco1, Maurizio Cavallini1, Andrea De Giorgio1, Anna M Padovan1, Stefania Pelosin1, Paolo Agagliati1, Marco Aguglia3
1A176
1Centro Cefalea, Ospedale G. Chidichimo, Trevisacce (CS), Italy; 2Department of Surgical Science, Woman’s Headache Center, University of Turin, Turin, Italy; 3SOC Neurology: Cardinal Masancy Hospital, Asti, Italy; 3eCampus University, Nodavere (CO), Italy

**Introduction:** Chronic tension-type headache (CTTH) is a clinical entity where high muscle tension level, in particular in the trapezius area, may induce a pain sensation in the same area. Quantum Molecular Resonance (QMR) has been proved to promote cell regeneration process through direct cell stimulation which is able to decrease local inflammatory reaction and consequently pain level. This study reports a clinical experience of QMR treatment for tension-type headache, associated to I. A.R.A. (Incontro, Alleanza, Responsabilità, Autonomia) model® which increases consciousness of patients who can participate actively to QMR therapy. Treatment has been administrated by specialised nurses.

**Materials and methods:** From March 2013 to May 2015 a group of 40 patients, (33 females / 7 males), suffering from CTTH, diagnosed according to the IHS criteria, underwent 8 sessions of QMR treatment protocol, 2 treatments per week, lasting 20 minutes each. During treatment 3 female patients withdrew their informed consent. QMR technique consists of applying 2 electrodes on the lower trapezius area, 1 electrode in the median part of the trapezius and a probe administration on the median trapezius area and on the forehead region. A prophylactic treatment for CTTH (antidepressants and/or muscle relaxants) was used by 89.2% of patients, 24.3% used a symptomatic and 13.5% both. They recorded
headache episodes and medication intake in a daily diary. Follow-up meetings were fixed at 1, 3, 6 months after the end of the program.

Results: Days of headache/month decreased significantly from 19±9.5 before treatment to 6±8.4 at 1-month follow-up (p<0.001) and to 6±8.6 at 3-month follow-up (p<0.001) (Figure 1). Patients did not report any side effects.

Conclusions: QMR seems to be effective for patients with CTTH and results are confirmed until the 3-month follow-up. Treatment is well tolerated and safe for patients. Further studies and longer follow-up will be necessary to confirm the efficacy of this innovative approach.

Written informed consent to publish was obtained from the patient(s).

ORAL PRESENTATIONS

A177
O068. A 2 years prospective evaluation study on onabotulinumtoxinA 195 U in chronic migraine
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The Journal of Headache and Pain 2015, 16(Suppl 1):A177

Background: OnabotulinumtoxinA (Botox®) is the first and so far the only treatment to receive a specific license for prevention of chronic migraine (CM). In our Headache Clinic the therapy with onabotulinumtoxinA is routinely administered to CM patients on a daily basis since 2001. Preventive treatment with onabotulinumtoxinA was offered to all patients that were 1) adults; 2) fulfilling the ICHD-II criteria for CM with or without analgesic overuse; and 3) with contraindications or lack of efficacy or tolerability to other preventive drugs.

Exclusion criteria were coexistent of neuromuscular disorders, psychiatric diseases considered incompatible with such kind of treatment, pregnancy and breast-feeding.

Objectives: To prospectively evaluate the variations in terms of headache days, migraine days, acute medication intake days through a period of 24 months in comparison to a one-month baseline period before starting the therapy.

Methods: Among all the patients that from 2011 to 2012 underwent treatment with onabotulinumtoxinA we randomly selected 100 CM patients (F 85 / M 15; mean age 45.4, range 18-75 years; 93% drugs overusers) that were able to fill diaries without any lack of information for a period of 2 years. OnabotulinumtoxinA 195 U was injected in 39 sites combining the PREEMPT “fixed sites/fixed doses” and the “follow the pain” injection paradigm every three months (± one week) [1]. Patients with criteria for medication overuse headache underwent withdrawal and detoxification therapeutic regimen before starting the treatment. Patients were not allowed to continue preventive oral medication during treatment with onabotulinumtoxinA.

Results: The efficacy results for each timeline are reported in Table 1. The reduction in terms of headache and migraine days, acute medication intake days and HIT-6 score increases strongly from the first injection to the fourth, and remains stable until the last injection at 24 months.

Conclusions: Our results support the findings of the PREEMPT study in a large cohort of patients and are representative of the patients observed in a tertiary headache centre.

Written informed consent to publish was obtained from the patient(s).

Reference
Materials and methods: As part of a larger study, 60 patients with chronic migraine, recruited from the Headache Center of the Istituto Clinico Città di Brescia, and Pavia Headache Center Patients, underwent electrical (n=30) or sham (n=30) stimulation, in 5 treatment sessions every other day for 10 minutes and at follow-up at t30, t60, t90 and t120. After 6 months from the last stimulation we selected all patients who had achieved and maintained a benefit from the treatment (n=12). They underwent electrical stimulation in 5 treatment sessions and at follow-up (t30 and t90).

For each patient, headache frequency, duration and intensity (VAS), headache days per month and the response to symptomatic therapy had also been evaluated; besides, a list of the 5 main precipitating factors was collected.

Results: Primary endpoint was the reduction of at least 50% of the headaches’ clinical parameters (frequency, severity, use of medication). Secondary endpoint was the assessment of plausible decreasing threshold of cortical excitability by evaluating response to trigger factors. At t30 a reduction of at least 50% of the parameters evaluated in almost 75% of the patients was observed, while at t60 the benefit was maintained for approximately 40% of treated patients, as well as at t90 and t120. Three months after the last stimulation, headache frequency, headache days, duration and intensity (VAS), per month were evaluated for each patient: 80% of the patients (n=9) obtained a further reduction of at least 50% of the headache parameters evaluated.

Discussion: There is increasing evidence that brainstem, as well as cortical dysfunction, are basically involved in the complex pathophysiology of migraine. Modified neuronal excitability might be one possible explanation of the efficacy of both pharmacological treatment and tDCS treatment.

Conclusions: tDCS has been introduced as a non invasive tool to guide neuromodulation and to modulate cortical function by tonic stimulation with weak direct currents. Studies involving patients affected by chronic migraine showed improvements regarding frequency, severity, disability and quality of life. Further studies are needed to confirm these findings.

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Written informed consent to publish was obtained from the patient(s).
the results of the headache diary, despite the reduction in the scores, did not produce significant results in the days of migraine attacks and medication taking (Figure 7).

Conclusions: This study suggests that OMT has a positive effect on pain reduction and quality of life improvement in patients with migraine without aura. Future studies, contemplate including assessment of anxiety and depression, the use of a control group and follow-up in the long term.

Written informed consent to publish was obtained from the patient(s).

References

A181
O054. Osteopathic manipulative treatment of headache in a polytrauma patient: case report
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http://www.thejournalofheadacheandpain.com/supplements/15/S1

Table 1 (abstract A180) Prevalence (%) of somatic dysfunction per OMT session. Other dysfunctions have reported lower prevalences

<table>
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<tr>
<th>Occ/Cl</th>
<th>SBS* compression</th>
<th>C3*</th>
<th>T3*</th>
<th>T4*</th>
<th>T5*</th>
<th>T9</th>
<th>Sacrum</th>
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<tr>
<td>OMT 1</td>
<td>100</td>
<td>87</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>OMT 2</td>
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<td>37</td>
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<td>37</td>
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<td></td>
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<tr>
<td>OMT 3</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
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<td>OMT 4</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Spheno-Basilar Sindrome. |Cervical vertebra. |Thoracic vertebra

Table 1 (abstract A180) Prevalence (%) of somatic dysfunction per OMT session. Other dysfunctions have reported lower prevalences

Figure 1 (abstract A180) Absolute frequency of total SD detected in the four OMT sessions. *t = 2.71 p = 0.01 CI = 0.61-5.62; t* = 3.96 p = 0.001 CI = 2.21-7.52

Figure 2 (abstract A180) Absolute frequency of Musculoskeletal SD detected in the four OMT sessions. *t = 2.64 p = 0.02 CI = 0.59-5.90

Figure 3 (abstract A180) Absolute frequency of DS craniosacral system detected in the four OMT sessions.

Figure 4 (abstract A180) Average scores of the HIT-6.

Figure 5 (abstract A180) Average scores of the MIDAS.

Background: The International Headache Society classification (ICHD-III) ranks among secondary headaches those arising as a result of a head and/or neck injury [1,2]. To the authors’ knowledge, there are no prior reports in the literature that describe an osteopathic manipulative treatment (OMT) approach for patients with chronic post-traumatic headache.

Case description: A woman 50 years of age had an automobile accident in 1994 with mild head trauma (Glasgow Coma Scale = 13), signs and symptoms of concessive syndrome; distraction of the cervical spine;
fractures of acetabulum, pelvis, femoral neck, knee, ulna and radius; dislocated shoulder was hospitalized for surgery. During hospitalization she began to suffer from headaches. A neurological examination and neuroradiological investigation were performed without relief from abnormality. She was then diagnosed with post-traumatic headache. From 1995 to 2005 she underwent surgeries for the removal of fixation and prosthetic hips with rehabilitation. In this period she developed a permanent recurrent headache: two/three attacks per month for a period of two/three days, not always tolerated and treated with ibuprofen. In 2012 tamponade, with a verticalization of the cervical spine. She was prescribed a Shanz collar brace, drug therapy and physiotherapy. Despite the therapy, she continued to have about three episodes of headache per month. In 2013, with a diagnosis of chronic post-traumatic headache attributed to mild head injury (ICHD-III codes: 5.2.2 - ICD-10: G44.31) she came to our consultation. In the previous fortnight she had had continuous headache.

Description of treatment: The osteopathic manipulative treatment (OMT) was applied individually and different techniques were used depending on the somatic dysfunctions (SD) that were found. Five treatments were performed. The first three, two weeks apart, the fourth after three weeks and the fifth at a distance of one month.

Results: Outcomes were measured by HIT-6 scale at the first (t0) and the last treatment (t1), and then at a distance of one month after the last treatment (t2) and by a scale of quantitative evaluation of pain NSR before each treatment (t0-1-2-3-4). For the HIT-6 (Figure 1) results were: t0=63; t1 and t2=38. For the NRS (Figure 2) results were: t0=8, t1=0, t2=2, t3 and t4=0.

Conclusions: The OMT was found to have changed the impact of headache on the quality of life of the patient, from important to minimum or no impact at all. One year after the last treatment, the patient reported having had only two episodes of headache but mild, lasting only one day and no longer needed to take medication. Written informed consent to publish was obtained from the patient(s).

References

POSTER PRESENTATIONS

A182
P025. Two-year follow-up with OnabotulinumtoxinA for chronic migraine: a real life evaluation of 113 patients
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The Journal of Headache and Pain 2015, 16(Suppl 1):A182

Background: OnabotulinumtoxinA (Botox®, Allergan) has shown its efficacy in chronic migraine (CM) in two phase III studies and up to 5 injection cycles [1]. However, few studies have been published based on its real life efficacy and few data are available on its efficacy beyond the 5th cycle of treatment [2].

Objective: To assess the real life efficacy of 15SU-19SU OnabotulinumtoxinA in CM patients in order to retrospectively investigate the benefits of such treatment and observe if the efficacy is sustained after one year.

Methods: We reviewed the charts of 134 patients treated with OnabotulinumtoxinA who received up to 9 cycles. Patients were injected regularly with a 3-month (±10 days) interval. They were assessed for headache days and hours, intensity of pain by Visual Analogue Scale

Figure 1(abstract A181) HIT-6 score

Figure 2(abstract A181) NRS score
Table 1 (abstract A182)

<table>
<thead>
<tr>
<th>Time in months</th>
<th>Headache Days</th>
<th>% of Reduction vs Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>24.1 (22.1 - 26.3)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>164 (148 - 181)</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>11.1 (9.7 - 12.7)</td>
<td>54</td>
</tr>
<tr>
<td>9</td>
<td>7.5 (6.3 - 9.1)</td>
<td>69</td>
</tr>
<tr>
<td>12</td>
<td>5.1 (4.0 - 6.5)</td>
<td>79</td>
</tr>
<tr>
<td>15</td>
<td>3.5 (2.6 - 4.7)</td>
<td>85.5</td>
</tr>
<tr>
<td>18</td>
<td>2.4 (1.7 - 3.3)</td>
<td>90</td>
</tr>
<tr>
<td>21</td>
<td>1.6 (1.1 - 2.4)</td>
<td>94.4</td>
</tr>
<tr>
<td>24</td>
<td>1.1 (0.7 - 1.7)</td>
<td>95.4</td>
</tr>
</tbody>
</table>

(VAS), number of any acute drug intake. Photophobia, phonophobia, osmophobia, nausea were assessed as well. The results were also analysed based on the CM onset.

Results: Since approval, we have treated a total of 134 patients. We collected the data of 113 CM patients (mean age 48 y.o.; 76% women) who represent the ones showing any response during the first two treatment cycles. Already after cycle two, those who were responders, showed a high decrease vs the baseline as follows: 54% in headache days reduction (from 24.1 to 11.1); 64% in headache hours (from 552.8 to 199). Also, pain intensity dramatically decreased 21% (from 9.6 to 7.6) and corresponding any drug intake went from an average of 51.65 to 16 tablets/month. In the case of those patients also taking i.v. drugs, these had been totally suspended from the second cycle since there was no need. Thirty-seven patients had been treated longer than one year and up to 9 cycles confirming an increasing improvement over time (Table 1). No difference in efficacy was recorded comparing patients suffering from CM from 5 up to 20 years.

Conclusions: Our real life experience demonstrated the efficacy and tolerability of the OnabotulinumtoxinA responders already after the first treatment cycles. Overtime, not only a sustained efficacy was observed but also a favorable trend of improvement with no significant adverse events. Moreover, our analysis confirmed that the efficacy outcomes were not affected by the CM onset thus allowing us to assume that OnabotulinumtoxinA can be considered a valuable first line treatment to allow more patients to benefit earlier and more consistently from this therapeutic option.

Written informed consent to publish was obtained from the patient(s).

References

Table 1 (abstract A183)

<table>
<thead>
<tr>
<th>TEST</th>
<th>T-0</th>
<th>T-6</th>
<th>T-12</th>
<th>T-18</th>
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<tbody>
<tr>
<td>HD</td>
<td>0.98±0.09</td>
<td>0.77±0.30</td>
<td>0.69±0.29</td>
<td>0.65±0.36</td>
</tr>
<tr>
<td>AC</td>
<td>1.79±1.59</td>
<td>1.33±1.90</td>
<td>0.70±0.43</td>
<td>0.61±0.42</td>
</tr>
<tr>
<td>HIT-6</td>
<td>63.95±6.91</td>
<td>62.14±8.06</td>
<td>58.55±9.41</td>
<td>52.29±8.69</td>
</tr>
<tr>
<td>SF-36 MENTAL</td>
<td>48.35±18.91</td>
<td>49.17±19.90</td>
<td>52.58±24.69</td>
<td>70.18±23.22</td>
</tr>
<tr>
<td>SF-36 PHYSICAL</td>
<td>46.35±18.91</td>
<td>49.17±19.90</td>
<td>52.58±24.69</td>
<td>70.18±23.22</td>
</tr>
<tr>
<td>VAS</td>
<td>7.98±1.26</td>
<td>6.02±1.89</td>
<td>5.13±1.61</td>
<td>4.25±1.49</td>
</tr>
</tbody>
</table>

Legend:
Data are expressed as mean +/- SD. Results differ significantly vs T0. p < 0.001 (ANOVA)
HD = Headache days
AC = Analgesic Consumption
HIT-6 = Headache Impact Test
SF-36 = Short-Form Health Survey (Physical and Mental)
VAS = Visual Analog Scale

P045. OnabotulinumtoxinA: long term treatment for chronic migraine with medication overuse
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The Journal of Headache and Pain 2015, 16(Suppl 1):A183

Introduction: Chronic migraine represents the most disabling condition among headaches, in particular when migraine is associated with drug abuse.

Patients with chronic migraine (CM) coming to our centres are difficult to treat, both because of their refractory to antimigraine prophylactic treatment and for the combination of several comorbidities, that often need a multidisciplinary approach that leads to a multi-prescription of drugs.

The treatment with OnabotulinumtoxinA (Botox®) is an important therapeutic option both for its efficacy in the long term, and for the safety profile, due to the lack of clinically significant side effects.

Materials and methods: In our Headache Centre we performed a retrospective study including a sample of 67 patients with a diagnosis of CM associated with drug abuse according to the ICHD-III (beta) classification. The patients were treated with OnabotulinumtoxinA according to the paradigm of the PREEMPT study (155 U to 31 injection sites) [1]. The purpose of our study was to evaluate the duration of the Botox’s efficacy in terms of headache days (HD), analgesic consumption (AC) and to assess the patients’ quality of life by some self-administered scales (SF-36, HIT-6) and pain scale (VAS) [2].

We recorded medical charts for 67 patients. However, we report the data concerning the results of only 57 patients since they represent the ones who were injected regularly every 3 months without interruption, some of them being injected up to cycle 7. Ten patients discontinued for regulatory reasons.

Results: Positive trend of the effectiveness of the treatment appears to be significant in all parameters evaluated as shown in the table 1.

Conclusions: This retrospective study confirms the safety and tolerability profile of repeated treatment with OnabotulinumtoxinA and shows a good consistency of the therapeutic effect over one year of treatment. The trend of the clinical parameters suggests other studies to further investigate the long-term efficacy of the treatment, as recently suggested by Pascual [3].

Moreover, it is important to outline that in our sample we did not register any clinically relevant side effect, besides slight pain in the site of injection, and two cases of transient hypotension during the injection protocol, spontaneously reversed.

Written informed consent to publish was obtained from the patient(s).

References
A184

P060. Vitamin D deficiency in episodic migraine, chronic migraine and medication-overuse headache patients
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1Center for Headache and Adaptive Disorders, Unit of Neurology, Department of Neuroscience and Sense Organs, Azienda Ospedaliero-Pugliese-Ciacco, Catanzaro, Italy; 3Unit of Clinical Pharmacology and Pharmacovigilance, Department of Health Science, Magna Graecia University, Catanzaro, Italy
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The Journal of Headache and Pain 2015, 16(Suppl 1):A184

Background: Various studies have hypothesized a common inflammatory pathogenesis for headache and hypovitaminosis D (HD), showing that migraine patients have low levels of vitamin D [1]. Other studies did not confirm this [2]. Recently, a relationship between HD and reduced pharmacological response has been hypothesized, while vitamin D supplementary intake in HD patients may contribute to clinical improvement [3]. Aim of our prospective study was to evaluate the relationship between vitamin D levels and headache frequency and management in a cohort of patients accessing to our Centre for Headache from April 2015 to October 2015. We present preliminary data about patients enrolled until June 2015.

Materials and methods: We enrolled 22 patients (6 males, 16 females; 45.4±11.22 mean age) accessing our Center from April 2015 to June 2015. We assigned patients to one of two groups according to headache frequency: Group A patients had a clinical history of episodic migraine (EM; n=7; < 8 headache days/month); Group B patients had a clinical history of chronic migraine and/or medication-overuse headache (CH/MO; n=15; > 8 headache days/month). We excluded < 18 and > 55 year old patients and patients already supplementing vitamin D. At access, all patients received neurological and headache assessment, pharmacological evaluation, disability assessment and psychological evaluation. We took blood samples to obtain the dosage of vitamin D (normal values = 30-100 ng/ml). Using SOFA Statistics 1.4.4 software, we calculated descriptive indicators and Pearson’s correlation coefficient (r) between headache frequency and vitamin D levels. We compared groups on vitamin D levels using independent samples Student’s t-test. We set p < 0.05 as threshold of statistical significance. The local ethical committee approved the study design. All patients signed an informed consent to the research.

Results: Vitamin D levels (M±DS) in all patients (n=22) fell below the normal range (13.05±5.70). Vitamin D levels were lower (M±DS) among Group A (CM +MOH) patients (11.73±5.98) than Group B (EM) patients (15.86±4.10); Student’s t-test showed no statistically significant difference between groups on vitamin D levels (t = 1.642; p = 0.116). While Pearson’s test did not show correlation between vitamin D levels and headache frequency (r = -0.308; p = 0.163), scatterplot suggests that such hypothetical inverse relationship, given a sample expansion, should be investigated (fig. 1).

Conclusions: Migraine patients appear to have a high rate of hypovitaminosis D. Since vitamin D may coadjuvate the absorption of medication, further studies should investigate HD role in reducing migraine pharmacological management efficacy.

Written informed consent to publish was obtained from the patient(s).

References

A185

P005. Efficacy Type-A Botulinum toxin treatment in a multidisciplinary setting for chronic headache
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E-mail: centrocefaleaopc@gmail.com
The Journal of Headache and Pain 2015, 16(Suppl 1):A185

Background: Type-A botulinum toxin (BoNTA) therapy has emerged as an effective treatment for chronic headache (CH) [1]. No conclusive data exists about BoNTA efficacy in CH comorbid with anxiety and depression disorders. Our open prospective study aimed to evaluate CH BoNTA treatment efficacy regarding clinical and psychopathological variables in a multidisciplinary setting.

Materials and methods: We treated 32 CH patients (8 males; 24 females; 44.76±11.23 mean age) with 190-units BoNTA injections. Sessions took place from January 2014 to June 2015 once every 3 months; patients received headache education; at the baseline (T0) and at the final follow-up (T1) patients completed a headache diary, pain Numerical Rating Scale (NRS), Migraine Disability Assessment (MIDAS), Zung Self-Rating Anxiety Scale (SAS) and Zung Self-Rating Depression Scale (SDS). We considered patients responders if they had > 50% reduction in headache frequency and/or pain intensity compared with baseline. Using SOFA Statistics 1.4.4 software, we calculated descriptive indicators and evaluated treatment effect using paired-samples Student’s t-test on clinical and psychosocial variables between T0 and T1. We set p < 0.05 as threshold of statistical significance.

Results: At T0 headache frequency (M±DS) was 23.71±5.38 headache days/month; NRS score was 9.10±0.94; MIDAS score was 57.59±24.72; SAS score was 48.38±12.16; SDS score was 46.68±14.31. At T1 headache frequency (M±DS) was 9.14±8.31 headache days/month; NRS score was 6.33±2.33; MIDAS score was 21.51±20.19; SAS score was 39.38±9.19; SDS score was 36.01±10.32. Twenty-one patients (65.25%) showed psychopathological comorbidity. We observed response to treatment in 23 patients (71.87%) with a statistically significant treatment effect on headache frequency (t = 5.839; p < 0.001), pain intensity (t = 5.451; p < 0.001), disability (t = 5.701; p < 0.001), anxiety (t = 3.457; p < 0.005) and depression (t = 2.39; p < 0.05).

Conclusions: Our data support that BoNTA in a multidisciplinary setting is an effective treatment for chronic headache, potentially addressing pain-related affective disorders. Further developments of our study could evaluate the effectiveness of enhanced psychological interventions, such as stress management, as a complement to the biomedical treatment.

Written informed consent to publish was obtained from the patient(s).

Reference
A186

P026. Pilot study on the use of coenzyme Q10 in a group of patients with episodic migraine without aura

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The Journal of Headache and Pain 2015, 16(Suppl 1):A186

Introduction: Coenzyme Q10 is a naturally occurring substance and essential element of the mitochondrial electron transport chain. There has been a recent interest in the role that mitochondria may play in migraine pathogenesis. If indeed migraine results from mitochondrial dysfunction, then coenzyme Q10 could be used as a successful migraine preventive therapy. Abnormal mitochondrial function translates into high intracellular penetration of Ca(2+), excessive production of free radicals, and deficient oxidative phosphorylation, which ultimately causes energy failure in neurons and astrocytes, thus triggering migraine mechanisms. The objective of this investigation was to confirm the efficacy of coenzyme Q10 as a preventive treatment for migraine headaches.

Materials and methods: We selected from the Headache Center of the “Istituto Clinico Città di Brescia” a population of 40 patients aged between 18 and 65 years, suffering from migraine without aura with a headache frequency between 3 to 6 crises/month (4 to 12 days with headache/month), not assuming other migraine preventive therapy. They were randomly assigned to treatment with coenzyme Q10 300 mg (20 patients) or 600 mg (20 patients) once a day for 3 months. Patients were evaluated for frequency, duration, intensity of pain, response to trigger factors and response to their habitual analgesic drug (data obtained from the diary of headache delivered at first visit). The improvement of the thermographic pattern was also evaluated.

Results: A reduction in frequency and intensity of more than 50% in 25 patients, 10 patients reported reduction of more than 50% in the intensity but not in frequency (<50%). 5 patients had no improvement of symptoms. In all patients the complexity of the accompanying symptoms were less severe and they noted a reduction of the response to trigger factors.

Discussion and conclusions: Coenzyme Q10 is an essential element of the mitochondrial electron transport chain and has been shown to improve mitochondrial oxidative phosphorylation in humans. Coenzyme Q10, which can be administered orally with an excellent side-effect profile, appears to be a good migraine preventive. Written informed consent to publication was obtained from the patient(s).

A187

P064. 12 years of Master Degree in Headache Medicine at Sapienza University of Rome

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The Journal of Headache and Pain 2015, 16(Suppl 1):A187

The Master in Headache Medicine has accomplished its 12th cycle of life [1]. At the time of its activation we acknowledged the necessity of an academic education thought to support the growth of a subspecialty included in major disciplines like neurology, internal medicine, emergency medicine, pharmacology and pain medicine. The challenge then was to reunite multidisciplinary skills in a common formative path recognized by National Health Systems [2]. The internationalization of the Faculty, the endorsement of the European Headache Federation, the educational arm of Lifting The Burden - The Global Campaign against Headache and the tight collaboration with the European Federation of Pain - Joint Campaign against Headache has allowed us to accomplish an innovative project that has been heavily criticized for its uncertain utility in a context where this educational strategy was considered only a redundant subspecialty [3,4]. The educational offer over time included frontal lectures, clinical seminar with tutorial support and mid-term evaluations available on the Moodle platform. The attendance in the outpatient and daily hospitalization wards of a University Hospital with a solid national experience avant-garde on these diseases completed the educational frame. Foreign students could benefit from distance e-learning platform and bursaries for those coming from developing countries. The qualified international profile of the Faculty guaranteed the excellence of the formative offer. Today, after 12 years of academic education, Sapienza University of Rome has released 119 master degree diplomas in headache medicine to as many students coming from all the six WHO geographical areas: Africa, Americas, Europe, Eastern Mediterranean, South-East Asia, Western Pacific. The Train-The-Trainers model, a top-down educational activity, has accomplished its path allowing all the master degree physicians to teach headache medicine locally in favour of GPs. The same Sapienza distance e-learning platform served also as source for this second level of education. This experience has shown to be fruitful in a mid-long term and particularly useful in geographical areas with a low presence of area experts. After more than 10 years the received feedbacks show the efficacy of this educational spreading model thought to reach the control of headache disorders now ranked as third most disabling disease in the world [5].

References

A188

P041. Analysis of body mass index, psychiatric comorbidity, sleep-wake pattern and occurrence of fatigue in episodic and chronic migraine patients

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The Journal of Headache and Pain 2015, 16(Suppl 1):A188

Background: Migraine clinical picture and life-time disease course can be highly heterogeneous, with a subgroup of patients developing chronic migraine, a highly disabling condition, associated with high socio-economic burden. Moreover, migraine clinical spectrum is expanded by the association with different comorbid/coexisting conditions and interictal dysfunctions, contributing to modulate migraine clinical profile. Taking this scenario into consideration, the aim of this study was to systematically evaluate migraine clinical features, body mass index (BMI), depressive and anxiety symptoms, sleep-wake pattern and occurrence of fatigue in a sample of episodic and chronic migraine patients, as well as their reciprocal interaction.

Methods: One hundred and fifty patients with a diagnosis of migraine without aura were enrolled; 75 patients fulfilled criteria for episodic migraine and 75 for chronic migraine (ICHD-3 beta). Patients with comorbid/coexisting conditions or in treatment with migraine preventive drugs were excluded. Data regarding age, gender, monthly frequency of migraine attacks, disease duration and BMI were collected. Migraine-related disability, presence of anxiety and depressive symptoms, subjective sleep quality, chronotype, fatigue and daily sleepiness were, respectively, evaluated using the following questionnaires: Migraine Disability Assessment Score (MIDAS), Generalized Anxiety Disorder 7-item scale (GAD-7), Patient Health Questionnaire 9-item scale (PHQ-9), Pittsburgh Sleep Quality Index (PSQI), reduced Morningness-Eveningness Questionnaire (MEQ), Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS).

Results: Mean age (p = 0.012), disease duration (p < 0.001), BMI score (p = 0.012) and MIDAS score (p = 0.005) were significantly higher in chronic compared to episodic migraineurs; furthermore, mean GAD-7 score (p = 0.019), PHQ-9 score (p < 0.001), PSQI score (p = 0.015) and FSS score (p < 0.001) were higher in chronic migraine patients. No statistically
significant differences were documented in gender distribution, mean ESS and rMEQ scores between episodic and chronic migraineurs. A correlation analysis (Rho coefficient of Spearman) carried out in the total sample of 150 migraineurs, documented a statistically significant, positive correlation between monthly frequency of migraine attacks and patients’ age (p < 0.001), disease duration (p < 0.001), BMI score (Rho 0.177, p = 0.049), MIDAS score (p < 0.001), GAD-7 score (p = 0.019), PHQ-9 score (p < 0.001), PSQI score (p = 0.006) and FSS score (p < 0.001).

Discussion: Data from the present report seem to expand the concept of migraine as a continuum or spectrum, with higher BMI score and greater occurrence of anxiety-depressive symptoms, poor sleep quality and fatigue in chronic migraine patients compared to episodic migraineurs; further investigation is certainly necessary in order to better define the biological basis and mechanisms associated with migraine transformation from episodic to chronic pattern.

Written informed consent to publish was obtained from the patient(s).

A189
P023. Reasons for headache investigation and findings in an experimental headache center
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The Journal of Headache and Pain 2015, 16(Suppl 1):A189

Background: Warning symptoms or “red flags” are useful in targeting which patients with headache require investigation. Many red flags, even with normal neurological examination, are the cause of neuroimaging (CT or MRI) overutilization, in addition to patient reassurance. Optimizing headache neuroimaging practices should be a major priority. The aim of our study was to evaluate the investigation rate in patients referred for the first time in the period from 2011 to 2013 to our Headache Center (HC) conducted by a general practitioner particularly an expert in headache management, and to correlate the reasons of investigation with neuroradiological findings.

Results: A total of 118 (10.9%) of 1,078 new patients (802 females, 276 males; mean age 43.1±15; range 7-90), 85% suffering from episodic or chronic migraine, were referred for neuroimaging; 107 MRI (20 MR angiography), 11 CT. Considering only the 676 subjects whom had never undergone neuroimaging, the percentage was 14.6. Sixteen out of 118 patients were investigated in the past (11 CT, 5 MRI).

The reasons for headache investigation were: recent change in characteristics (18%), significant increased frequency from 1-12 months (55, in 21 daily headaches), recent (1-12 months) onset (25, in 14 daily headaches ab initio from 1-6 months), recent onset in patients over 40 years (19), abnormal neurological signs (12): alteration of Mingazzini or Romberg test, precipitated by exertion (8), atypical aura (8), first-degree relatives died from cerebral aneurism (4), memory deficit (4), migraine associated vertigo (7), paresthesia not typical of aura (7), nighttime onset (3), atypical cluster headache (1), trigeminal neuralgia first branch (1), recent thunderclap headache (1).

Twenty-two patients currently in good health had not performed the requested neuroimaging. Information regarding 9 residents outside the region was unavailable. The analysis of neuroimaging findings (82 MRI, 5 CT) therefore concerned 87 patients aged 14-78 years, 53 of them with migraine without aura and 11 with migraine with aura.

Insignificant abnormalities were found in 33 patients: parasanal sinus thickening (13), septum pellucidum cyst (2), pineal cyst (3), arachnoid cyst (3), circle of Willis variants (6), signs of chronic cerebral ischemia (5), doubtful small subependymoma (1). Significant abnormalities possibly related to headache were found in two patients (2.2%) with cavernous angioma and intracranial hypotension.

Conclusions: The rate of headache patients investigated through neuroimaging was largely inferior to that previously reported in various clinical settings [1-3]. We suggest that a major study should evaluate if some red flags such as changes in headache characteristics but with normal neurological examination require investigation.

A190
P011. The use of electronic pain diaries via telemmedicine for managing chronic pain
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Chronic pain is defined as pain that persists for longer than 3 to 6 months with persistence beyond “normal healing time” of an injury [1]. Pain is a subjective experience, which is difficult to accurately measure. Current approaches to evaluate chronic pain suffer from methodological problems. A real-time data capture approach using electronic diaries has been proposed as a new standard for pain measurement. The formulation of a correct diagnosis and the delivery of optimal care depend on accurate communication between patients and clinicians regarding patients’ symptoms that necessitate reliance on memory, which is often imprecise. Data suggest that remote clinical assessments via telemedicine can improve clinical monitoring, diagnosis and care, and facilitate research participation.

Our aim was to evaluate the feasibility and the reliability of using a handheld electronic communication device via telemedicine as a method for assessing and monitoring pain and discomfort in chronic pain patients.

In collaboration with TERIN, an Italian ICT (information and communication technology) consortium, we have developed an easy-to-use smartphone-based electronic pain diary (IHCS AID Diary) which enables assessment of clinical features of pain over time. Data are transferred via internet to the central server that provides the web interface to access the system (IHCS - Chronic pain, Advocate Health Care System), to which we can connect to explore processed data and to interact with it. Fifty-three headache patients were selected. The subject’s task, during pain, was to indicate the location of pain (on a bodymap), the intensity of pain (on a visual analogue scale -VAS), the state of discomfort (on the Wong-Baker FACES pain rating scale), other pain associated manifestations and therapeutic response by using the AID Diary. All subjects also completed paper pain diaries.

Preliminary results showed that 27 patients (51%) were compliant in using the AID Diary during pain, 18 patients (34%) had issues with application malfunctioning and transferring data and 8 patients (15%) were noncompliant. Paper pain diaries returned by the group of compliant patients contained more errors and omissions compared to the AID Diary.

The potential use of a smartphone-based electronic pain diary via telemedicine seems to be a feasible and reliable method for conducting remote assessments of clinical features of pain in chronic pain patients over a longer period of time, thus improving clinical monitoring, differential diagnosis and treatment of pain.

Written informed consent to publish was obtained from the patient(s).

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P056. Clinical case: headache as a symptom of another disease detector
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O002. Did Picasso and De Chirico really suffer from migraine au-sas?
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O073. Proposal guidelines for epilepsy and headache
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O193. Proposal guidelines for epilepsy and headache
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Methods: We performed an extensive review of the literature including the terms covered in the ICHD and the terms recently proposed. We rated how the recent literature has influenced the change of the third edition of the ICHD (ICHD 3-beta).

Results and discussion: Despite a high number of papers in this field, no significant changes have been added in the association between headache and epilepsy in the ICHD 3-beta. Migralepsy has been confirmed and only shifted by encoding code remaining between the forms for chronic migraine. The term “Hemicrania epileptica” still remains, but the diagnostic criteria have changed whereas this can also be encoded as headache contralateral to the ictal discharge (in the past only ipsilateral). Diagnosis requires the simultaneous onset of headache with EEG-demonstrated ictal discharge. In our opinion, for proper classification of the cases with a strictly temporal association between a headache attack and an epileptic seizure, an ictal EEG is essential for the diagnosis. To our knowledge, it is a feasible guideline proposal shared among the scientific societies that deal with headaches and epilepsy.

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